NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Dapagliflozin for treating chronic kidney disease [ID3866]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Dapagliflozin for treating chronic kidney disease [ID3866]

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The following documents are made available to consultees and commentators:

The **final scope** and **final stakeholder list** are available online. Access the scope and stakeholder list on the NICE website..

The latest update to the NICE guideline on assessment and management of chronic kidney disease was published in August 2021. Access the NICE CKD guideline.

1. **Company submission** from AstraZeneca

2. **Clarification questions and company responses**
   - **a.** Main response
   - **b.** Updated response to question B31

3. **Patient group, professional group and NHS organisation submission** from:
   - **a.** Kidney Care UK
   - **b.** St George's University Hospitals NHS Foundation Trust – London Kidney Network

4. **Evidence Review Group report** prepared by the School of Health and Related Research (ScHARR)

5. **Evidence Review Group – factual accuracy check**

6. **Technical engagement response** from AstraZeneca

7. **Technical engagement responses and statements from experts**:
   - a. Professor James Burton, Professor of Renal Medicine and Honorary Consultant Nephrologist – clinical expert, nominated by AstraZeneca
   - b. Dr Rosa Montero, Consultant Nephrologist – clinical expert, nominated by Renal Association
     - i. Main response
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8. **Technical engagement response from consultees and commentators:**
   - a. Primary Care Diabetes Society
   - b. St George's University Hospitals NHS Foundation Trust – London Kidney Network
   - c. Novartis

9. **Evidence Review Group critique of company response to technical engagement** prepared by School of Health and Related Research (ScHARR)

10. **Expert personal perspectives** from:
    a. Ann Harpur-McGrath – patient expert, nominated by Kidney Care UK
    b. Mark Smith – patient expert, nominated by Kidney Care UK
    c. Dr Andrew Lewington, Consultant Renal Physician – clinical expert

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

Dapagliflozin for treating chronic kidney disease

ID 3866

Document B

Company evidence submission

April 2021

File name	Version	Contains confidential information	Date
ID 3866_Dapagliflozin Company Submission Document B_April 2021_[REDACTED]	1.0	Yes	27th April 2021

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This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Please note that the information requirements for submissions are summarised in this template; full details of the requirements for pharmaceuticals and devices are in the user guide.

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Abbreviations

Abbreviation	Definition
ACE	Angiotensin converting enzyme
ACR	Albumin-to-creatinine ratio
AE	Adverse event
AIC	Akaike information criterion
AKI	Acute kidney injury
ANCA	Anti-neutrophil cytoplasmic antibody
ARB	Angiotensin receptor blocker
BIC	Bayesian information criterion
BL	Baseline
BMI	Body mass index
BP	Blood pressure
CCB	Calcium channel blocker
CI	Confidence interval
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CPRD	Clinical Practice Research Datalink
CRT	Cardiac resynchronization therapy
CSED	Common study end date
CV	Cardiovascular
CVD	Cardiovascular disease
CVOT	Cardiovascular outcomes trials
DAG	Diagnostic coronary angiography
DKA	Diabetic ketoacidosis
eGFR	Estimated glomerular filtration rate
EMA	European medicines agency
eMIT	Electronic market information tool
EPAR	European public assessment report
EQ-5D	EuroQoL- 5 Dimension
ESA	Erythropoietic stimulating agent
ESKD	End-stage kidney disease
FAS	Full analysis set
GFR	Glomerular filtration rate
HCHS	Hospital and Community Health Services
HCP	Healthcare professional
HCRU	Healthcare resource utilisation
HF	Heart failure
HFrEF	Heart failure with reduced ejection fraction
HFS	Hypoglycaemia fear survey
hHF	Hospitalisation for heart failure
HRG	Healthcare resource groups

Abbreviation	Definition
HRQoL	Health related quality of life
HTA	Health technology assessment
HTAD	Health technology assessment database
HTN	Hypertension
ICD	Implantable cardioverter defibrillator
ICER	Incremental cost-effective ratio
IPD	Individual patient-level data
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITC	Indirect treatment comparison
ITT	Intention-to-treat
KDQOL	Kidney Disease Quality of Life Instrument
KM	Kaplan Meier
LCED	Limited Claims and Electronic Health Record Database
LYG	Life years gained
MAIC	Matching adjusted indirect comparison
MHRA	Medicines and Healthcare products Regulatory Agency
MIMS	Monthly Index of Medical Specialities
MRA	Mineralocorticoid receptor antagonist
NHS	National Health Service
NHS-EED	NHS economic evaluation database
NICE	National Institute for Health and Care Excellence
NSAIDS	Non-steroidal anti-inflammatory drugs
OR	Odds ratio
PCI	Percutaneous coronary intervention
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis
PSS	Personal social services
PSSRU	Personal social services research unit
PTDV	Premature treatment discontinuation visit
PY	Person years
QALY	Quality adjusted life year
QIC	Quasi-information criterion
RAAS	Renin-angiotensin-aldosterone system
RCT	Randomised controlled trial
RRT	Renal replacement therapy
SAE	Serious adverse event
SAS	Safety analysis set
SCV	Study closure visit
SE	Standard error
SF-12	12-item Short Form Survey
SGLT2	Sodium-glucose cotransporter-2
SIRS	Systemic inflammatory response syndrome

Abbreviation	Definition
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SOC	Standard of care
STA	Single Technology Appraisal
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TSD	Technical support document
uACR	Urine albumin-to-creatinine ratio
UK	United Kingdom
UKPDS	UK Prospective Diabetes Study
ULN	Upper limit of normal
UTI	Urinary tract infection
WTP	Willingness-to-pay

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

B.1.1 *Decision problem*

The submission covers the full anticipated marketing authorisation for dapagliflozin in this indication; i.e. in [redacted].

The decision problem addressed within this submission is consistent with the NICE final scope for this appraisal as outlined in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the NICE final scope
Population	Adults with CKD who are receiving individually optimised standard care.	As per NICE final scope.	[redacted]
Intervention	Dapagliflozin in combination with optimised standard care (including treatment with an ACE inhibitor or ARB).	Dapagliflozin + SOC	Intervention aligned with NICE final scope.
Comparator(s)	Established clinical management without dapagliflozin.	Placebo + SOC	Comparator aligned with NICE final scope. Established clinical management without dapagliflozin comprises individually optimised SOC alone, which is represented by the placebo arm of the dapagliflozin clinical trial.
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 • Adverse effects of treatment	As per NICE final scope.	N/A

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the NICE final scope
	• 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 • 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	As per NICE final scope.	N/A
Subgroups to be considered	• People with diabetes • People with CVD • People with other causes of CKD	• People with comorbid T2DM • People with comorbid CVD • People without comorbid T2DM and without comorbid CVD	It is most relevant in clinical practice to group patients by comorbidity rather than by cause of CKD, as it is difficult to accurately establish the cause of CKD in most cases. The third subgroup requested in the final scope has been clarified during the decision problem meeting to be the subgroup of patients without comorbid T2DM and without comorbid CVD.
Special considerations including issues related to equity or equality	None stated.	Considerations related to current use and availability of dapagliflozin in primary and secondary care for patients with T2DM, T1DM and HFrEF.	Dapagliflozin is currently available across primary and secondary treatment settings for patients with T2DM, T1DM and HFrEF.[1] A positive recommendation for dapagliflozin in CKD is expected to extend the benefits of dapagliflozin to all eligible patients with CKD, including patients with CKD but without T2DM or HFrEF. A NICE recommendation that permitted the initiation of dapagliflozin for the treatment of CKD in the primary care setting is needed to deliver equitable

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the NICE final scope
			access to treatment, given access to specialist CKD care varies considerably by geography.

Abbreviations: ACE: angiotensin-converting enzyme; ARB: angiotensin II receptor blockers; CKD: chronic kidney disease; CV: cardiovascular; CVD: cardiovascular disease; eGFR: estimated glomerular filtration rate; ESKD: end-stage kidney disease; HF: heart failure; HFrEF: heart failure with reduced ejection fraction; HTN: hypertension; N/A: not applicable; NICE: National Institute for Health and Care Excellence; T1DM: type 1 diabetes; T2DM: type 2 diabetes mellitus; SOC: standard of care.
Sources: Dapagliflozin NICE final scope [ID 3866].[2]

B.1.2 *Description of the technology being appraised*

A description of the technology being appraised is summarised in Table 2. The SmPC for dapagliflozin in this indication was not available at the time of writing this document; AstraZeneca will share this with NICE when possible.

Table 2: Technology being appraised

UK approved name and brand name	Dapagliflozin (Forxiga®)
Mechanism of action	• Dapagliflozin is a highly potent, selective and reversible SGLT2 inhibitor[1] • SGLT2 is a co-transporter protein localised primarily in the proximal tubule of the nephron in the kidney, which mediates the active transport of glucose and sodium from the filtrate into the blood, thereby controlling the level of sodium present in the filtrate[3] • In the context of CKD, inhibition of SGLT2 is anticipated to improve renal outcomes independently of blood glucose, via mechanisms relevant to disease processes common to multiple CKD aetiologies • In CKD, a progressive loss of nephrons triggers harmful changes such as glomerular hypertension (high pressure), single nephron hyperfiltration (abnormally high filtration rate) and glomerular hypertrophy (swelling). Resulting increases in wall tension and shear stress promote a proinflammatory and profibrotic state which together contribute to declining kidney function and disease progression[4, 5] • SGLT2 inhibition reduces sodium reabsorption in the proximal tubule, leading to increased sodium delivery to the macula densa and altered glomerular haemodynamics, reducing glomerular hypertension and hyperfiltration[6, 7] • The reduction of glomerular pressure alleviates hypertension-associated damage to the glomerulus, reduces urinary albumin filtration and excretion, and reduces proinflammatory pathway activation and direct tubular toxicity; these changes may contribute to reduction of tubular interstitial fibrosis[8, 9] • SGLT2 inhibition also exerts a variety of additional systemic effects which may modify risk factors for the progression of CKD and thereby contribute to reduced kidney damage, including reduced blood pressure, albuminuria and body weight[8, 10]
Marketing authorisation/CE mark status	The marketing authorisation for dapagliflozin in this indication is expected to be granted by the [redacted].
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The anticipated marketing authorisation for dapagliflozin in this indication is for [redacted]. Dapagliflozin is also currently indicated for:[1] • Treatment of adult patients with insufficiently controlled T2DM as an adjunct to diet and exercise, either as a monotherapy when metformin is considered inappropriate due to intolerance or in addition to other medicinal products for treatment of T2DM • Treatment of adult patients with insufficiently controlled T1DM

	as an adjunct to insulin in patients with BMI ≥27 kg/m^2, when insulin alone does not provide adequate glycaemic control despite optimal insulin therapy • Treatment of adult patients with symptomatic chronic HFrEF Dapagliflozin has the following contraindications:[1] • Hypersensitivity to the active substance or to any of the excipients A full list of special warnings and precautions for use is provided in the current SmPC, available here: https://www.ema.europa.eu/en/documents/product-information/forxiga-epar-product-information_en.pdf.
Method of administration and dosage	10 mg oral dapagliflozin once daily.
Additional tests or investigations	No additional tests or investigations are required prior to the administration of dapagliflozin.
List price and average cost of a course of treatment	The list price of dapagliflozin is £36.59 per pack of 28 x 10 mg tablets.[11, 12] The yearly cost of treatment with dapagliflozin is £476.98. Dapagliflozin is a treatment for a chronic disease, and therefore treatment is long-term (lifetime) or until the patient's clinician determines that treatment should be discontinued.
Patient access scheme (if applicable)	No patient access scheme is included as part of this appraisal.

Abbreviations: BMI: body mass index; CKD; chronic kidney disease; EMA: European Medicines Agency; eGFR: glomerular filtration rate; HFrEF: heart failure with reduced ejection fraction; MHRA: Medicines and Healthcare products Regulatory Agency; SGLT2: sodium-glucose co-transporter 2; SmPC: Summary of Product Characteristics; T1DM: type 1 diabetes mellitus; 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 the position of the technology

- Chronic kidney disease (CKD) is a complex, progressive disorder which frequently co-occurs with other conditions such as type 2 diabetes mellitus (T2DM), hypertension (HTN) and cardiovascular disease (CVD) such as heart failure (HF)[13-15]
- CKD is defined in national and international guidelines as abnormalities of kidney structure or function present for at least three months with implications for health[13, 16]
- Even in early stage CKD patients are at an increased risk of cardiovascular (CV) events, end stage kidney disease (ESKD) and premature mortality compared to the general population, and this risk increases with disease severity[17]
- Health-related quality of life (HRQoL) also declines with disease progression, and is particularly poor once ESKD is reached, with one study reporting greater decreases in HRQoL compared with the general population in patients with ESKD than in patients with other chronic diseases such as arthritis and cancer.[18, 19] Renal replacement therapy for ESKD also accounts for the majority of the cost burden of CKD (overall cost burden

estimated to be £1.45 billion a year in the United Kingdom (UK) in 2009–10)[20, 21]

- Timely diagnosis and treatment to slow the progression of CKD are key in reducing the substantial clinical, HRQoL and economic burden associated with CKD, and particularly late stage CKD[22]
- Prior to the development of sodium-glucose co-transporter 2 (SGLT2) inhibitors, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) were the only treatments to have demonstrated efficacy in slowing CKD progression to ESKD in a clinical trial, with no clinical development in this area for several decades[23]
- The current treatment pathway for CKD in the UK focuses on CV risk management and management of complications such as anaemia alongside delaying progression of CKD. This involves a combination of treatment strategies individually adapted to a patient's specific characteristics, which may include ACE inhibitors and ARBs[16]
- However, only one ACE inhibitor (ramipril) is licensed for the treatment of patients with CKD without comorbid T2DM in Europe; the majority of ACE inhibitors and ARBs are licenced for use in patients with CKD with comorbid T2DM and macroalbuminuria only[24-26]
- A substantial residual risk of CKD progression and mortality remains despite treatment with current standard of care (SOC), and ACE inhibitors and ARBs are also associated with tolerability and dose titration challenges which can limit the ability to reach maximally efficacious doses[27-29]
- Dapagliflozin is already frequently prescribed in primary and secondary care for patients with T2DM or HF, which are common comorbidities of CKD
- As the first novel treatment for two decades to slow progression of CKD in patients with and without T2DM, as well as the only treatment to significantly reduce all-cause mortality in patients with CKD, dapagliflozin is well positioned to address the significant unmet need for additional treatment options for these patients[23]

B.1.3.1 CKD overview

CKD is characterised by declining kidney function over time

CKD is a complex progressive disorder defined in national and international guidelines as abnormalities of kidney structure or function present for at least three months with implications for health.[13-15] The kidneys are composed of small functional units called nephrons and are responsible for filtering the blood to remove waste products (e.g. urea) and excess water, which are converted into urine and excreted.[30] Nephrons contain a filtering unit called a glomerulus, a unit of very small blood vessels within the nephron.[30] In CKD, progressive loss of nephrons triggers harmful changes which cause kidney function to decline over time, eventually leading to kidney failure (ESKD) in some patients, at which point the kidneys no longer function sufficiently to maintain health and homeostasis.[15]

CKD is a heterogenous condition, but a common disease pathway is shared across aetiologies

CKD occurs primarily in older individuals, and may result from:[13, 31]

- **Systemic disease** affecting the kidney such as type 2 diabetes mellitus (T2DM; CKD in

patients with T2DM is often referred to as “diabetic kidney disease”) or hypertension (HTN)

- **Primary kidney disease** such as glomerulonephritis (inflammation of the glomeruli, often caused by the immune system attacking healthy tissue)

A common disease pathway is shared across CKD aetiologies.[4] Progressive loss of nephrons results in hypertrophy (swelling) and hyperfiltration (abnormally high filtration rates) in the remaining functional nephrons as they compensate for reduced filtration ability.[4] Resulting increases in wall tension and shear stress promote a proinflammatory and profibrotic state which together contribute to and maintain a cycle of nephron loss, fibrosis (formation of scar tissue), declining kidney function and disease progression.[4, 5]

Conditions such as T2DM, HTN and CVD can be both a cause and a result of CKD

In addition to contributing to the development of CKD, as outlined above, conditions such as T2DM, HTN and cardiovascular disease (CVD; including conditions such as heart failure [HF]) can also develop as a result of reduced kidney function.[32, 33] T2DM and CVD therefore commonly co-occur with CKD, as illustrated by the results of a 2021 analysis of the UK Clinical Practice Research Datalink (CPRD) summarised in Figure 1.

Figure 1: Overview of commonly co-occurring conditions in UK patients with CKD

Abbreviations: CKD: chronic kidney disease; HF: heart failure; MI: myocardial infarction; T2DM: type 2 diabetes mellitus; UK: United Kingdom.
Sources: AstraZeneca Data on File 2021b: REF-109687 (CPRD Analysis).[34]

CKD is often asymptomatic in earlier stages of disease, and the severity of CKD is captured by a combination of eGFR and uACR categories

People with CKD do not usually have symptoms during the early stages of the disease, but symptoms such as weight loss and poor appetite, swollen ankles, feet or hands, shortness of breath, tiredness, feeling sick and itchy skin can develop as the disease progresses.[14, 16, 35]

Reduced kidney function can also result in abnormalities such as dyslipidaemia and electrolyte imbalances, as well as complications such as anaemia, acute kidney injury (AKI) and infections.[13, 15, 36-38]

CKD is diagnosed based on laboratory measures of kidney function and kidney damage such as estimated glomerular filtration rate (eGFR; an estimation of the volume of blood filtered through the glomeruli each minute, which provides a measure of kidney function) and urine albumin-to-creatinine ratio (uACR; a measure of albuminuria [the concentration of a protein called albumin in the urine: high concentrations indicate that the kidney is damaged and too much protein is "leaking" out of the blood]).[14, 39, 40]

CKD varies in severity and can be characterised based on eGFR and uACR categories, which can be used to predict the risk of adverse disease outcomes as shown in Table 3. eGFR can be categorised into one of six categories:[16, 41]

- Normal (G1: ≥90 ml/min/1.73m^2)
- Mild reduction (G2: 60–89 ml/min/1.73m^2)
- Mild to moderate reduction (G3a: 45–59 ml/min/1.73m^2)
- Moderate to severe reduction (G3b: 30–44 ml/min/1.73m^2)
- Severe reduction (G4: 15–29 ml/min/1.73m^2)
- Kidney failure (G5: <15 ml/min/1.73m^2)

Albuminuria concentration (uACR) is divided into three categories:

- Normal to mildly increased, also referred to as normoalbuminuria (uACR <3 mg/mmol)
- Moderately increased, also referred to as microalbuminuria (uACR 3-30 mg/mmol)
- Severely increased, also referred to as macroalbuminuria (uACR >30 mg/mmol)

ESKD, the most severe stage of CKD, is defined as eGFR consistently <15 ml/min/1.73m^2.[14] Increased uACR and decreased eGFR are independently associated with an increased risk of adverse outcomes (Table 3), and these parameters are therefore used to guide decisions for monitoring, treatment and referral to specialist care.[13, 14]

Table 3: Classification of CKD by risk of adverse outcomes, based on eGFR and uACR categories

	uACR category A1 Normal to mildly increased (<3 mg/mmol)	**uACR category A2** Moderately increased (3 to 30 mg/mmol)	**uACR category A3** Severely increased (>30 mg/mmol)
eGFR category G1 Normal and high (≥90 ml/min/1.73m^2)	Low risk *No CKD if there are no other markers of kidney damage*	Moderate risk	High risk
eGFR category G2 Mild reduction related to normal range for a young adult (60 to 89 ml/min/1.73m^2)	Low risk *No CKD if there are no other markers of kidney damage*	Moderate risk	High risk
eGFR category G3a	Moderate risk	High risk	Very high risk

	uACR category A1 Normal to mildly increased (<3 mg/mmol)	**uACR category A2** Moderately increased (3 to 30 mg/mmol)	**uACR category A3** Severely increased (>30 mg/mmol)
Mild to moderate reduction (45 to 59 ml/min/1.73m^2)			
eGFR category G3b Moderate to severe reduction (30 to 44 ml/min/1.73m^2)	High risk	Very high risk	Very high risk
eGFR category G4 Severe reduction (15 to 29 ml/min/1.73m^2)	Very high risk	Very high risk	Very high risk
eGFR category G5 Kidney failure (<15 ml/min/1.73m^2)	Very high risk	Very high risk	Very high risk

Footnotes: Risk categories refer to risk of adverse outcomes.
Abbreviations: CKD: chronic kidney disease; eGFR: glomerular filtration rate; uACR: urine albumin-creatinine ratio.
Source: Draft NICE Guideline for Chronic Kidney Disease, 2021.[16]

CKD is highly prevalent, and many patients with early-stage CKD may not be identified in current clinical practice

Approximately 1.9 million adults in England are recorded in the NHS Quality and Outcomes Framework (QoF) as having a diagnosis of CKD with an eGFR category of G3a–G5 (estimated prevalence: 4.05%).[42] A substantial proportion of patients may also remain undiagnosed; the Kidney and Liver Disease Heath Survey for England in 2016 reported that while 13% of adults surveyed had CKD (stages 1–5) based on eGFR and uACR measurements, only 2% of patients self-reported having a formal diagnosis of CKD.[43] One UK study further indicated that the proportion of undiagnosed patients with stage 1–5 CKD could be approximately 44%.[44]

Diagnosis of early-stage CKD (stage 1–2) is only possible using an assessment of uACR (as eGFR remains within normal ranges [≥60 ml/min/1.73 m^2]). However, rates of uACR testing for patients at high risk of CKD are low in UK clinical practice and most patients with CKD in the UK are therefore diagnosed at stage 3 or later.[45, 46] Data from the UK National CKD Audit of patients with CKD in primary care conducted in 2015/16 showed that only 54% of patients with comorbid T2DM received annual uACR testing, whereas 86% received annual eGFR testing. [45] For other groups, such as patients with comorbid HTN, annual uACR testing rates were lower than 30%.[45]

B.1.3.2 Burden of CKD

CKD is associated with declining eGFR and progression to ESKD

Patients with CKD experience worsening kidney function over time, which can be observed as declining eGFR, and this may eventually lead to ESKD and a requirement for dialysis or kidney transplant (collectively termed renal replacement therapy) in some patients.[15] A small proportion of patients (approximately 5% in the UK) may also choose conservative management of their ESKD, which entails supportive care only without dialysis or transplant, with the primary objective of optimising quality of life.[47, 48] eGFR may decline at different rates depending on patient characteristics, and a proportion of patients may experience particularly rapid decline in kidney

function: rapid progression has been defined in some studies as a loss of eGFR >3 ml/min/1.73m^2 per year.[49]

Patients with CKD are at increased risk of CV events and premature mortality even in early-stage disease, with the risk increasing as CKD progresses

CKD is also associated with a significant clinical burden outside of adverse renal outcomes, encompassing an increased risk of CV events, CV and all-cause mortality, and also morbidity resulting from complications such as anaemia. Despite the asymptomatic nature of early-stage CKD, even patients with earlier stages of CKD have a significantly increased risk of these adverse outcomes compared to patients without CKD. However, later stages of CKD and higher albuminuria categories are associated with a particularly elevated risk compared with earlier stages.[17]

CKD is associated with up to a four times greater risk of CV events (e.g. HF, acute myocardial infarction) compared to individuals without CKD.[37] A 2021 systematic literature review (SLR) which identified 29 studies quantifying the risk of mortality by CKD stage, of which one was conducted in the UK, found that the risk of CV events (HF, coronary heart disease, myocardial infarction and stroke) was significantly increased at later stages of disease and in higher albuminuria categories, as shown in Table 4.[17]

In the same SLR, similar results were observed for all-cause mortality: stage 3 CKD with microalbuminuria was associated with a ~3-fold increased risk of all-cause mortality (HR: 3.24; 95% CI: 2.74, 3.84) compared to patients with stage 1 CKD and normoalbuminuria (uACR <3 mg/mmol), whereas stage 4 CKD with macroalbuminuria was associated with a ~6 fold increase in risk (HR 6.03; 95% CI: 5.26, 6.91) as shown in Table 4. Furthermore, a 2004 UK study found that CKD is associated with up to a five times greater risk of mortality compared to individuals without CKD, and patients with microalbuminuria or macroalbuminuria were ~50% and ~300% more likely to die over an average follow-up of 6.3 years than patients with normoalbuminuria respectively, with age-adjusted hazard ratios (HRs) of 1.54 (95% CI: 1.27, 1.76) and 3.65 (95% CI: 2.53, 5.27).[50]

Table 4: HRs for all-cause mortality and CV events by CKD stage and albuminuria category

	Normoalbuminuria (uACR <3 mg/mmol)	Microalbuminuria (uACR 3–30 mg/mmol)	Macroalbuminuria (uACR >30 mg/mmol)
CV events			
Stage 1 (or no) CKD	Referent	2.23 (1.74–2.85)	3.20 (2.30–4.46)
Stage 2 CKD	1.25 (1.14–1.37)	2.15 (1.86–2.50)	3.10 (2.52–3.81)
Stage 3a CKD	1.69 (1.44–1.99)	2.96 (2.28–3.85)	3.76 (2.93–4.83)
Stage 3b CKD	2.46 (2.14–2.83)	4.03 (3.41–4.76)	5.67 (4.65–6.92)
Stage 4 CKD	5.24 (3.97–6.91)	5.34 (3.85–7.67)	7.83 (5.70–10.75)
Stage 5 CKD	14.31 (7.76–26.39)	8.46 (5.04–14.20)	12.46 (8.12–19.12)
All-cause mortality			
Stage 1 (or no) CKD	Referent	2.03 (1.74–2.38)	2.80 (2.24–3.51)
Stage 2 CKD	1.14 (1.07–1.21)	1.82 (1.69–1.97)	2.59 (2.40–2.81)
Stage 3a CKD	1.46 (1.30–1.64)	2.27 (1.90–2.71)	3.27 (2.84–3.77)

	Normoalbuminuria (uACR <3 mg/mmol)	Microalbuminuria (uACR 3–30 mg/mmol)	Macroalbuminuria (uACR >30 mg/mmol)
Stage 3b CKD	1.97 (1.76–2.20)	3.24 (2.74–3.84)	4.20 (3.71–4.75)
Stage 4 CKD	3.40 (3.03–3.81)	4.42 (3.615.42)	6.03 (5.26–6.91)
Stage 5 CKD	7.67 (6.18–9.51)	7.63 (5.68–10.25)	11.77 (9.66–14.36)

Footnotes: Data are median (IQR) hazard ratios for each CKD stage versus. Stage 1 (or no) CKD and normoalbuminuria
Abbreviations: CKD: chronic kidney disease; CV: cardiovascular; IQR: interquartile range; uACR: urine albumin-creatinine ratio.
Source: Darlington et al. 2021.[17]

CKD progression is also associated with reduced quality of life for patients and caregivers, particularly once dialysis is required

CKD has a considerable impact on the HRQoL of patients and caregivers, including physical, emotional and social wellbeing, and this impact increases as the disease progresses.[18] Analysis of data from the 2010 Health Survey for England indicate that patients with stage 4/5 CKD reported significantly reduced EuroQol- 5 Dimension (EQ-5D) scores for mobility, usual activity and pain/discomfort compared to those with normal kidney function and stage 1 CKD.[51] This is supported by a 2015 observational study conducted in England that reported EQ-5D utility scores decreased from 0.85 in patients with stage 1/2 CKD to 0.73 in patients with stage 5 CKD not on dialysis.[52]

The requirement for dialysis for patients with ESKD can be distressing and further reduces HRQoL, as patients may have to attend lengthy appointments three times a week and adhere to strict dietary and fluid restrictions.[53] [54] A population-based cross-sectional study conducted in Wales in 2005 reported EQ-5D utility scores of 0.44 (SD 0.32) and 0.53 (SD 0.34) for patients receiving haemodialysis and peritoneal dialysis, respectively.[55] One study reported that patients with ESKD experienced greater decreases in HRQoL compared with the general population than patients with other chronic diseases such as arthritis and cancer.[19]

CKD and the requirement for dialysis can also affect families and caregivers, who are often responsible for providing transport to appointments and administering treatment including home dialysis, which reduces their own HRQoL. For example, a 2019 SLR which identified 61 studies, of which two were in a UK population, found that QoL for caregivers of CKD patients receiving dialysis was poorer compared to the general population and was largely comparable to carers of patients with other chronic conditions, such as cancer and frailty in old age.[56]

Healthcare resource use and costs increase rapidly once CKD progresses beyond stage 3: hospitalisation costs may be ~12x higher in patients with pre-dialysis stage 5 CKD compared with stage 3[57]

CKD and related complications such as HF are associated with a high hospitalisation rate. A matched cohort study of 242,349 pairs of patients in the primary care setting in the UK found that patients with CKD (eGFR <60 ml/min/1.73 m^2 for ≥3 months) had an increased risk of hospitalisation due to conditions such as AKI (HR: 4.90; 95% CI: 4.47, 5.38), HF (HR 1.66; 95% CI: 1.59, 1.75) and myocardial infarction (HR: 1.40; 95% CI: 1.34, 1.46) compared with individuals without CKD.[58] The relative risk for cause-specific hospitalisations between matched patients with and without CKD are summarised in Table 5 below.[58]

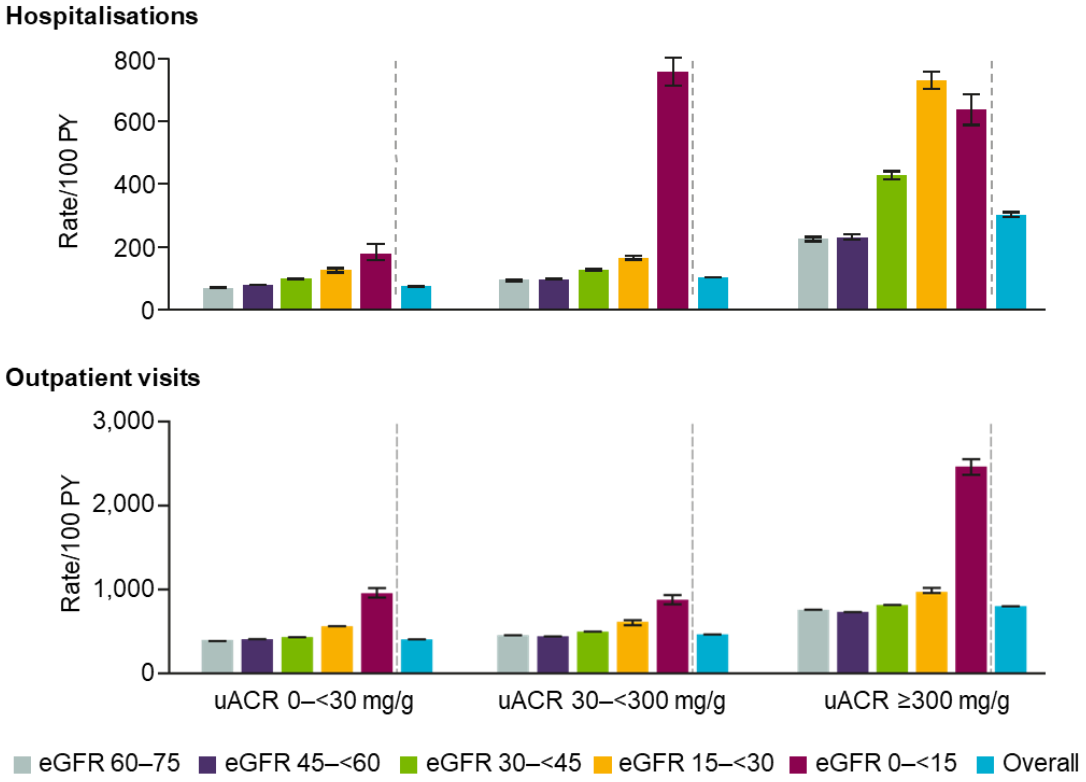
Table 5: Relative risk of hospitalisation cause between matched patients with and without CKD by fully adjusted hazard ratio

Cause of hospitalisation	Hazard ratio (95% CI)[a]
AKI	4.90 (4.47, 5.38)
Heart failure	1.66 (1.59, 1.75)
Venous thromboembolism	1.55 (1.46, 1.64)
Myocardial infarction	1.40 (1.34, 1.46)
Urinary tract infection	1.39 (1.35, 1.43)
Gastrointestinal bleeding	1.34 (1.28, 1.40)
Cerebral infarction	1.27 (1.22, 1.33)
Pneumonia	1.24 (1.20, 1.29)
Hip fracture	1.11 (1.07, 1.15)
Intracranial bleeding	1.10 (1.02, 1.19)

Footnotes: [a] Adjusted hazard ratio (patients with CKD versus those without) was estimated in a Cox regression models: stratified by matched set to account for the matching on age, sex, general practice, and calendar time, with adjustment for ethnicity, socioeconomic and smoking status, body mass index, and comorbidities such as diabetes mellitus, chronic obstructive pulmonary disease, osteoporosis, stroke. Please refer to the reference for full details.
Abbreviations: AKI: acute kidney injury; CI: confidence interval.
Source: Iwagami et al. 2018.[58]

In addition, a 2020 analysis of the UK cohort of the DISCOVER CKD study (an international real-world evidence study describing the characteristics of patients with CKD) found that, in the UK CPRD, rates of all-cause hospitalisation and outpatient visits increased with declining eGFR and were greater in patients with higher uACR (Figure 2).[59]

Figure 2: Rates of all-cause hospitalisation and outpatient visits, stratified by eGFR, from the UK CPRD cohort of DISCOVER CKD



Footnotes: Error bars signify 95% confidence intervals. Units for eGFR are ml/min/1.73 m^2. Vertical dashed lines are intended to visually separate the eGFR groups from the overall groups.
Abbreviations: eGFR: estimated glomerular filtration rate; HCRU: healthcare resource utilisation; LCED: Limited Claims and Electronic Health Record Database; PY: person years: uACR: urine albumin to creatine ratio; UK: United Kingdom.
Source: Sanchez et al. 2020.[59]

This high hospitalisation rate translates into a substantial economic burden, which is greatest in later stages of disease.[20] The median annual cost of hospitalisations for a patient with CKD was estimated to be £1,342.0 (IQR: 446.4–3,340.4) in a 2020 analysis of patients with CKD included in the UK CPRD (n=99,186), and one economic modelling study estimated that CKD stages 3–5 cost the NHS in England £1.44–1.45 billion in 2009–10.[21, 59] A 2015 cost study based on the SHARP cohort also reported increased costs in later stages of disease; the annual all-cause hospital cost per person-year of follow-up was £1,055 for patients with CKD stage 1–3b, £3,694 for patients with CKD stage 4 and £12,952 for patients with CKD stage 5 not on dialysis, representing an ~12x increase in hospitalisation costs between stage 3 and stage 5 CKD (pre-dialysis).[57]

ESKD is associated with the greatest economic burden

Although only a small proportion of patients with CKD reach ESKD overall, as the majority die before reaching this stage, ESKD is associated with a substantial proportion of the total CKD-related costs in the UK.[15] Dialysis is estimated to cost £32,360 per patient per year, and in the UK patients often require dialysis for between two and a half to three years while waiting for a kidney transplant.[60, 61] A substantial proportion of patients rely on dialysis rather than kidney transplant: the UK Renal Registry Annual Report reported that, in 2017, only 10.2% of the patient population receiving renal replacement therapy received a kidney transplant at day 90 of renal

replacement therapy start.[62] As a result, of the £1.45 billion spent on treatment of CKD stages 3–5 in England in 2009-10, >50% was spent on renal replacement therapy, which was required for just 2% of the CKD population.[21] This further emphasises the need to prevent or delay CKD progression to reduce the economic burden associated with later stage disease.

CKD and COVID-19 in 2020

The 2020 COVID-19 pandemic has increased the burden on dialysis units due to the difficultly in maintaining appropriate social distancing for in-centre dialysis patients and the need to isolate COVID-positive patients requiring dialysis. Strict lockdowns, personal protective equipment (PPE) supply chain interruptions and staffing issues have led to disruptions to dialysis services for patients with CKD.[63] Many patients have been offered fewer dialysis sessions per week, and dialysis treatment has been delayed where possible in new incident cases.[64, 65] Self-monitoring (including blood pressure monitoring) and home dialysis are currently recommended where possible, to avoid exposing patients and healthcare professionals to COVID risks unnecessarily.[64, 65]

Treating early stages of CKD to prevent or delay progression to ESKD may therefore be particularly important during the COVID-19 pandemic, to alleviate the burden on dialysis centres and prevent these potentially life-threatening interruptions to regular dialysis treatments.[63]

B.1.3.3 Current clinical pathway of care for CKD

The NICE guidelines for the assessment and management of CKD (CG182, published in 2014) are currently under review, with revised guidelines due to be published in July 2021. The draft 2021 NICE guideline (GID-NG10118) defines patients with CKD as all people with markers of kidney damage (uACR >3 mg/mmol) and/or those with a eGFR <60 ml/min/1.73 m^2 on at least two occasions separated by a period of at least 90 days (with or without markers of kidney damage).[16] CKD is almost always diagnosed in a primary care setting; reduced eGFR or albuminuria may be identified as an incidental finding, as part of a basic metabolic panel for example, or may be observed as a result of routine eGFR and uACR testing as is recommended for adults with key risk factors such as T2DM, CVD or HTN.[16, 66]

Investigations to establish the most likely cause of CKD are also conducted as this is helpful to evaluate prognosis. The risk of adverse disease outcomes and the need for renal replacement therapy can be assessed using a patient's eGFR and uACR categories to inform the most appropriate treatment strategy.

Management of CKD focuses on slowing disease progression and reducing CV risk

The primary goals of treatment for CKD are slowing disease progression, thus delaying ESKD, reducing CV risk and reducing the risk of premature death. Management of patients with CKD therefore encompasses a variety of treatment strategies to manage both the CKD itself and any underlying conditions and complications.[15, 36] Patients with CKD and comorbid T2DM, HTN or CVD are at particular risk of CV events and other complications.[17]

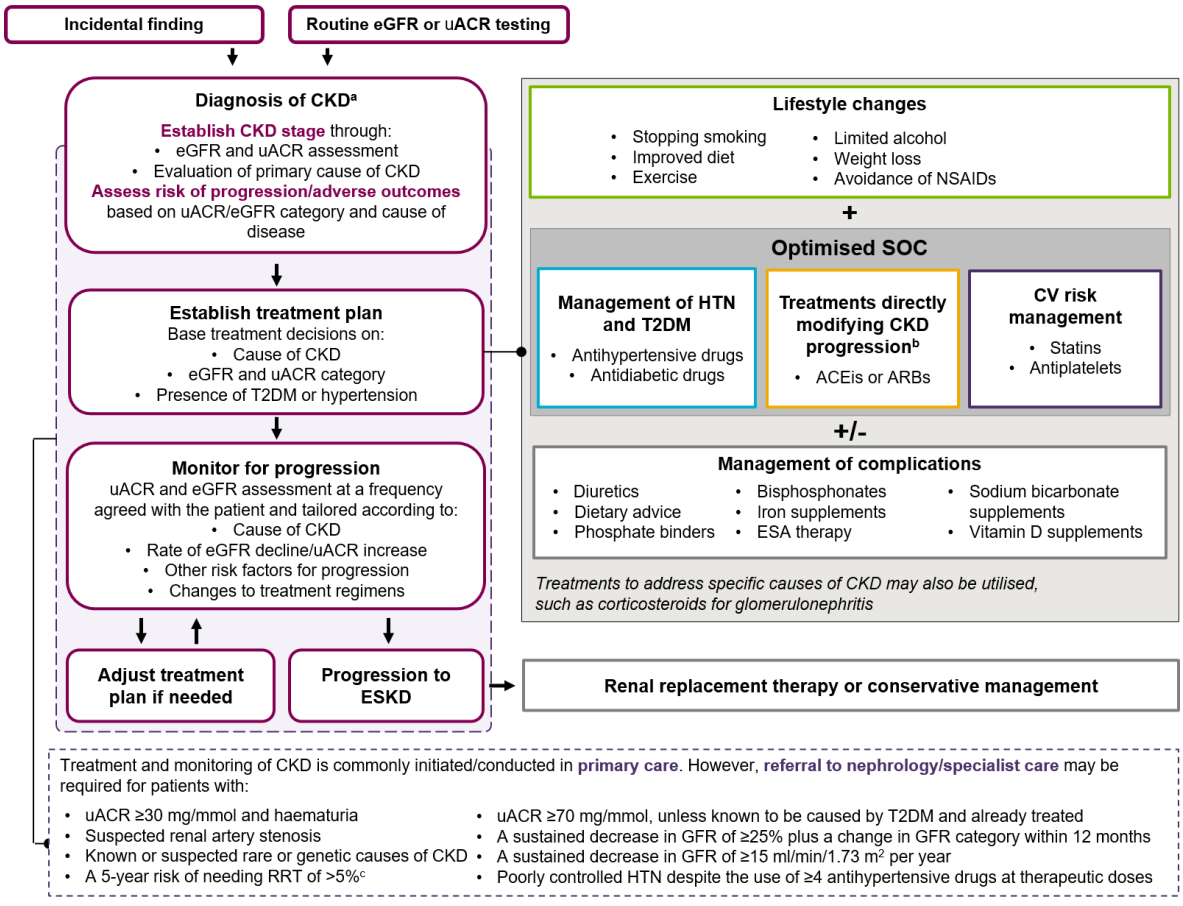
Patients with CKD also require regular monitoring to monitor progression of CKD and the development of complications such as anaemia: the recommended minimum number of annual

monitoring appointments per year increases with CKD stage. While the majority of patients with CKD up to stage 3b can continue to be monitored and managed in primary care, GPs may request advice from a nephrologist or refer patients for specialist assessment for reasons including: a 5-year risk of needing renal replacement therapy of >5%, patient is at high risk of rapid progression to ESKD, eGFR is rapidly deteriorating or if a patient without comorbid T2DM has a uACR ≥70 mg/mmol. A full list of referral criteria is provided in Figure 3.[16, 67, 68]

After specialist assessment, patients may be managed in either the primary care or nephrology setting as appropriate for the individual, with routine follow up usually taking place at a GP surgery rather than in a specialist clinic depending on the severity of the disease.[16, 67] Analyses of data derived from the UK QoF and CPRD and published sources indicate that ~[redacted]% of patients with stage 3–5 CKD are managed in primary care.[68] General CKD management at a GP surgery is encouraged wherever appropriate for increased patient convenience and to enable specialists to focus on managing more complex patients at advanced disease stages, thereby reducing the likelihood that nephrology clinics will be overwhelmed.[16, 67] There is also the possibility for primary care providers to request initial advice and guidance on CKD management from a specialist prior to referral. In some cases, appointments with a nephrologist can be conducted virtually for advice and guidance, however the availability of virtual consultations varies by region.[67]

An overview of the treatment pathway for CKD in the UK is provided in Figure 3, with further details on pharmacotherapy provided in the following section.

Figure 3: Summary of the current guideline-recommended treatment pathway for CKD in the UK



Footnotes: [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/1.73 m2 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.
Abbreviations: ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker; CKD: chronic kidney disease; CV: cardiovascular; eGFR: estimated glomerular filtration rate; ESA: erythropoietic stimulating agent; ESKD: end-stage kidney disease; HTN: hypertension; NSAIDS: non-steroidal anti-inflammatory drugs; RRT: renal replacement therapy; SOC: standard of care; T2DM: type 2 diabetes mellitus; uACR: urine albumin to creatine ratio.
Source: NICE draft guidelines for CKD, 2021.[16]

Current SOC for CKD consists of a combination of therapies tailored to specific patient characteristics

Current SOC for the management of CKD in England comprises individually optimised therapy which may include a variety of treatment strategies. These include CV risk management using statins and antiplatelets, management of underlying T2DM and/or HTN, ACE inhibitors or ARBs for the management of disease progression and management of additional complications such as anaemia or mineral and bone disorders as necessary.[13, 16, 69, 70]

Antiplatelets are recommended for the secondary prevention of CV disease in patients with existing CV disease, but are avoided in patients with advanced stages of CKD. Statins are recommended for the primary prevention of CV disease in patients who have 10% or greater risk of developing CV disease within the next 10 years or for secondary prevention in patients with established CV disease.[16] CPRD data from 2019/20 indicate that [redacted]% of patients with CKD may receive statins in UK clinical practice, and [redacted]% may receive antiplatelet or anticoagulant therapies.[34]

Despite the investigation of many new treatments for CKD over the past two decades, ACE inhibitors and ARBs remained the only treatments to demonstrate efficacy in slowing the progression of CKD to ESKD in clinical trials for several decades, until the development of SGLT2 inhibitors.[23] In the UK, ACE inhibitors and ARBs are recommended only for patients in higher uACR categories (Table 6): patients with a uACR of >70 mg/mmol regardless of underlying comorbidities; patients with comorbid HTN and uACR>30 mg/mmol; or patients with comorbid T2DM and uACR >3 mg/mmol.[16] There is currently a lack of treatments to modify disease progression in patients with lower uACR categories; no specific pharmacotherapy recommendations are made to minimise disease progression in these patients.[14] Moreover, some patients are unable to tolerate ACE inhibitor or ARB therapy due to low blood pressure, age, hyperkalaemia or angioedema, and therefore cannot benefit from these treatments.[67]

The 2021 draft NICE guidelines for the treatment of CKD also recommend SGLT2 inhibitors for patients with a uACR of >30 mg/mmol and T2DM, if they meet the criteria in the respective marketing authorisation.[16] However, uptake of the only SGLT2 inhibitor to include renal outcomes trial data within its label in the UK (canagliflozin) has so far been limited in clinical practice [67, 71] Due to low usage in clinical practice, canagliflozin is not considered part of SOC for patients with CKD and comorbid T2DM. Therefore, canagliflozin is not a relevant comparator for dapagliflozin in this submission, in line with the final scope.

Table 6: NICE guidelines for pharmacotherapy in adults with CKD

	uACR			
	Normal/mild (<3 mg/mmol)	Moderate (3–30 mg/mmol)	Severe	
			(>30 mg/mol)	(≥70 mg/mol)
BP target	≤140/ 90 mmHg			≤130/ 80 mmHg
Patients with HTN	Follow the NICE recommendations for treating HTN in adults:[69] *Offer lifestyle advice and:* • *An ACE inhibitor/ARB to adults who are under 55 or have T2DM* • *A CCB to adults who are over 55, without T2DM or are of African or African-Caribbean family origin*)		Offer ACE inhibitor or ARB	
Patients with T2DM	No specific disease-modifying treatment recommended	Offer ACE inhibitor or ARB[a]		
Patients without T2DM and without HTN	No specific disease-modifying treatment recommended			ACE inhibitor or ARB

Footnotes: The majority of ACE inhibitors and ARBs are licenced for use in patients with T2DM and macroalbuminuria, and as such use in patients with CKD without comorbid T2DM or in patients with lower levels of albuminuria is off-label.[24-26] [a]The 2021 draft NICE guidelines for the treatment of CKD recommend SGLT2 inhibitors only in patients with comorbid T2DM and a uACR of ≥30 mg/mmol, if they meet the criteria in the respective marketing authorisation. Patients treated with SGLT inhibitors should be monitored for volume depletion and eGFR decline.
Abbreviations: ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker; BP: blood pressure; CCB: calcium channel blocker; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; HTN: hypertension; NICE: National Institute of Health and Care Excellence; SGLT2: sodium glucose co-transporter 2; T2DM: type 2 diabetes mellitus.
Source: NICE draft guidelines for CKD, 2021;[16] NICE NG136.[69]

A variety of specific ACE inhibitors or ARBs may be prescribed in UK clinical practice as the efficacy of these drugs is considered to be interchangeable between classes, and between agents within each class.[67] CPRD data from 2019/20 estimate that a higher proportion of patients with CKD receive ACE inhibitors than ARBs in clinical practice ([redacted]% versus [redacted]%, respectively).[34] The majority of ACE inhibitors and ARBs are licenced for use in patients with T2DM and macroalbuminuria, and as such use in patients with CKD without comorbid T2DM or in patients with lower levels of albuminuria is off-label.[24-26]

Overall, current SOC for patients with CKD in the UK comprises individually optimised therapy for CV risk management, management of underlying T2DM or HTN, and ACE inhibitors or ARBs for management of disease progression in some patients.

B.1.3.4 Limitations associated with current SOC for CKD and expected positioning of dapagliflozin within the treatment pathway

There is a considerable residual risk of disease progression and mortality despite treatment with ACE inhibitor or ARB therapy alone

Current SOC for patients with CKD includes ACE inhibitors and ARBs for patients in higher uACR categories, but a substantial residual risk of CKD progression remains despite treatment with these therapies. This is demonstrated by the proportion of patients progressing to ESKD despite treatment with SOC (the majority of patients received an ACE inhibitor or an ARB) in the placebo arms of two large RCTs which enrolled patients with CKD, DAPA-CKD and CREDENCE, in which 161/2,152 (7.5%) and 165/2,199 (7.5%) of patients progressed to ESKD over a median follow up of 2.4 years and 2.62 years respectively.[72, 73]

Furthermore, meta-analyses of the effect of ACE inhibitors and ARBs alone on all-cause mortality have also demonstrated mixed results. Some studies have suggested that ACE inhibitors are able to reduce all-cause mortality compared with active controls (other anti-hypertensive drugs; OR 0.72; 95% credible interval 0.53, 0.92), whereas ARBs are not (OR 0.81; 95% credible interval 0.61, 1.03), while others have found that neither ACE inhibitors nor ARBs alone reduced the risk of all-cause mortality compared with placebo (ACE inhibitors OR 1.03, 95% CI 0.88, 1.21; ARBs OR 0.99, 95% CI 0.82, 1.20).[27, 74] Overall, 40–45,000 premature deaths occur in the UK every year due to CKD.[47] The 2015/16 National Chronic Kidney Disease Audit reported that for every 100 patients with stage 3 CKD there were 7 deaths per year, and for every 100 patients with stage 4 CKD there were 19 deaths per year.[45]

There is therefore a critical unmet need for patients receiving optimised SOC alone in the UK to receive additional treatment options to address the residual risk of disease progression and mortality.

There is limited clinical trial evidence on the efficacy of ACE inhibitors and ARBs in patients without comorbid T2DM, and these therapies are associated with challenges in attaining optimal dosing

The majority of ACE inhibitor and ARB therapy trials were conducted in patients with T2DM and macroalbuminuria only, with the few trials that included patients without T2DM recruiting very small numbers.[75-81] As such, there is a paucity of trial evidence for the effectiveness of ACE inhibitor and ARB therapy alone in non-diabetic patients with CKD and in microalbuminuric patients, and only one ACE inhibitor is licensed for the treatment of patients with CKD without comorbid T2DM in Europe (ramipril).[1] As such, use of other ACE inhibitors and ARBs in patients with CKD without comorbid T2DM or in patients with lower levels of albuminuria is off-label.[24-26]

Moreover, the beneficial treatment effect of ACE inhibitors and ARBs has been primarily demonstrated in clinical studies of patients receiving high doses of study therapy.[28, 29, 77, 79] However, ACE inhibitors and ARBs are associated with adverse events such as hyperkalaemia and hypotension which may necessitate discontinuation or reduced doses of ACE inhibitor/ARB therapy, preventing upward dose titration towards the doses used in clinical trials.[82] As a result, patients with CKD in UK clinical practice often receive lower doses of ACE inhibitors and ARBs than those used in clinical trials, and are therefore unable to gain the full treatment benefit of these therapies.

SGLT2 inhibitors are currently recommended only for patients with comorbid T2DM in the 2021 draft NICE guidelines for the treatment of CKD, and uptake has been limited in UK clinical practice

Reimbursement of dapagliflozin for the treatment of adults with CKD would allow patients with CKD without comorbid T2DM or HFrEF, and patients with comorbid T2DM and an eGFR of

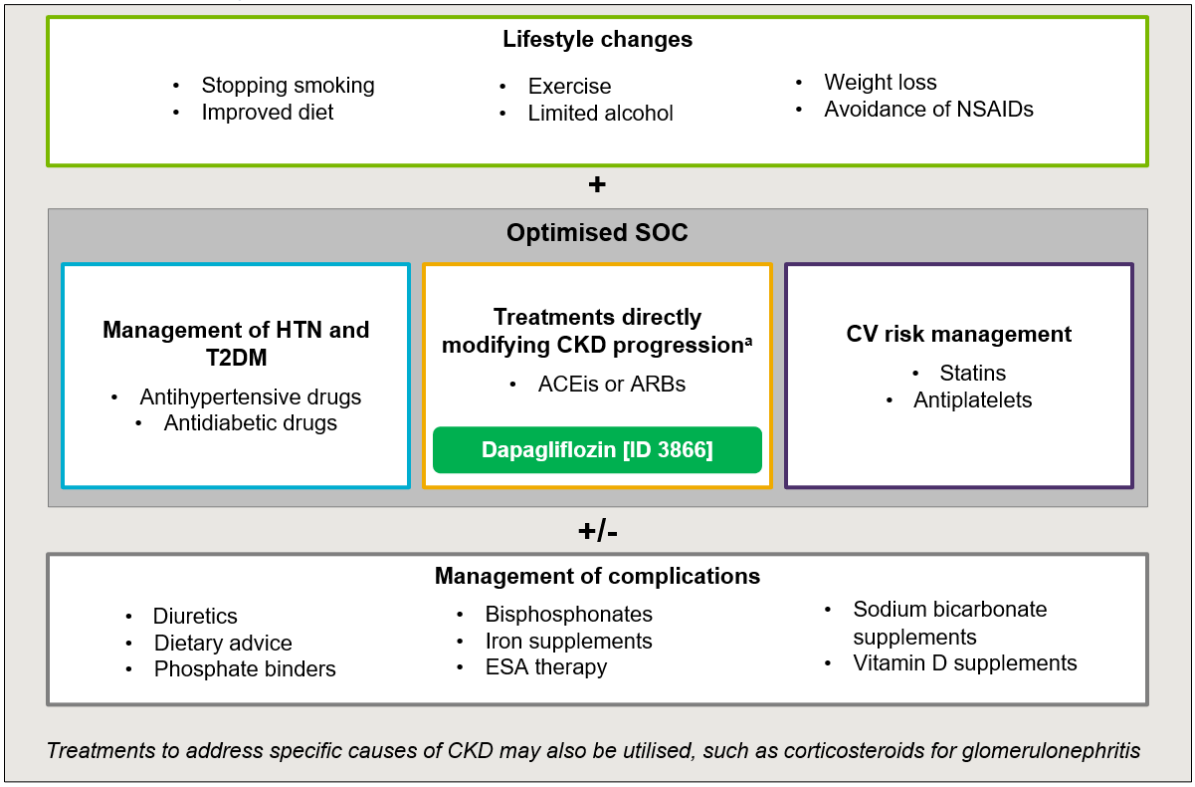
eGFR <45 ml/min/1.73m^2, to benefit from the renal and CV-protective effects of SGLT2 inhibition. The treatment landscape for CKD has evolved rapidly over the past few years, with the introduction of SGLT2 inhibitors representing the first major clinical development in this therapeutic area for several decades. The renal and CV-protective effects of SGLT2 inhibitors have been demonstrated in both Cardiovascular Outcomes Trials (CVOTs) and dedicated renal outcomes trials, and this has been recognised in global guidelines; the recently published KDIGO guideline on T2DM management in CKD recommends SGLT2 inhibitors in combination with metformin for all eligible patients with CKD and comorbid T2DM irrespective of baseline albuminuria levels.[41, 72, 73, 83-85]

Prior to DAPA-CKD, the only completed SGLT2 inhibitor renal outcomes trial was CREDENCE, which included only patients with CKD and T2DM.[72] Consequently, until dapagliflozin is granted marketing authorisation for the treatment of CKD in [redacted], the only SGLT2 inhibitor to include renal outcomes trial data within its label in the UK (canagliflozin) is limited to the treatment of patients with comorbid T2DM.[72, 86] As such, the 2021 draft NICE guidelines for the treatment of CKD recommend the use of SGLT2 inhibitors only in patients with T2DM and a uACR of ≥30 mg/mmol who meet the criteria in the respective marketing authorisation.[16] Patients with CKD without comorbid T2DM are not currently included in the 2021 draft guideline as a population eligible to benefit from the renal and CV-protective effects of SGLT2 inhibition, and uptake of canagliflozin has been low in clinical practice for patients with CKD and comorbid T2DM.[16, 67, 71] Finally, CREDENCE did not demonstrate a significant reduction in all-cause mortality with canagliflozin, and therefore there remains a high unmet need for new treatments for CKD, particularly in patients without comorbid T2DM.[72]

Dapagliflozin will address a high unmet need as the first licensed therapy for the treatment of CKD with or without comorbid T2DM

Dapagliflozin is expected to be used in line with its anticipated marketing authorisation, for [redacted] in patients with or without comorbid T2DM (as shown in Figure 4). Based on UK clinical expert input from GPs and nephrologists, dapagliflozin is expected to be used in addition to optimised SOC, which may include ACE inhibitors and ARBs, in the primary or secondary care setting upon diagnosis of CKD to prevent disease progression.[67] The substantial margin of benefit observed in the DAPA-CKD study versus placebo (as detailed in Section B.2.6) provides justification for the use of dapagliflozin in patients with CKD, regardless of T2DM status.

Figure 4: Suggested positioning of dapagliflozin within the guideline-recommended treatment pathway for CKD in the UK



Footnotes: [a]The 2021 draft NICE guidelines for the treatment of CKD currently recommend SGLT2 inhibitors in patients withT2DM only, in patients who meet the criteria in the relevant marketing authorisation.
Abbreviations: ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker; CKD: chronic kidney disease; ESA: erythropoiesis stimulating agents; HTN: hypertension; NSAIDS: non-steroidal anti-inflammatory drugs; T2DM: type 2 diabetes mellitus.
Source: Draft NICE Guideline for Chronic Kidney Disease 2021.[16]

A positive recommendation for dapagliflozin in this setting would allow patients with CKD to benefit from improved outcomes compared with optimised SOC alone. This would also provide the first novel therapeutic option to date to demonstrate a treatment benefit on all-cause mortality in patients with CKD with and without comorbid T2DM. Preventing or delaying progression to ESKD aligns with the prevention focussed NHS Long Term Plan, and represents a major opportunity to reduce the economic burden of kidney disease.[87]

Dapagliflozin is frequently initiated in primary care for the treatment of patients with T2DM and HF, which often co-occur with CKD

As described above, many patients with CKD are also affected by comorbid conditions such as T2DM, HTN and CVD (such as HF). CPRD data from 2019/20 reports that [redacted]% of patients with CKD had comorbid T2DM, and [redacted]% had comorbid HF.[34] Dapagliflozin is currently licensed in patients with T2DM and an eGFR ≥45 ml/min/1.73 m^2, in patients with T1DM, and in patients with heart failure with reduced ejection fraction (HFrEF) with and without comorbid T2DM.[1] A proportion of patients with CKD in the UK may therefore already be receiving SGLT2 inhibitor therapy for the management of their comorbid HFrEF or T2DM, and dapagliflozin is regularly initiated in the primary care setting in the UK for the treatment of T2DM.

There is a therefore a wealth of experience with the prescription of dapagliflozin in primary care from its use for over 7 years as an antidiabetic medication, primarily in primary care. CKD is also a common comorbid condition of T2DM, and clinicians may already have experience in using

dapagliflozin in patients with CKD who also have T2DM. In line with the draft NICE guidelines, GPs are therefore the most appropriate HCPs to initiate treatment with dapagliflozin in the majority of cases, especially given that most monitoring and CKD maintenance care in the UK is offered by local GP practices ([redacted]% of patients with stage 3–5 CKD are treated in primary care).[16, 68] This is supported by feedback from UK GPs and nephrologists which suggests dapagliflozin treatment should be initiated shortly after CKD diagnosis to enable patients to receive treatment benefits as soon as possible to reduce disease progression.[67] Expert clinical opinion also indicates that dapagliflozin is simpler to prescribe than ACE inhibitors and ARBs as it does not require dose titration and has a well-characterised tolerability profile.[88]

The introduction of SGLT2 inhibitors into the CKD disease space presents an opportunity for collaborative treatment of these complex interrelated conditions, offering integrated care and ensuring simplicity of management between specialisms. SGLT2 inhibitors, and dapagliflozin in particular, represent a substantial step-change in the treatment of CKD for patients who have not benefited from any advancements in pharmacotherapy for more than 20 years. This is especially significant for CKD patients without T2DM as there are currently minimal treatment options available for this patient population and the treatment options that are available are only recommended once the disease has progressed to high uACR levels.

B.1.4 *Equality considerations*

Dapagliflozin is currently available across primary and secondary care treatment settings for patients with T2DM, T1DM and HFrEF. A positive recommendation for dapagliflozin in CKD is expected to extend the benefits of dapagliflozin to all eligible patients with CKD, including patients with CKD who do not have comorbid T2DM or HFrEF. A NICE recommendation that permits the initiation of dapagliflozin for the treatment of CKD in the primary care setting is needed to deliver equitable access to treatment, given access to specialist CKD care varies considerably by geography

B.2 Clinical effectiveness

Summary of clinical effectiveness

- A clinical systematic literature review (SLR) was conducted to identify relevant clinical evidence for dapagliflozin and the relevant comparators in adults with CKD. Four trials investigating dapagliflozin were identified, which included the pivotal DAPA-CKD trial and three smaller trials which provide only supporting data to this appraisal (as they were conducted in small populations of patients with T2DM and comorbid CKD only, and evaluated only surrogate markers of kidney disease)[73, 89-91]
- DAPA-CKD was a double-blind, placebo-controlled phase III RCT, with a median follow up of 2.4 years, that compared dapagliflozin (n=2,152) to placebo (n=2,152) alongside SOC in both arms, for the treatment of CKD in patients with and without comorbid T2DM[73]
- Dapagliflozin significantly reduced the risk of the primary composite endpoint of sustained decline in eGFR ≥50%, ESKD or death from renal or CV causes compared with placebo (9.2% versus 14.5%, respectively, HR 0.61;95% CI: 0.51, 0.72; p<0.001)[73]
    - Exploratory analyses showed that the event rates for each component of the primary endpoint favoured dapagliflozin, including ESKD and chronic dialysis[73]
- Secondary efficacy endpoints were supportive of the treatment benefit observed in the primary endpoint: dapagliflozin was superior to placebo for all secondary endpoints, including all-cause mortality (HR 0.69 [95% CI: 0.53, 0.88; p=0.004]), a renal composite of ≥50% sustained decline in eGFR, ESKD, or renal death (HR 0.56; 95% CI: 0.45, 0.68; p=<0.001) and a composite endpoint of hospitalisation for HF or CV death(HR 0.71; 95% CI: 0.55, 0.92; p=0.0089)[73]
- The KM curves for the composite primary outcome and the secondary outcomes separated early and continued to separate throughout the study, indicating an early and sustained treatment benefit for dapagliflozin[73]
- The effect of dapagliflozin was consistent across analysed subgroups, including patients with or without comorbid T2DM, with or without prior CVD and in patients with no T2DM and no CVD at baseline, as well as across the range of included eGFR and uACR categories[73]
- Dapagliflozin was generally well tolerated in patients with CKD, consistent with the known safety profile. SAEs occurred less frequently in the dapagliflozin treatment group compared with the placebo group (29.5% versus 33.9%, respectively), and AEs of special interest were balanced across treatment groups:
    - There were fewer occurrences of definite or probable diabetic ketoacidosis (0% versus <0.1%), major hypoglycaemic events (0.7% versus 1.3%), amputations (1.6% versus 1.8%) and renal adverse events (7.2% versus 8.7%) in patients who received dapagliflozin compared with placebo.[73] An increased number of patients experienced volume depletion (5.9% versus 4.2%) and fractures (4.0% versus 3.2%) in the dapagliflozin group compared with the placebo group[73]

B.2.1 *Identification and selection of relevant studies*

A systematic literature review (SLR) was conducted in March 2020 and subsequently updated in November 2020 to identify published RCT evidence of pharmacological treatments for CKD. Full details of the SLR search strategy, study selection process and results are presented in Appendix D.

MEDLINE, Embase and the Cochrane library databases were searched, in addition to hand searching of congresses and clinical trial registries. Records were eligible for inclusion if they reported phase III or IV RCTs of adult (≥ 18 years old) patients with any stage of CKD receiving any pharmacological agent for the treatment of CKD for at least 12 weeks, and where at least 50 patients were randomised per arm. Due to limitations in reporting, studies were included unless explicitly stated as a phase I or II trial. Studies without a baseline measurement of albuminuria or in which patients with macroalbuminuria were explicitly excluded from the study were not eligible for inclusion in the SLR.

Overall, 20,529 unique records were identified in the SLR searches, of which 20,263 were excluded following abstract review and a further 167 records were excluded following full text review. A total of 100 publications reporting on 89 clinical trials were therefore ultimately included in the SLR.

The primary trials of interest for this appraisal were those of dapagliflozin in combination with SOC, as specified in the decision problem. As such, in preparing for this appraisal, the included studies were filtered to exclude trials of other therapies (such as ACE inhibitors and ARBs). These therapies are either used as background therapies (ACE inhibitors and ARBs) that would be used in addition to dapagliflozin or are not SOC in England, and therefore do not represent relevant comparators to dapagliflozin in this appraisal. As such, they are not included in the NICE final scope for this appraisal.

The SLR included four relevant trials of dapagliflozin (DAPA-CKD,[73] DERIVE,[89] DELIGHT,[90] and Kohan 2014[91]). Of these, only one was a directly relevant RCT for the current appraisal of dapagliflozin in the treatment of adults with CKD: the pivotal DAPA-CKD trial.[73] The DERIVE, DELIGHT and Kohan 2014 studies provide further supporting evidence of the efficacy of dapagliflozin in patients with CKD, and a summary of these studies can be found in Appendix L. It should also be noted that the DECLARE-TIMI 58 and DAPA-HF trials provide evidence for the efficacy of dapagliflozin in patients with a wide range of eGFR and uACR categories, including a proportion of patients with comorbid CKD, either with or at risk of atherosclerotic CVD (DECLARE-TIMI 58) or with HF (DAPA-HF), as described in Section B.2.13.2.[84, 92] These studies either did not include a requirement for a baseline measurement of albuminuria and/or did not specify CKD as an enrolment criteria, and as such were not included in the SLR, but included a proportion of patients with CKD relevant to the decision problem and provide important data that is relevant to this appraisal.

Finally, as described in later in the submission, a comparison versus canagliflozin has been conducted as a scenario analysis. As such, trials of canagliflozin that were included in the SLR were also considered of interest in order to inform an indirect treatment comparison. Full details of the indirect treatment comparison are presented in more detail in Appendix D and later in Section B.2.9.

B.2.2 *List of relevant clinical effectiveness evidence*

As highlighted above in Section B.2.1, the SLR included four trials investigating the efficacy of dapagliflozin in CKD. The pivotal trial for dapagliflozin in this indication is DAPA-CKD, a double-blind, placebo-controlled phase III RCT that compared dapagliflozin (n=2,152) to placebo (n=2,152) alongside SOC in both arms, for the treatment of CKD in patients with and without comorbid T2DM. DAPA-CKD is described in full in the following sections.[73]

The three other trials (DERIVE, DELIGHT and Kohan 2014) also evaluated the efficacy of dapagliflozin. However, these trials were conducted in small populations, exclusively in patients with T2DM and comorbid CKD. In addition, these trials evaluated only surrogate markers of kidney disease (eGFR or uACR levels) rather than kidney disease outcomes such as ESKD, dialysis and kidney transplant, and both DERIVE and Kohan 2014 were designed primarily to assess the effect of dapagliflozin on glycaemic control rather than outcomes of relevance to this appraisal. They therefore provide only supporting data to this appraisal.[89-91] A brief summary of these trials is provided in Table 7 and further detail is provided in Appendix L.

Table 7: Clinical effectiveness evidence

Study	DAPA-CKD (NCT03036150)[73]	DERIVE (NCT02413398)[89]	DELIGHT (NCT02547935)[90]	Kohan 2014 (NCT00663260)[91]
Study design	Phase III, randomised, double-blind, placebo-controlled multicentre study	Phase III, randomised, double-blind, placebo-controlled multicentre study	Phase II/III, randomised, double-blind, placebo-controlled multicentre study	Phase II/III, randomised, double-blind, placebo-controlled multicentre study
Population	• Adults (≥18 years) with CKD • With or without comorbid T2DM • eGFR ≥25 and ≤75 ml/min/1.73 m^2 • uACR ≥200 mg/g to ≤5,000 mg/g (≥22.6 to ≤565 mg/mmol) • Stable dose of ACE inhibitor or ARB for ≥4 weeks before screening (patients who were documented to be unable to take ACE inhibitors or ARBs were	• Adults (18–75 years) with T2DM for >12 months, inadequate glycaemic control and CKD Stage 3a • eGFR ≥45 and ≤59 ml/min/1.73 m^2 • Stable glucose-lowering treatment regimen	• Adults (≥18 years) with T2DM for >12 months • eGFR ≥25 and ≤75 ml/min/1.73 m^2 • uACR ≥30 to ≤3,500 mg/g (≥3.4 to ≤395.5 mg/mmol) • Stable glucose-lowering and anti-hypertensive treatments for ≥12 weeks before randomisation	• Adults (≥18 years) with T2DM and inadequate glycaemic control (HbA1c ≥7.0 and ≤11.0%) • eGFR ≥30 and ≤59 ml/min/1.73m^2 • Stable antidiabetic regimen

	allowed to participate)			
Intervention(s)	Dapagliflozin 10 mg, once daily	Dapagliflozin 10 mg, once daily	Dapagliflozin 10 mg, once daily, or dapagliflozin 10 mg plus saxagliptin 2.5 mg, once daily	Dapagliflozin 5 mg once daily, or dapagliflozin 10 mg once daily
Comparator(s)	Matching placebo, once daily	Matching placebo, once daily	Matching placebo, once daily	Matching placebo, once daily
Indicate if trial supports application for marketing authorisation	Yes	No	No	No
Indicate if trial used in the economic model	Yes	No	No	No
Rationale for use/non-use in the model	DAPA-CKD represents the primary source of efficacy and safety data for dapagliflozin in this indication. Data reported from DAPA-CKD are relevant to the decision problem and have been used in the model	DERIVE was conducted in a small population, exclusively in patients with CKD and comorbid T2DM, and evaluated only surrogate markers of kidney disease. As such, DERIVE does not represent the primary source of efficacy and safety data in this indication, as outlined above	DELIGHT was conducted in a small population, exclusively in patients with CKD and comorbid T2DM, and evaluated only surrogate markers of kidney disease. As such, DELIGHT does not represent the primary source of efficacy and safety data in this indication, as outlined above	Kohan 2014 was conducted in a small population, exclusively in patients with CKD and comorbid T2DM, and evaluated only surrogate markers of kidney disease. As such, Kohan 2014 does not represent the primary source of efficacy and safety data in this indication, as outlined above
Reported outcomes specified in the decision problem **Outcomes incorporated in the model are marked in bold**	• Morbidity including CV outcomes (**hospitalisation for HF**) • **Disease progression (such as renal replacement, ESKD)**	• Change from baseline in uACR • Change from baseline in eGFR	• Change from baseline in uACR • Change from baseline in eGFR	• Change from baseline in eGFR and creatinine clearance • Change in uACR category

	and markers of disease progression (such as eGFR, albuminuria) • **All-cause mortality**, CV mortality, renal mortality • **Adverse effects of treatment** • **HRQoL**			
Other outcomes reported in this submission	• **Doubling of serum creatinine** (AKI)	N/A	N/A	N/A

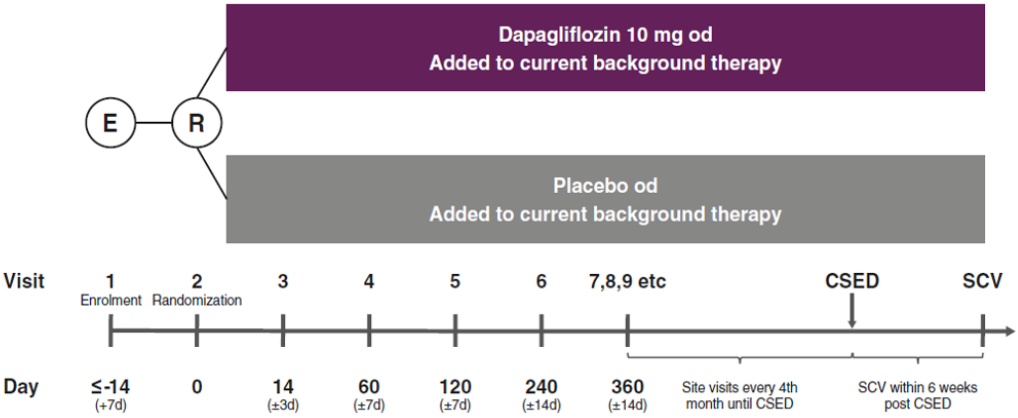
Abbreviations: ACE: angiotensin-converting enzyme; AKI: acute kidney injury; ARB: angiotensin receptor blocker; CKD: chronic kidney disease; CV: cardiovascular; eGFR: estimated glomerular filtration rate; ESKD: end-stage kidney disease; HbA1c: glycated haemoglobin; HF: heart failure; HRQoL: health related quality of life; N/A: not applicable; T2DM; type 2 diabetes mellitus; uACR: urine albumin-to-creatinine ratio.
Sources: Heerspink et al. 2020b,[73] Pollock et al. 2019,[90] Fioretto et al. 2018,[89] and Kohan et al. 2014.[91]

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

B.2.3.1 Trial design

DAPA-CKD was a large, multicentre, double-blind, placebo-controlled phase III RCT which examined the effect of dapagliflozin, in addition to SOC, on renal and CV outcomes in a broad range of patients with CKD, including those with and without comorbid T2DM. An overview of the DAPA-CKD study design is shown in Figure 5.

Figure 5: DAPA-CKD study design



Abbreviations: CSED: common study end date (date when the predetermined number of adjudicated primary events are anticipated; E: enrolment; od: once daily; R: randomisation; SCV: study closure visit.
Source: Heerspink et al. 2020a.[93]

Patients were randomised using an Interactive Voice/Web Response System, with the use of balanced blocks to ensure an approximate 1:1 ratio between either dapagliflozin (10 mg once daily) or matching placebo.[73] Randomisation was stratified to ensure balance in the proportion of patients with and without comorbid T2DM and patient baseline uACR (≤1,000 or >1,000 mg/g [113 mg/mmol]) between treatment groups. Recruitment was monitored to ensure a minimum of 30% of patients were recruited to either the diabetic or non-diabetic subpopulation and the number of patients with an eGFR between 60–75 ml/min/1.73m^2 at randomisation was capped so that no more than 10% of patients started the trial with an eGFR range corresponding to stage 2 CKD. All patients and investigators were blinded to treatment allocation.[93]

Study visits were scheduled for 2 weeks, 2 months, 4 months and 8 months after randomisation and at 4-month intervals thereafter. Information about potential trial outcomes, adverse events (AEs), concomitant therapies and study drug adherence were obtained at each follow up visit, in addition to recording of vital signs and collection of blood and urine. Within six weeks of the study ending, a final study closeout visit was planned for when the primary outcome event was experienced by 681 patients.[93]

B.2.3.2 Eligibility criteria

Key inclusion and exclusion criteria for DAPA-CKD are listed in Table 8. Eligible participants were adults with or without comorbid T2DM who had an eGFR of ≥25 to ≤75 ml/min/1.73 m^2 and a uACR of ≥200 mg/g (≥22.6 mg/mmol) to ≤5,000 mg/g (≤565 mg/mmol).[73, 93, 94]

Table 8: Inclusion and exclusion criteria of the DAPA-CKD study

Inclusion criteria	Exclusion criteria
• ≥18 years of age at the time of consent • eGFR ≥25 to ≤75 ml/min/1.73 m^2 at screening • uACR ≥200 mg/g (≥22.6 mg/mmol) to ≤5,000 mg/g (≤565 mg/mmol) at screening • Stable and, for the patient, maximum tolerated labelled dose of an ACE inhibitor or ARB for at least four weeks before screening, if not medically contraindicated	• T1DM • Autosomal dominant or autosomal recessive polycystic kidney disease, lupus nephritis or ANCA-associated vasculitis • Receiving cytotoxic therapy, immunosuppressive therapy or other immunotherapy for primary or secondary renal disease within six months prior to enrolment • New York Heart Association Class IV congestive HF at time of enrolment • Myocardial infarction, unstable angina, stroke or transient ischaemic attack within 12 weeks prior to enrolment • History of organ transplantation • Receiving therapy with an SGLT2 inhibitor within eight weeks prior to enrolment or previous intolerance of an SGLT2 inhibitor • Coronary revascularisation (percutaneous coronary intervention or coronary artery bypass grafting) or valvular repair/replacement within 12 weeks prior to enrolment or is planned to undergo any of these procedures after randomisation • Any condition outside the renal and cardiovascular study area with a life expectancy of <2 years based on investigator's clinical judgement • Active malignancy requiring treatment at the time of Visit 1 (with the exception of successfully treated basal cell or treated squamous cell carcinoma) • Known blood-borne diseases • Hepatic impairment (aspartate transaminase or alanine transaminase >3 times the ULN or total bilirubin >2 times the ULN at the time of enrolment)

Abbreviations: ACE: angiotensin-converting enzyme; ANCA: anti-neutrophil cytoplasmic antibody; ARB: angiotensin receptor blocker; eGFR: estimated glomerular filtration rate; HF: heart failure; SGLT2: sodium glucose co-transporter 2; T1DM: type 1 diabetes mellitus; uACR: urine albumin-to-creatinine ratio; ULN: upper limit of normal.
Sources: Heerspink et al. 2020b (Supplemental Methods).[73]

B.2.3.3 Settings and locations where the data were collected

DAPA-CKD was a multicentre study conducted in 386 study centres in 21 countries (Argentina, Brazil, Canada, China, Denmark, Germany, Hungary, India, Japan, Korea, Mexico, Peru,

Philippines, Poland, Russia, Spain, Sweden, Ukraine, United Kingdom, United States and Vietnam).[73]

B.2.3.4 Trial drugs and concomitant medications

Trial drugs

Both dapagliflozin 10 mg and placebo were provided as film-coated tablets and were taken orally once daily by the respective study populations at approximately the same time every day.[94]

CKD medications

To be eligible for DAPA-CKD, patients needed to be on stable and, for the patient, maximum tolerated labelled daily dose of an ACE inhibitor or ARB for at least 4 weeks before Visit 1, if not medically contraindicated. Permitted CKD-related treatments included renin-angiotensin-aldosterone system inhibitors (RAAS inhibitors: ACE inhibitors, ARBs, renin inhibitors, mineralocorticoid antagonists), diuretics, phosphate binders, potassium binders and treatments for underlying kidney disease (cytotoxic agents, immunosuppressive agents, other immunotherapy).[94]

Concomitant treatments

All patients were treated for CV risk factors (e.g. blood pressure, lipids, and antithrombotic treatment), T2DM and CKD complications (e.g. hyperphosphatemia, hyperparathyroidism, hyperkalaemia, acidosis and renal anaemia).[94]

Diabetes treatment

The subset of patients with comorbid T2DM at randomisation continued their T2DM treatment, based on established clinical guidelines and local laboratory values. Patients treated with insulin or sulfonylurea have a higher risk of experiencing hypoglycaemic events compared with those treated with other diabetic agents, therefore, lower doses of insulin and insulin secretagogues could be required to minimise risk of hypoglycaemia when used in combination with study medication. Reduction of insulin by 10% to 20% (total daily dose) and sulfonylurea by 25% to 50% and increased frequency of blood glucose monitoring could be considered in patients receiving insulin and/or sulfonylurea and with baseline HbA1c ≤7% at randomisation. [94]

Other concomitant treatment

Other medications considered necessary for the patient's safety and well-being could be given at the discretion of the investigator.[94]

Concomitant treatment with open-label SGLT2 inhibitors and fixed-dose combinations containing these drugs was not permitted. Treatment with non-steroidal anti-inflammatory drugs was also restricted as much as possible during the study.[94]

B.2.3.5 Outcomes

The primary and secondary endpoints of the DAPA-CKD study are shown in Table 9. Definitions for the components of the composite primary endpoint, and for CV death, renal death and chronic dialysis, are provided in Table 10.

Table 9: Summary of endpoints from the DAPA-CKD study

Priority	Objective	Endpoint measure and assessment
Primary[a]	To determine whether dapagliflozin is superior to placebo in reducing the incidence of the primary composite endpoint of ≥50% sustained decline in eGFR, reaching ESKD, CV or renal death	Time to first occurrence of any of: • ≥50% sustained decline in eGFR from baseline • Reaching ESKD • CV death • Renal death
Secondary[a]	To determine whether dapagliflozin compared with placebo will result in a reduction of the incidence of the composite endpoints of worsening of renal function	Time to first occurrence of any of: • ≥50% sustained decline in eGFR from baseline • Reaching ESKD • Renal death
	To determine whether dapagliflozin compared with placebo will result in a reduction of the incidence of the composite endpoint of hospitalisation for HF or CV death	Time to first occurrence of any of: • CV death • Hospitalisation for HF
	To determine whether dapagliflozin compared with placebo will result in a reduction of the incidence of all-cause mortality	Time to death from any cause
Exploratory outcomes of relevance to this appraisal	To determine whether dapagliflozin compared with placebo will have an effect on eGFR over time	The effect on eGFR over time: • From baseline to end of treatment • From first on treatment measurement to end of treatment
	To determine whether dapagliflozin compared with placebo will result in a reduction of the incidence of patients reaching CKD stage 4 (eGFR <30 ml/min/1.73 m^2)	Proportion of patients with eGFR >40 ml/min/1.73 m^2 at baseline that enter CKD stage 4 (eGFR <30 ml/min/1.73 m^2) during the study
	To determine whether dapagliflozin compared with placebo will result in a reduction of the incidence of events of doubling of serum creatinine	Time to the first occurrence of an event of doubling of serum creatinine (compared to the most recent central laboratory measurement)
	To compare the effect of dapagliflozin versus placebo on the KDQOL-36 questionnaire	Change from baseline in the overall summary score of the KDQOL-36 questionnaire
	To compare the effect of dapagliflozin versus placebo on health status assessed by EQ-5D-5L questionnaire to support	Changes in health status measured by the EQ-5D-5L

Priority	Objective	Endpoint measure and assessment
	health economic analysis and health technology assessment	
	To determine whether dapagliflozin compared with placebo will result in a reduction in the incidence of the composite endpoint of chronic dialysis, renal death or receiving a renal transplant	Time to the first occurrence of any of the components of this composite: • Chronic dialysis • Receiving renal transplant • Renal death
	To determine whether dapagliflozin compared with placebo will have effect on uACR	Changes in uACR from baseline
Safety	To evaluate the safety and tolerability of dapagliflozin in this patient population	• Serious AEs • Discontinuation of investigational product due to AEs • Changes in clinical chemistry/haematology parameters • AEs of special interest

Footnotes: [a]Endpoints are listed in order of the hierarchical testing sequence.
Abbreviations: AE: adverse event; CKD: chronic kidney disease; CV: cardiovascular; eGFR: estimated glomerular filtration rate; EQ-5D-5L: EuroQol 5-dimensional 5-level; ESKD: end-stage kidney disease; KDQOL-36: Kidney Disease Quality of Life-36.
Sources: AstraZeneca Data on File 2020: DAPA-CKD Clinical Study Report Section 2[94] and Heerspink et al. 2020a.[93]

Table 10: Definitions of primary composite endpoint components

Endpoint	Definition
≥50% sustained decline in eGFR	A ≥50% reduction in eGFR from baseline measured in two consecutive central laboratory eGFR assessments at least 28 days apart, with eGFR calculated by central laboratory creatinine measurements using the CKD-EPI formula
Reaching ESKD	• The need for maintenance dialysis (peritoneal or haemodialysis) for at least 28 days, or • Renal transplantation, or • Sustained eGFR <15ml/min/1.73m^2 for at least 28 days
CV death	• Death due to MI, HF, cardiogenic shock, stroke, cardiovascular procedures, cardiovascular haemorrhage, or other cardiovascular causes • Deaths adjudicated as “cause undetermined” with regard to CV death or non-CV death were included in the analyses as CV deaths
Renal death	• Death due to ESKD when dialysis treatment was deliberately withheld (dialysis was not started or discontinued) for any reason • Deaths adjudicated as “cause undetermined” with regard to CV death or non-CV death were not considered as renal deaths
Chronic dialysis	The treatment had been ongoing for at least 28 days, or the dialysis treatment was stopped before Day 28 due to

	death, futility or patient electing to stop dialysis and the renal deterioration was deemed irreversible

Abbreviations: AE: adverse event; CKD: chronic kidney disease; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; CV: cardiovascular; eGFR: estimated glomerular filtration rate; ESKD: end-stage kidney disease; HF: heart failure; MI: myocardial infarction.
Sources: AstraZeneca Data on File 2020: DAPA-CKD Clinical Study Report Section 2[94] and Heerspink et al. 2020a.[93]

B.2.3.6 Pre-specified subgroups

Pre-planned subgroup analyses included: [73]

- Age (≤65 years, >65 years)
- Sex (male, female)
- Race (White, Black or African American, Asian, other)
- Geographical region (Asia, Europe, North America, Latin/South America)
- Comorbid T2DM at baseline (yes, no)
- uACR at baseline (≤1,000 mg/g, >1,000 mg/g [113 mg/mmol])
- eGFR at baseline (<45 ml/min/1.73m^2, ≥45 ml/min/1.73m^2)
- Systolic blood pressure at baseline (≤130 mmHg, >130 mmHg)

Post hoc subgroup analyses conducted to address requests included in the NICE final scope were:

- Comorbid CVD at baseline (yes, no)[95]
- People without comorbid T2DM and without comorbid CVD (yes, no)[95]

B.2.3.7 Duration of study and follow-up

The first participant was enrolled on 2nd February 2017 and the first randomisation occurred on 13th February 2017. Recruitment closed in the majority of participating countries on 6th July 2018. Recruitment in India, the USA and Canada was open until 19th October 2018. Recruitment in China opened on 2nd December 2019 and was ongoing until the trial end date of 3rd April 2020.[96]

The trial was stopped early after recommendation by the Independent Data Monitoring Committee because of clear efficacy based on 408 primary outcome events. At the end of the trial, the median follow-up was 2.4 years (IQR 2.0–2.7).[73]

B.2.3.8 Baseline characteristics

A total of 4,304 patients with an eGFR 25–75 ml/min/1.73 m^2 and a uACR of 200–5,000 mg/g (22.6–565 mg/mmol) were randomised in DAPA-CKD from February 2017 to October 2018.[96] The DAPA-CKD study enrolled a representative patient cohort with a broad range of comorbidities, including patients with and without comorbid T2DM. [96] An overview of baseline demographics and clinical characteristics for the DAPA-CKD study population are shown in Table 11.

Patients were well-balanced across the dapagliflozin and placebo treatment arms in terms of all demographics and characteristics.[73] The majority of patients had a baseline eGFR equivalent to stage 3 CKD (30–59 ml/min/1.73 m^2; 44.1% and 30.9% had an eGFR of 30–44 and 45–59

ml/min/1.73m^2 respectively), with a smaller group falling into stages 2 (10.5%; eGFR 60–75 ml/min/1.73 m^2) and 4 (14.5%; eGFR 25–30 ml/min/1.73 m^2).[96] Mean eGFR at baseline was 43.2 ±12.3 ml/min/1.73 m^2 for the dapagliflozin group and 43.0 ±12.4 ml/min/1.73 m^2 for the placebo group.[73] All patients had at least moderately increased albuminuria at baseline, as per the study inclusion criteria (uACR ≥200 mg/g [22.6 mg/mmol]), but ~50% of patients in both treatment groups had severely increased albuminuria (uACR >1,000 mg/g [113 mg/mmol).[73] Median uACR (IQR) at baseline was 965 mg/g (472–11,903 mg/g) (109.05 mg/mmol [53.34–1,345.04]) for the dapagliflozin group and 934 mg/g (482–1,868 mg/g) (105.54 mg/mmol [54.47–211.08]) for the placebo group.[73]

Approximately two-thirds of patients had comorbid T2DM (dapagliflozin: 67.6%, placebo: 67.4%), over a third of patients had comorbid CVD (dapagliflozin: 37.8%, placebo: 37.0%) and just over 10% had comorbid heart failure (dapagliflozin: 10.9%, placebo: 10.8%).[73] The use of concomitant medications was generally well balanced across treatment arms. The most common previous medications were ARBs (dapagliflozin: 67.1%, placebo: 66.3%) and statins (dapagliflozin: 64.8%, placebo: 65.0%).[73]

Table 11: Baseline patient demographics and clinical characteristics

Characteristic	Dapagliflozin (n=2,152)	Placebo (n=2,152)
Age, years	61.8±12.1	61.9±12.1
Female sex, n (%)	709 (32.9)	716 (33.3)
Race, n (%)[a]		
White	1,124 (52.2)	1,166 (54.2)
Black	104 (4.8)	87 (4.0)
Asian	749 (34.8)	718 (33.4)
Other	175 (8.1)	181 (8.4)
Weight, kg	81.5±20.1	82.0±20.9
BMI[b]	29.4±6.0	29.6±6.3
Current smoker, n (%)	283 (13.2)	301 (14.0)
Blood pressure, mmHg		
Systolic	136.7±17.5	137.4±17.3
Diastolic	77.5±10.7	77.5±10.3
Estimated GFR (ml/min/1.73 m^2)		
Mean	43.2±12.3	43.0±12.4
≥60	234 (10.9)	220 (10.2)
≥45–<60	646 (30.0)	682 (31.7)
≥30–<45	979 (45.5)	919 (42.7)
<30	293 (13.6)	331 (15.4)
Haemoglobin (g/l)	128.6±18.1	127.9±18.0
Serum potassium (mEq/l)	4.6±0.5	4.6±0.6
uACR (mg/g)		
Median (IQR)	965 (472–1,903)	934 (482–1,868)
>1,000, n (%)	1,048 (48.7)	1,031 (47.9)
T2DM, n (%)	1,455 (67.6)	1,451 (67.4)
Cardiovascular disease, n (%)[c]	813 (37.8)	797 (37.0)
Heart failure, n (%)	235 (10.9)	233 (10.8)

Characteristic	Dapagliflozin (n=2,152)	Placebo (n=2,152)
Background medication at randomisation, n (%)		
ACE inhibitors	673 (31.3)	681 (31.6)
ARB	1,444 (67.1)	1,426 (66.3)
Diuretic	928 (43.1)	954 (44.3)
Statin	1,395 (64.8)	1,399 (65.0)

Footnotes: Percentages may not total 100 because of rounding. uACR of 1,000 mg/g = 113 mg/mmol. [a]Race was reported by the investigators; the designation "other" includes Native Hawaiian or other Pacific Islander, American Indian or Alaska Native, and other. [b]The body-mass index is the weight in kilograms divided by the square of the height in meters. [c] History of peripheral artery disease, angina pectoris, myocardial infarction, percutaneous coronary intervention, coronary-artery bypass grafting, heart failure, valvular heart disease, abdominal aorta aneurysm, atrial fibrillation, atrial flutter, ischemic stroke, transient ischemic attack, haemorrhagic stroke, carotid artery stenosis, cardiac-pacemaker insertion, vascular stent, coronary-artery stenosis, ventricular arrhythmia, implantable cardioverter–defibrillator, noncoronary revascularization, or surgical amputation.
Abbreviations: ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; BMI: body mass index; GFR: glomerular filtration rate; IQR: interquartile range; T2DM; type 2 diabetes mellitus; uACR: urine albumin-to-creatinine ratio.
Source: Heerspink et al. 2020b.[73]

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

B.2.4.1 Statistical analyses and study populations

A summary of the analysis populations for efficacy and safety outcomes for the DAPA-CKD study is presented in Table 12, while details of the statistical analyses conducted for DAPA-CKD are presented in Table 13.

Table 12: Summary of analysis populations

Study population	Description
FAS	• All patients who were randomised to the dapagliflozin (n=2,152) or placebo (n=2,152) treatment arms, irrespective of their protocol adherence and continued participation in the study (the ITT population) • Patients were analysed according to their randomised therapy assignment, irrespective of the treatment actually received • The FAS was considered the primary analysis set for the primary and secondary variables and for the exploratory efficacy variables
SAS	• All patients who received at least one dose of dapagliflozin (n=2,149) or placebo (n=2,149) • Patients were analysed according to the treatment actually received[a] • The SAS was considered the primary analysis set for all safety variables

Footnotes: [a]For any patients given incorrect treatment, the treatment group was allocated as follows: patients who received both the incorrect and correct treatment were allocated to their randomised treatment group; and patients who received only the incorrect treatment were allocated to that treatment group.
Abbreviations: FAS: full analysis set; SAS: safety analysis set, ITT: intent-to-treat.
Source: AstraZeneca 2020: DAPA-CKD Clinical Study Report Section 9.8.2[94]

Table 13: Summary of statistical analyses in DAPA-CKD

DAPA-CKD	
Hypothesis objective	Treatment with dapagliflozin was hypothesised to be superior to placebo in reducing the risk of renal and cardiovascular events in patients with CKD (with or without comorbid T2DM) already receiving a stable dose of an ACE inhibitor or an ARB (unless ACE inhibitors/ARBs were contraindicated)

Statistical analysis	• The primary efficacy analysis was based on the FAS. In the analysis of the primary composite endpoint, the treatments (dapagliflozin and placebo) were compared using a Cox proportional hazards regression model stratified by the factors used at randomisation (T2DM and uACR) and adjusted for baseline eGFR. The analysis used each patient's last assessment as the censoring date for patients without any primary outcome event. The contribution of each component of the primary composite endpoint to the overall treatment effect were also examined and no multiplicity adjustment was made to confidence intervals or p values
	• [redacted]
	• The secondary efficacy outcomes were tested in a similar manner as the primary efficacy outcomes using a closed testing procedure including a pre-specified hierarchical order of the primary and secondary outcomes. The secondary outcomes were tested in hierarchical order as follows:
	  ○ Composite renal endpoint consisting of 50% eGFR decline, ESKD or renal death
	  ○ Composite endpoint of hospitalisation for HF or CV death
	  ○ Time to death from any cause
	• The testing procedure continued down the hierarchy if the preceding endpoint was rejected at a one-sided 0.025 level and stopped if the null hypothesis for the preceding endpoint was not rejected
	• A mixed model for repeated measurements was used to analyse changes in the eGFR in the on-treatment population
	• Cox proportional hazards models were used to examine treatment effects within relevant subgroups separately
	• Safety data are summarised according to trial group and safety analyses were performed on all AEs occurring before or at the trial closure visit. All analyses were performed with SAS software, version 9.4 (SAS Institute)

Sample size, power calculation	• DAPA-CKD was an event-driven trial • 681 primary endpoint events were needed to provide 90% power to detect a 22% lower relative risk in the dapagliflozin group compared with the placebo group (hazard ratio of 0.78) using a one-sided alpha level of 0.025. Assuming an annual event rate for the primary outcome of 7.5% in the placebo group, 4,000 patients were estimated to provide the required number of primary events
Data management and patient withdrawals	• Quality of study data was assured through monitoring of investigational sites, provision of appropriate training for study personnel, and use of data management procedures. The impact of missing data with respect to the primary endpoint was assessed via a sensitivity analysis and a descriptive summary • For any patient that withdrew, the rationale for withdrawal and presence of any AE were recorded. The investigator followed up AEs reported outside of the clinical study. If a patient was lost to follow-up, the

	measures taken to contact the patient and determine the reason for discontinuation/withdrawal had to be documented • For incorrectly randomised patients, the study drug was discontinued in all cases where continued treatment was deemed to pose a safety risk. Where continuation with study drug was judged not to present a safety concern, the rationale for continuing study therapy was documented. Regardless of what was decided, all randomised patients were to remain in the study and the patients were to be followed up in accordance with the defined study procedures

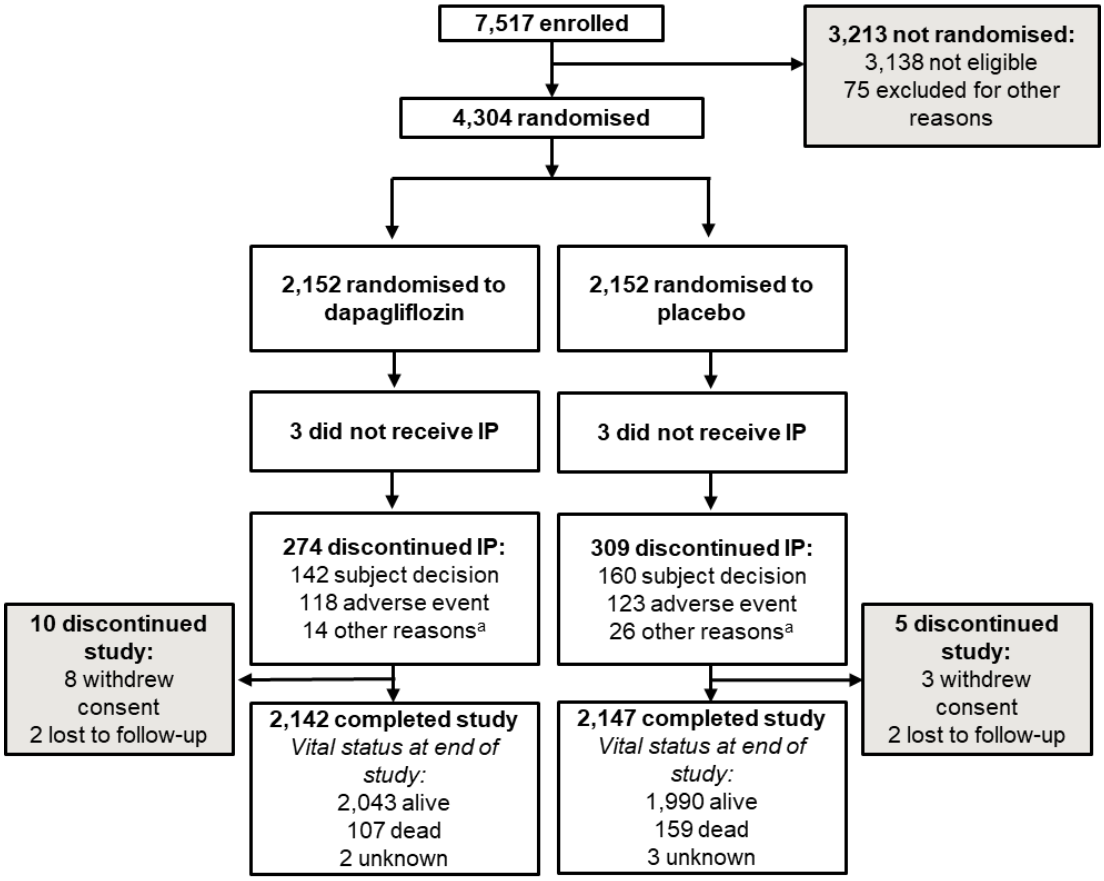
Abbreviations: ACE: angiotensin-converting enzyme; AE: adverse event; ARB: angiotensin receptor blocker; CV: cardiovascular; eGFR: estimated glomerular filtration rate; PTDV: premature treatment discontinuation visit; T2DM: type 2 diabetes mellitus; uACR: urine albumin-to-creatinine ratio.
Source: AstraZeneca 2020: DAPA-CKD Clinical Study Report Section 9.8.[94]

B.2.4.2 Study population and patient disposition

Patient disposition

In total, 4,304 patients were randomised to dapagliflozin or placebo; of these patients 4,289 (99.7%) completed the study and [redacted] discontinued the study: 11 patients withdrew consent during the study and [redacted] were lost to follow-up.[73, 94] A similar percentage of patients in each treatment arm prematurely and permanently discontinued the investigational product (dapagliflozin: n=274 [12.7%], placebo: n=309 [14.4%]).[73] A similar percentage of patients in each treatment arm discontinued due to AEs (dapagliflozin: n=118 [5.5%], placebo n=123 [5.7%]).[73] The median time in study until the primary analysis censoring date was [redacted] months (range [redacted] months) and the median time until last visit was [redacted] months (range [redacted] months).[94] Patient disposition is summarised in Figure 6.

Figure 6: Patient disposition and study participation



Footnotes: [a]Severe non-compliance to protocol, development of study specific discontinuation criteria (confirmed DKA, positive pregnancy test, other). [b]Defined as all randomised patients that did not discontinue study.
Abbreviations: DKA: diabetic ketoacidosis; IP: investigational product.
Source: AstraZeneca Data on File 2020: DAPA-CKD Clinical Study Report Figure 2.[94]

B.2.5 *Quality assessment of the relevant clinical effectiveness evidence*

A quality assessment for DAPA-CKD, in accordance with the NICE-recommended checklist for assessment of bias in RCTs is provided in Table 14 and Appendix D.

Table 14: Overview of quality assessment for DAPA-CKD

DAPA-CKD (NCT03036150)	Risk of bias
Was randomisation carried out appropriately?	Yes. Patients were randomised in a 1:1 ratio stratified by comorbid T2DM status and uACR at baseline. Randomisation was performed based on a sequestered, fixed randomisation schedule using balanced blocks[73]
Was the concealment of treatment allocation adequate?	Yes. An interactive voice/web-response system was used to determine treatment assignment and matching placebo was used[73]
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes. The baseline characteristics, including medications for comorbid T2DM and kidney disease, were balanced between the dapagliflozin and placebo groups[73]

DAPA-CKD (NCT03036150)	Risk of bias
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes. This study had a double-blind design. No trial personnel had access to the randomisation scheme. Dapagliflozin and placebo were packaged identically, with uniform tablet appearance, labelling, and administration schedules[97]
Were there any unexpected imbalances in drop-outs between groups?	No. Discontinuations of study medication were low and well-balanced between treatment arms[73]
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No. Based on the clinical study report all outcomes are reported in detail[94]
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes. Efficacy analysis was performed on the FAS[73]
Did the authors of the study publication declare any conflicts of interest?	Yes, the DAPA-CKD trial was sponsored by AstraZeneca. The sponsor was involved in the design and write up of the trial[96]

Abbreviations: FAS: full analysis set; ITT: intention-to-treat; uACR: urine albumin-to-creatinine ratio; T2DM: type 2 diabetes mellitus.

B.2.5.1 Applicability to clinical practice

The patient population enrolled in the DAPA-CKD trial is considered broadly similar to the CKD patient population seen in UK clinical practice. Minor differences are noted in the age and ethnicity of the trial population and in the background therapies received by patients enrolled in the trial compared to clinical practice, as described below. However, these differences are not expected to significantly affect the applicability of the DAPA-CKD trial results to the UK setting. In addition, considerable evidence outside of the DAPA-CKD trial population supports the use of dapagliflozin [redacted] This is discussed in detail in Section B.2.13.2.

Clinical expert feedback from UK GPs and nephrologists indicates the DAPA-CKD trial population was slightly younger than patients typically seen in clinical practice; a small proportion of patients in the trial were aged >75 years (n=[redacted]).[67, 94] However, subgroup analyses of DAPA-CKD (Section B.2.7) showed that the treatment benefit of dapagliflozin was consistent in patients aged ≥65 and <65, suggesting that the results of DAPA-CKD are consistent in older individuals and therefore are generalisable to the UK population with CKD.[73]

Representation of Black/African American [redacted] in DAPA-CKD was lower than would be expected in UK clinical practice.[67] However, this is not expected to significantly affect the generalisability of the trial results to UK clinical practice. Firstly, the treatment benefit of dapagliflozin versus placebo was observed in White, Black/African American and Asian subgroups in the DAPA-CKD study for the primary endpoint (Figure 14; p value for interaction=[redacted]) and secondary endpoints.[73, 94] Secondly, feedback from UK GPs and nephrologists indicates dapagliflozin may in fact be associated with a greater absolute treatment benefit in a population with a higher proportion of Black/African American and Southern Asian patients, as the rate of CKD progression, CV events, and renal events is expected to be higher for Black/African American and Southern Asian patients compared with White patients.[67] Finally, NICE guidelines do not include specific recommendations for ACE inhibitor or ARB treatment for

CKD in Black and Southern Asian patients, reflecting the suitability of a consistent treatment approach across ethnicities.[16]

There are some differences in the specific ACE inhibitor and ARB therapies received in the DAPA-CKD trial compared with UK clinical practice. However, there were no significant differences in the proportion of patients receiving other important components of SOC compared with clinical practice. For example, the proportions of patients receiving statins or antiplatelets at baseline were 64.9% and 43.7% respectively, which are similar to the proportion of patients receiving these medications in preliminary analyses of the UK CPRD database (statins: [redacted]%; antiplatelets: [redacted]%).[34, 96] In terms of ACE inhibitors and ARBs, a higher proportion of patients were receiving an ARB (66.7%) than an ACE inhibitor (31.5%) at baseline in the DAPA-CKD trial, whereas CPRD data suggest that the inverse is true in UK clinical practice ([redacted] versus [redacted] respectively).[34, 96] However, feedback from UK GPs and nephrologists suggests that the efficacy of these drugs is seen as interchangeable between classes and therefore this is not expected to affect the generalisability of the trial results.[67]

In the DAPA-CKD trial, eligible patients were those receiving the maximum tolerated dose of an ACE inhibitor or an ARB, unless this was medically contraindicated (at randomisation, 3.0% of patients were not receiving an ACE inhibitor or an ARB).[96] As discussed in Section B.1.3.4, in UK clinical practice, patients with CKD often receive lower doses of ACE inhibitors and ARBs than those used in key clinical trials due to tolerability issues, and are therefore unable to gain the full treatment benefit of these therapies. Dapagliflozin may therefore be associated with an even greater absolute treatment benefit over and above SOC in clinical practice compared with the DAPA-CKD trial; lower rates of ACE inhibitor and ARB use may result in higher overall event rates than were observed in the DAPA-CKD trial population, so the absolute treatment effect of dapagliflozin may be even more pronounced in clinical practice. There is also considerable supporting data outside of the DAPA-CKD trial that demonstrates a consistent positive treatment effect of dapagliflozin versus placebo in patients not currently receiving an ACE inhibitor or an ARB, and this is discussed in Section B.2.13.2.

Overall, the minor differences in age, ethnicity and background therapies received by the DAPA-CKD trial population compared to clinical practice are not considered to significantly affect the applicability of the trial results to UK clinical practice.

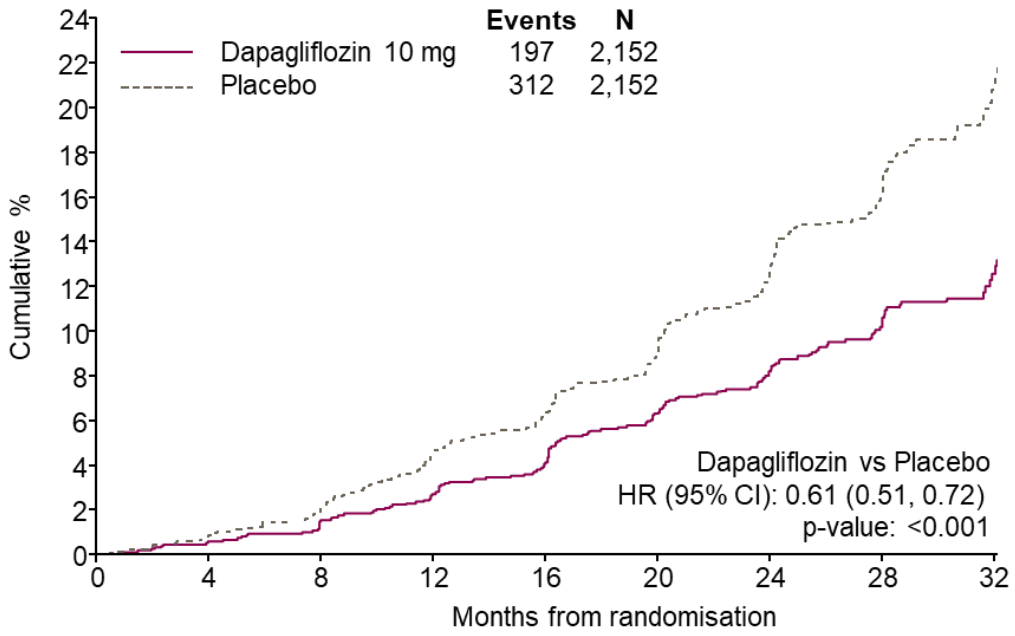
B.2.6 *Clinical effectiveness results of the relevant trials*

B.2.6.1 Primary endpoint (composite of sustained decline in eGFR ≥50%, ESKD or death from renal or CV causes)

Dapagliflozin reduced the relative risk of the primary composite outcome by 39% compared with placebo

Dapagliflozin significantly reduced the risk of a composite outcome of sustained decline in eGFR ≥50%, ESKD or death from renal or CV causes, which occurred in 197 participants (9.2%) of the dapagliflozin group and 312 participants (14.5%) of the placebo group (HR 0.61; 95% CI: 0.51, 0.72; p<0.001).[73] The Kaplan-Meier plot in Figure 7 shows that the treatment curves for the DAPA-CKD primary endpoint separated early, and continued to separate across the study, indicating that patients treated with dapagliflozin gained an early and sustained treatment benefit.[73]

Figure 7: Kaplan-Meier plot of the composite of ≥50% eGFR decline, ESKD and renal or CV death



Footnotes: N at risk is the number of patients at risk at the beginning of the period. One month corresponds to 30 days. 2-sided p value is displayed. HR, CI and p value are from the Cox proportional hazard model.
Abbreviations: CI: confidence interval; CV: cardiovascular; D: dapagliflozin 10 mg; eGFR: estimated glomerular filtration rate; ESKD: end stage kidney disease; HR: hazard ratio; P: placebo.
Source: Heerspink et al 2020b.[73]

The event rates for each component of the primary endpoint favoured dapagliflozin (Table 15): fewer patients in the dapagliflozin group experienced significant kidney decline than those in the placebo group, and they were also less likely to reach ESKD.[94] Importantly, a 34% reduction in the relative risk of chronic dialysis was observed with dapagliflozin compared with placebo.[73] There was also a smaller number of renal deaths in the dapagliflozin group (n=2) compared with placebo (n=6), and fewer CV deaths (n=65 and n=80 respectively).[94]

Table 15: Primary composite outcome across dapagliflozin and placebo treatment groups

Outcome, n (%)	Dapagliflozin (N=2,152)	Placebo (N=2,152)	Hazard ratio (95% CI)	p value (primary outcome)	p value (exploratory analysis)
Primary composite outcome	197 (9.2)	312 (14.5)	0.61 (0.51, 0.72)	<0.001	N/A
Exploratory analysis – individual components of the primary outcome					
Sustained ≥50% decline in eGFR	112 (5.2)	201 (9.3)	0.53 (0.42, 0.67)	N/A	[redacted]
End-stage kidney disease	109 (5.1)	161 (7.5)	0.64 (0.50, 0.82)	N/A	[redacted]
eGFR of <15 ml/min/1.73 m^2	84 (3.9)	120 (5.6)	0.67 (0.51, 0.88)	N/A	[redacted]
Chronic dialysis	68 (3.2)	99 (4.6)	0.66 (0.48, 0.90)	N/A	[redacted]
Kidney transplantation	3 (0.1)	8 (0.4)	N/A[a]	N/A	N/A[b]
Death from renal causes	2 (<0.1)	6 (0.3)	N/A[a]	N/A	N/A[b]
Death from CV causes[c]	65 (3.0)	80 (3.7)	0.81 (0.58, 1.12)	N/A	[redacted]

Footnotes: [a]Not calculated for this endpoint due to an insufficient number of events, [b]N/A denotes not applicable because p values for efficacy outcomes are reported only for outcomes that were included in the hierarchical testing strategy .[c] Deaths adjudicated as "cause undetermined" with regard to CV death or non-CV death were included in as CV deaths in the analysis of the primary endpoint. Undetermined cause of death refers to a death not attributable to a CV or non-CV cause due to the lack of information or insufficient supporting information to assign the cause of death.
Abbreviations: CI: confidence interval; GFR: glomerular filtration rate; N/A: not applicable.
Source: Heerspink et al. 2020b.[73] and AstraZeneca Data on File 2020: DAPA-CKD Clinical Study Report Table 13.[94]

B.2.6.2 Secondary endpoints

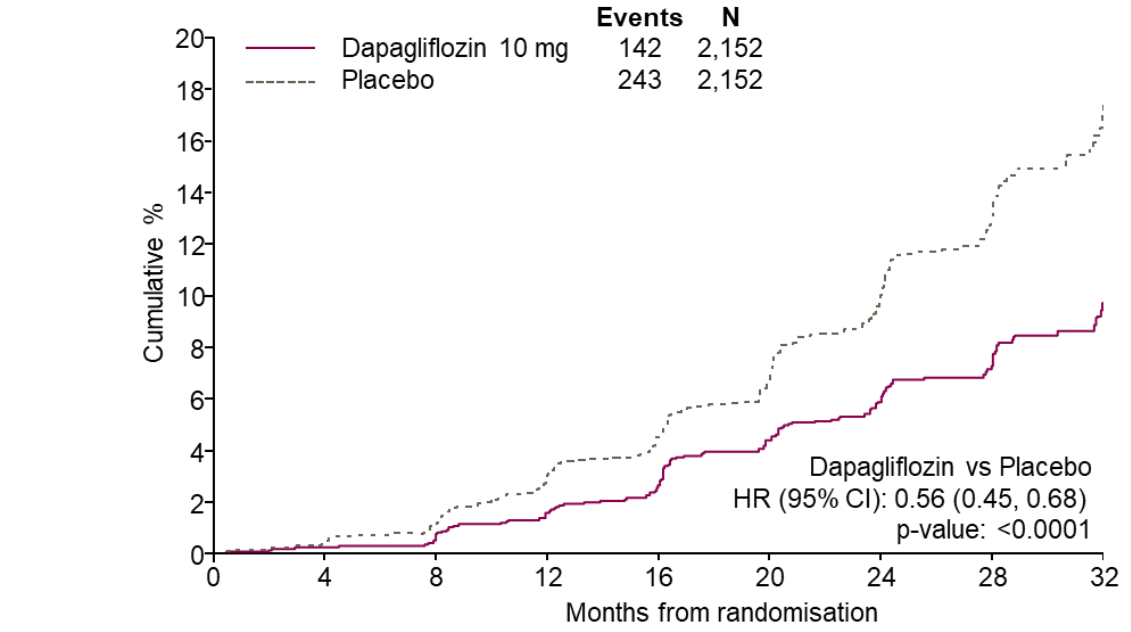
B.2.6.2.1 Time to first event of the composite of ≥50% sustained decline in eGFR, ESKD, and renal death

The positive renal treatment effect was confirmed by a significant reduction in the renal-specific composite outcome compared with placebo

Dapagliflozin demonstrated a significant risk reduction of 44% in the renal-only composite endpoint versus placebo (HR 0.56; 95% CI: 0.45, 0.68; p<0.001).[73, 94] There were 142 (6.6%) and 243 (11.3%) patients with any event of the composite endpoint in the dapagliflozin and placebo groups, respectively.[73]

The KM treatment curves for the composite of ≥50% sustained decline in eGFR, ESKD, and renal death separated early and continued to separate across the study, indicating patients treated with dapagliflozin gained an early and sustained treatment benefit (Figure 8).[73]

Figure 8: Kaplan-Meier Plot of Composite ≥50% eGFR Decline, ESKD and Renal Death (FAS)



Footnotes: N at risk is the number of patients at risk at the beginning of the period. One month corresponds to 30 days. 2-sided p value is displayed. HR, CI and p value are from the Cox proportional hazard model.
Abbreviations: CI: confidence interval; FAS: Full Analysis Set; HR: hazard ratio.
Source: Heerspink et al. 2020b.[73]

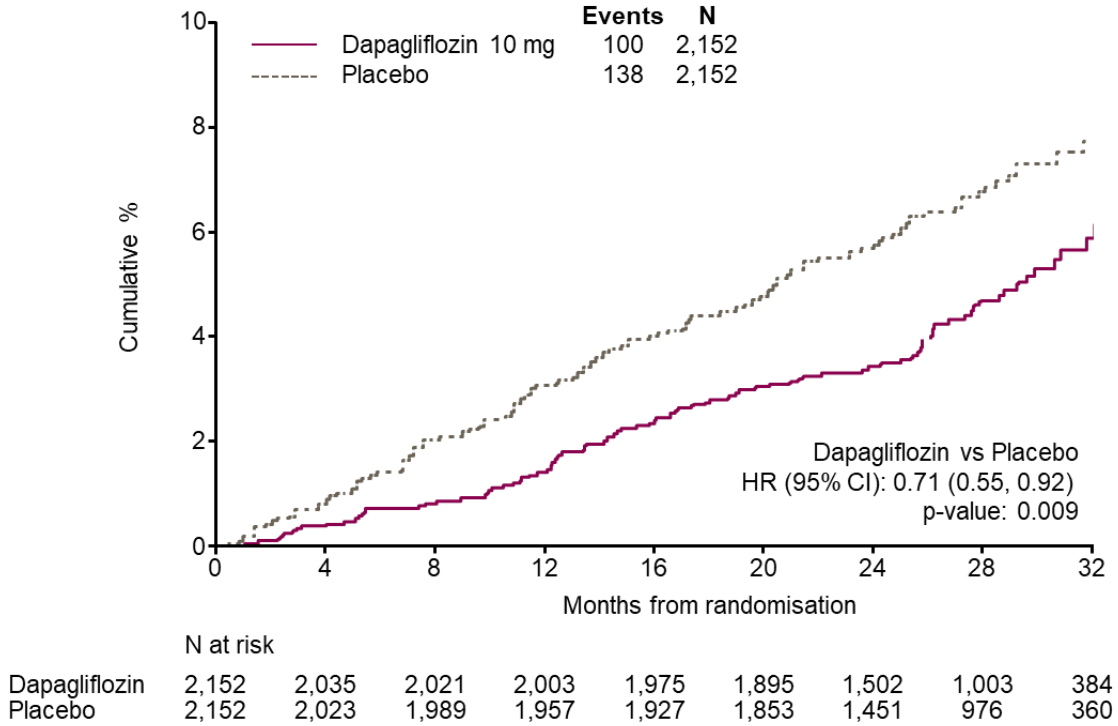
B.2.6.2.2 Time to first event of the composite of CV death and hospitalisation for heart failure

Dapagliflozin demonstrated a significant reduction in the composite risk of hospitalisation for HF or CV death compared with placebo

Treatment with dapagliflozin was associated with a 29% reduction in the risk of hospitalisation for HF or CV death (HR 0.71; 95% CI: 0.55, 0.92; p=0.0089).[73, 94] There were 100 (4.6%) and 138 (6.4%) patients with any event of the composite endpoint in the dapagliflozin and placebo groups, respectively.[73] The main driver of the effect on this composite endpoint was a 49% reduction in the relative risk of hospitalisation for HF in the dapagliflozin group compared with placebo (HR 0.51; 95% CI: 0.34, 0.76; [redacted]).[94, 98]

The KM treatment curves for the composite of CV death and hospitalisation for HF separated earlier than other endpoints and continued to separate across the study, indicating patients treated with dapagliflozin gained an early and sustained treatment benefit (Figure 9).[73]

Figure 9: Kaplan-Meier plot of composite of hospitalisation for HF or CV Death (FAS)



Footnotes: N at risk is the number of patients at risk at the beginning of the period. One month corresponds to 30 days. 2-sided p value is displayed. HR, CI and p value are from the Cox proportional hazard model.
Abbreviations: CI: confidence interval; FAS: Full Analysis Set; HR: hazard ratio.
Source: Heerspink et al. 2020b.[73]

B.2.6.2.3 Time to death from any cause

All-cause mortality was significantly reduced in patients treated with dapagliflozin compared with placebo

Dapagliflozin demonstrated a 31% relative risk reduction in all-cause mortality compared with placebo (HR 0.69; 95% CI: 0.53, 0.88; p=0.004).[73, 94] There were 101 (4.7%) deaths in the dapagliflozin group and 146 (6.8%) deaths in the placebo group. Reductions in both CV and non-CV deaths contributed to this reduction in all-cause mortality, as shown in Table 16. [94]

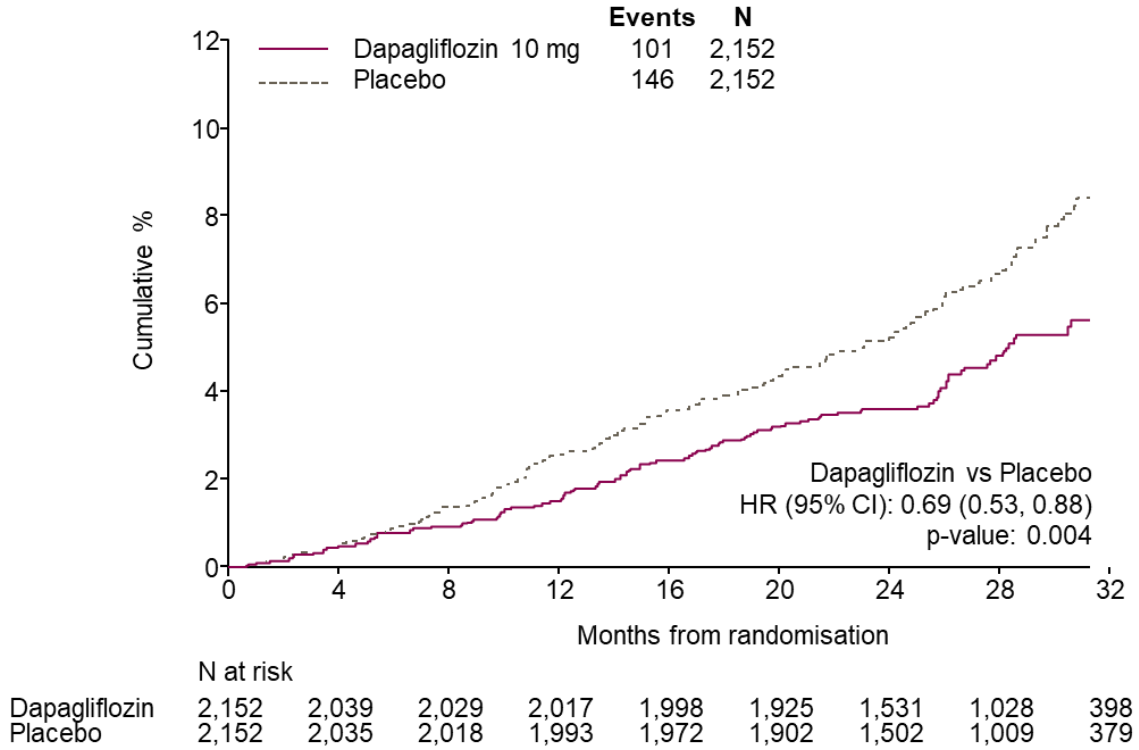
The Kaplan-Meier treatment curves for all-cause mortality separated early, and continued to separate across the study, indicating that patients treated with dapagliflozin gained an early and sustained treatment benefit (Figure 10).[73]

Table 16: Causes of death across dapagliflozin and placebo groups

Cause of death n (%)	Dapagliflozin (N=2,152)	Placebo (N=2,152)	Total (N=4304)
All deaths	101 (4.7)	146 (6.8)	247 (5.7)
CV death	41 (1.9)	50 (2.3)	91 (2.1)
Non-CV death	36 (1.7)	66 (3.1)	102 (2.4)
Undetermined cause of death	24 (1.1)	30 (1.4)	54 (1.3)

Footnotes: Undetermined cause of death refers to a death not attributable to a CV or non-CV cause due to the lack of information or insufficient supporting information to assign the cause of death. Please note that deaths adjudicated as "cause underdetermined" were included as CV deaths in the analysis of the primary endpoint, but are presented separately here.
Abbreviations: CV: cardiovascular; SIRS: systemic inflammatory response syndrome.
Source: Heerspink et al. 2021.[99]

Figure 10: Kaplan-Meier plot of death of any cause (FAS)



Footnotes: N at risk is the number of patients at risk at the beginning of the period. 1 month corresponds to 30 days. 2-sided p value is displayed. HR, CI and p value are from the Cox proportional hazard model.
Abbreviations: CI: confidence interval; FAS: Full Analysis Set; HR: hazard ratio.
Source: Heerspink et al. 2020b.[73]

B.2.6.3 Exploratory analyses

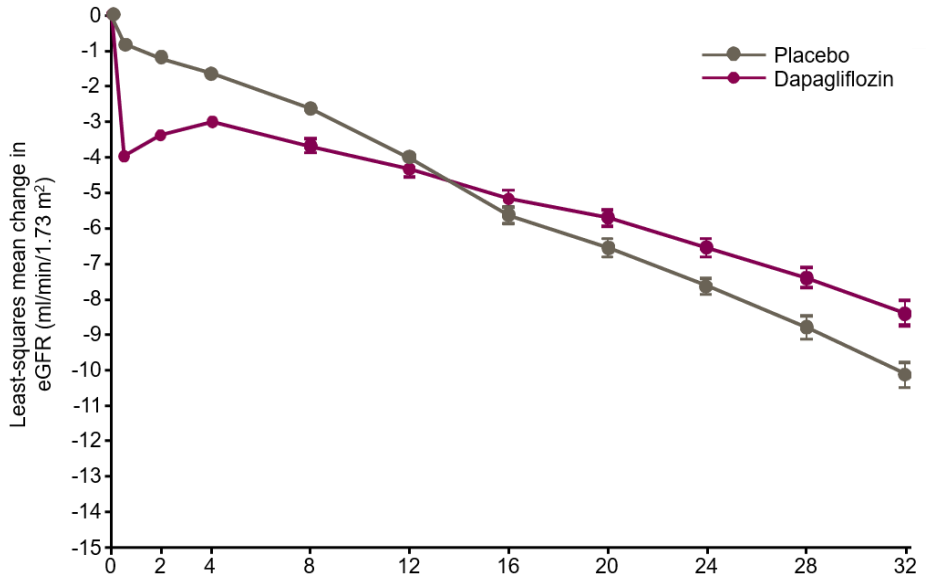
B.2.6.3.1 Change in eGFR slope

The rate of declining renal function over time was reduced in patients treated with dapagliflozin compared with placebo

As is consistently observed in trials of SGLT2 inhibitors, there was an initial drop in eGFR in patients receiving dapagliflozin (Figure 11) followed by a stabilisation.[72, 73, 100-102] Overall, the rate of decline in renal function was reduced in the dapagliflozin group compared with placebo. This initial drop in eGFR is physiological and results from reduction in blood pressure within the afferent arteriole of the glomerulus induced by SGLT2 inhibition. In the long term, this helps to protect the glomerulus from damage caused by the high intra-glomerular pressure observed in many patients with CKD.[103]

The slope in eGFR (baseline to 30 months, LS mean ± SE) was -2.86 ± 0.11 and -3.79 ± 0.11 ml/min/1.73 m^2 per year in the dapagliflozin and placebo groups, respectively, resulting in a difference of 0.93 ml/min/1.73 m^2 per year (95% CI: 0.61,1.25; [redacted]) between dapagliflozin and placebo.[73, 94] This demonstrates that treatment with dapagliflozin reduced the speed of declining renal function (corresponding to CKD progression) over time, compared with placebo.

Figure 11: Change from baseline in eGFR over time



No. of Participants										
Placebo	2,152	2,029	1,981	1,866	1,795	1,753	1,672	1,443	935	447
Dapagliflozin	2,152	2,031	2,001	1,896	1,832	1,785	1,705	1,482	978	496

Abbreviations: GFR: glomerular filtration rate.
Source: Heerspink et al. 2020b.[73]

B.2.6.3.2 Proportion of early-stage patients (eGFR >40 ml/min/1.73m² at baseline) reaching stage 4 CKD

The proportion of early-stage patients progressing to stage 4 CKD was reduced in patients treated with dapagliflozin compared with placebo

In the dapagliflozin treatment group [redacted] of patients with early-stage CKD at baseline (eGFR >40 ml/min/1.73 m^2) reached stage 4 CKD (eGFR <30 ml/min/1.73 m^2), compared with [redacted] of patients in the placebo group (Figure 12; [redacted]).[94]

Figure 12: Proportion of early-stage CKD patients in the dapagliflozin and placebo groups progressing to CKD stage 4

Abbreviations: CI: confidence interval; CKD: chronic kidney disease; OR: odds ratio; SoC: standard of care.
Source: AstraZeneca Data on File 2020: DAPA-CKD Clinical Study Report.[94]

B.2.6.3.3 Time to first event of the composite endpoint of chronic dialysis, renal transplant and renal death

Dapagliflozin demonstrated a reduction in the risk of chronic dialysis, renal transplant and renal death compared with placebo

Dapagliflozin demonstrated a risk reduction of [redacted] in the risk of chronic dialysis, renal transplant and renal death versus placebo ([redacted]). There were [redacted] and [redacted] patients with any event of this composite endpoint in the dapagliflozin and placebo groups, respectively. [94]

B.2.6.3.4 Health-related quality of life assessment

[redacted]

[redacted] [94]

[redacted] [94]

Patients with CKD are generally asymptomatic until they reach an advanced stage of disease.[35, 104]

[redacted]

B.2.6.3.5 Doubling of serum creatinine (AKI)

[redacted]

The effect of dapagliflozin on AKI was evaluated as the doubling of serum creatinine compared to the most recent laboratory measurement.
[redacted]. Serum creatinine doubling occurred in [redacted] of patients in the dapagliflozin group compared with [redacted] of patients in the placebo group.[94]

B.2.6.3.6 Change in uACR from baseline

[redacted]

Analysis of percentage change from baseline uACR over time demonstrated a [redacted] in uACR for dapagliflozin compared with placebo.[94]
[redacted], as shown in Figure 13 below. Albuminuria is a marker of kidney damage, and elevated albuminuria is strongly associated with an increased risk of mortality and adverse renal and CV outcomes.[17] As such, reduction in uACR is considered a surrogate outcome for a reduction in renal outcomes;
[redacted], reducing the risk of adverse disease outcomes in treated patients.

Figure 13: Adjusted mean percentage change in uACR from baseline (FAS)

[redacted]

Footnotes: *p<0.0001. The repeated measures model includes terms for randomised treatment group, baseline measurement, visit and visit by treatment group interaction. Data were log transformed for analysis.
Abbreviations: CI: confidence interval; Dapa: dapagliflozin; FAS: full analysis set; uACR: urine albumin creatinine ratio.
Source: AstraZeneca Data on File 2020: DAPA-CKD Clinical Study Report Figure 12 and Table 14.2.7.5.[94]

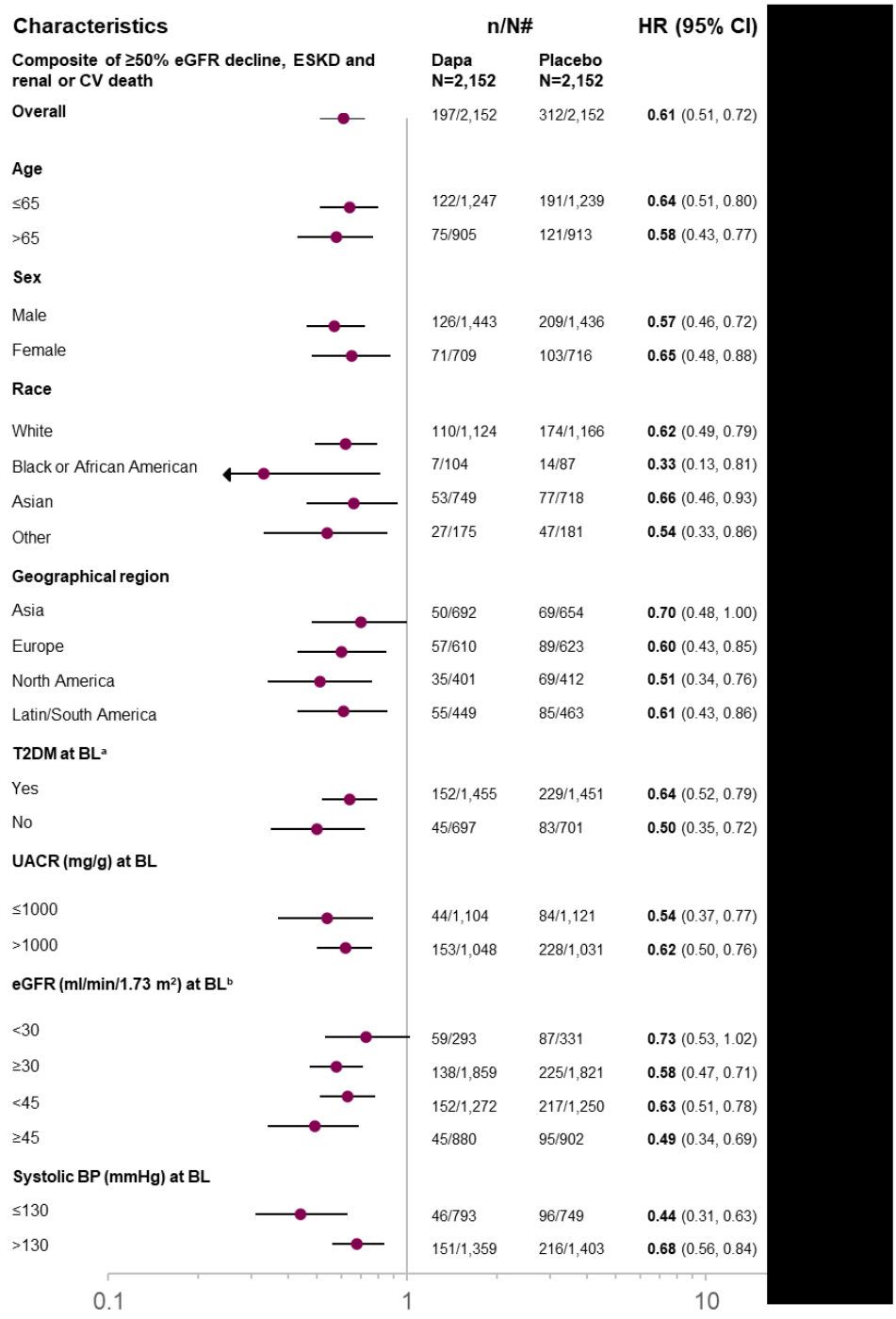
B.2.7 *Subgroup analyses*

Pre-specified subgroup analyses of the primary efficacy outcome were performed for the eight subgroups listed in Section B.2.3.6, including patients with or without comorbid T2DM and across the range of included eGFR and uACR measurements. Post hoc subgroup analyses were also conducted to address the requests in the NICE final scope, for patients with comorbid CVD and for patients without comorbid T2DM and without comorbid CVD.

The effect of dapagliflozin on the primary outcome was consistent across clinically relevant subgroups

The effect of dapagliflozin on the primary outcome was consistent across all pre-specified subgroups (Figure 14), demonstrating that dapagliflozin was an effective treatment for CKD regardless of CKD severity or T2DM.[73] Dapagliflozin displayed a positive treatment effect across all key subgroups, although a difference in treatment effect was observed between systolic BP subgroups (≤130 mmHg versus >130 mmHg; [redacted]), with patients with systolic BP of ≤130 mmHg at baseline experiencing a greater treatment benefit.[73, 94] However, this p value for interaction should be interpreted in the context of multiple testing across many different subgroups, which increases the likelihood of a chance finding. The positive treatment effect of dapagliflozin was also consistent in post hoc subgroup analyses of patients with or without comorbid CVD (p value for interaction: [redacted]; Figure 15) and patients without comorbid T2DM and without comorbid CVD versus those with comorbid CVD or T2DM (p value for interaction: [redacted]).[95]

Figure 14: Forest plot of the composite of ≥50% eGFR decline, ESKD and renal death or CV death by subgroups



Footnotes: [a]Defined as history of T2DM or HbA1c ≥6.5% at both visit 1 and visit 2. n/N#: number of patients with event/number of patients in subgroups. [b] This analysis does not adjust for baseline eGFR. Event rates are presented as the number of patients with event per 100 patient-years of follow-up. Hazard ratio, CI and p value are calculated from Cox proportional hazards model stratified by randomisation stratification of T2DM status and uACR, adjusting for baseline eGFR, with factors for treatment group, subgroup, and the interaction between treatment group and the subgroup variable. Subgroup analyses for T2DM only use uACR as stratification variable in the model and vice versa. Hazard ratio estimates are not presented for subgroups with less than 15 events in total, both arms combined.
Abbreviations: CI: confidence interval; CV: cardiovascular; eGFR: estimated glomerular filtration rate; ESKD: end stage kidney disease; HbA1c: glycated haemoglobin; N: number of patients; n: number of patients included in analysis; T2DM: type 2 diabetes mellitus; uACR: urine albumin creatinine ratio.
Source: AstraZeneca Data on File 2020: DAPA-CKD Clinical Study Report Figure 5.[94]

Figure 15: Post hoc subgroup analyses of the primary efficacy outcome for DAPA-CKD

Footnotes: [a]CVD was defined as any of the following: coronary heart disease (angina pectoris, myocardial infarction, coronary artery stenosis, percutaneous coronary intervention, coronary artery bypass surgery); cerebrovascular disease (ischemic stroke, haemorrhagic stroke, carotid artery stenosis, transient ischemic attack); peripheral artery disease (peripheral arterial occlusive disease, aneurysm of the abdominal aorta, non-coronary revascularization, vascular stent); heart failure (heart failure, cardiac resynchronization therapy [CRT]); valvular heart disease; atrial fibrillation or atrial flutter; ventricular arrhythmia; pulmonary embolism, and cardiac devices other than CRT (cardiac pacemaker, implantable cardioverter defibrillator [ICD]).
Abbreviations: CI: confidence interval; CVD: cardiovascular disease; HR: hazard ratio.
Source: AstraZeneca Data on File 2021d: Post-hoc analyses of DAPA-CKD.[95]

B.2.8 *Meta-analysis*

DAPA-CKD was designed based on a renal primary endpoint and represents the pivotal trial for dapagliflozin in this indication. Additional trials (DERIVE, DELIGHT and Kohan 2014) were identified in the SLR that investigated the efficacy of dapagliflozin in patients with T2DM and comorbid CKD only, and evaluated only surrogate markers of kidney disease (eGFR or uACR levels) rather than kidney disease outcomes such as ESKD, dialysis and kidney transplant.[89-91] In addition, both DERIVE and Kohan 2014 were designed primarily to assess the effect of dapagliflozin on glycaemic control rather than outcomes of relevance to this appraisal. These substantial differences in the eligibility criteria and outcomes of these trials compared with DAPA-CKD do not allow for the conduct of a robust meta-analysis, and therefore no meta-analyses of dapagliflozin trials have been conducted as part of this appraisal.

B.2.9 *Indirect and mixed treatment comparisons*

Canagliflozin is not considered a relevant comparator for this appraisal, as is reflected in the NICE final scope. However, as described in Section B.3.8.3, a comparison versus canagliflozin has been conducted as a scenario analysis in the subgroup of patients with comorbid T2DM (as canagliflozin is only licenced in patients with comorbid T2DM). As such, an indirect treatment comparison of dapagliflozin versus canagliflozin has been conducted to inform this scenario analysis.

[redacted]. Full details of the methodology and results of the indirect treatment comparison are presented in Appendix D.

B.2.10 *Adverse reactions*

Summary of safety of dapagliflozin

- The safety profile of dapagliflozin has been previously well reported in other indications. In DAPA-CKD, data were collected on all SAEs and AEs of special interest
- Dapagliflozin was generally well tolerated in patients with CKD, consistent with the known safety profile
- SAEs, including events with outcome of death, were less frequent with dapagliflozin (29.5%) compared with placebo (33.9%)
- SAEs occurring in ≥0.5% of patients were less frequent with dapagliflozin (27.6%) compared with placebo (34.1%)
- Rates of AEs of special interest (amputation, diabetic ketoacidosis, fracture, renal events, major hypoglycaemia and volume depletion) and AEs leading to discontinuation were generally low and balanced between treatment arms

Extensive safety data already exist for dapagliflozin in other indications, and the safety profile of dapagliflozin has been previously well reported.[1] A summary of common and uncommon adverse drug reactions which have been experienced in these indications is therefore provided in Section B.2.10.3 based on the Summary of Product Characteristics for dapagliflozin.[1]

In DAPA-CKD, the AEs recorded were those that qualified as:[73, 94]

- SAEs
- AE as a reason for permanent discontinuation from investigational product (IP)
- AE as a reason for IP interruption or dose reduction
- AEs of special interest
    - Symptoms of volume depletion
    - Renal events
    - Major hypoglycaemic events
    - Fractures
    - Potential DKAs
    - AEs leading to amputation
    - AEs leading to a risk for lower limb amputations (“preceding events”)
- AE leading to a potential endpoint

Summaries of AEs, safety laboratory data and vital signs in the DAPA-CKD trial are primarily based on the on-treatment period, which includes AEs with an onset date on or after date of first dose and up to and including 30 days following last dose of study drug. Additional presentations include all events with onset on or after first dose of study drug regardless of whether patients were on study treatment or not at the time of the event (the on- and off- treatment period).[94]

The median duration of exposure during this study was [redacted] months (range: [redacted] months) in the dapagliflozin group and [redacted] months (range: [redacted] months) in the placebo group.[94] In total, there were [redacted] patient-years of exposure to dapagliflozin in the study.[94]

Dapagliflozin was generally well-tolerated by patients with CKD, consistent with the known safety profile.[73] An overview of AEs observed in the DAPA-CKD trial is presented in Table 17. The numbers of patients with an AE with an outcome of death and of patients with SAEs were lower in the dapagliflozin treatment group than in the placebo group.
[redacted] AEs of special interest (diabetic ketoacidosis, major hypoglycaemic events, renal events, and amputations) were balanced between the treatment arms. Diabetic ketoacidosis, major hypoglycaemic events, renal events and amputation were all reported by fewer patients in the dapagliflozin group than the placebo group. Events of fracture and symptoms of volume depletion were reported by more patients in the dapagliflozin group than the placebo group.

Table 17: Number of patients with AEs in any category

AE category, n (%)[a]	Dapagliflozin (N=2,149)	Placebo (N=2,149)
Any AE with outcome of death (on- treatment)	[redacted]	[redacted]
Any AE with outcome of death (on- and off- treatment)	[redacted]	[redacted]
Any SAE, including events with outcome of death (on-treatment)	[redacted]	[redacted]
Any SAE, including events with outcome of death (on- and off-treatment)	633 (29.5)	729 (33.9)
Any AE leading to discontinuation of dapagliflozin	118 (5.5)	123 (5.7)
Any AE leading to dose interruption	[redacted]	[redacted]
Any AE leading to dose reduction	[redacted]	[redacted]
Any AE possibly related to dapagliflozin	[redacted]	[redacted]
AEs of special interest (on- and off- treatment)		
Definite or probable diabetic ketoacidosis[b]	0	2 (<0.1)
Major hypoglycaemic event[c]	14 (0.7)	28 (1.3)
Volume depletion	127 (5.9)	90 (4.2)
Fracture[d]	85 (4.0)	69 (3.2)
Renal-related AE[d]	155 (7.2)	188 (8.7)
Amputation[e]	35 (1.6)	39 (1.8)

Footnotes: The on-treatment period includes events with onset on or after first dose of randomised study drug and on or before 30 days after the last dose. Additional presentations include all events with onset on or after first dose of study drug, regardless of whether patients were on study treatment at the time of the event (on- and off-treatment period). Safety analyses included all the participants who had undergone randomisation and received at least one dose of dapagliflozin or placebo. [a]Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories. [b]Events adjudicated as definite or probable diabetic ketoacidosis. [c]AE with the following criteria confirmed by the investigator: i) Symptoms of severe impairment in consciousness or behaviour ii) need of external assistance iii) intervention to treat hypoglycaemia iv) prompt recovery of acute symptoms following the intervention. [d]Based on predefined list of preferred terms. [e]Surgical or spontaneous/non-surgical amputation, excluding amputation due to trauma. Refer to Table 19 for AEs of special interest for on- treatment patients.
Abbreviations: AE: adverse event; SAE: serious AE.
Sources: AstraZeneca Data on File 2020: DAPA-CKD Clinical Study Report Table 17 [94] and Heerspink et al. 2020b.[73]

B.2.10.1 Serious AEs

During the on-treatment period, a total of [redacted] patients in the dapagliflozin group and [redacted] patients in the placebo group reported SAEs.[94] This was similar when the on- and off-treatment periods were both considered (dapagliflozin: n=633 [29.5%], placebo: n=729 [33.9%]).[73]

The three most commonly reported SAEs for both treatment groups were [redacted] and [redacted][94] An overview of SAEs is shown in Table 18.

Table 18: Number of patients with SAEs (occurring in ≥0.5% in either treatment group) by preferred term (on treatment)

AE category, n (%)[a]	Dapagliflozin (N=2,149)	Placebo (N=2,149)
Patients with any SAE	[redacted]	[redacted]
Acute kidney injury	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Cardiac failure	[redacted]	[redacted]
Acute myocardial infarction	[redacted]	[redacted]
End stage renal disease	[redacted]	[redacted]
Ischaemic stroke	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]
Chronic kidney disease	[redacted]	[redacted]
Cellulitis	[redacted]	[redacted]
Angina unstable	[redacted]	[redacted]
Renal impairment	[redacted]	[redacted]
Transient ischaemic attack	[redacted]	[redacted]
Cardiac failure congestive	[redacted]	[redacted]
Cerebrovascular accident	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]

AE category, n (%)[a]	Dapagliflozin (N=2,149)	Placebo (N=2,149)
Osteomyelitis	[redacted]	[redacted]
Prostate cancer	[redacted]	[redacted]
Hypoglycaemia	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]
Death	[redacted]	[redacted]
Hyperkalaemia	[redacted]	[redacted]
Hyperglycaemia	[redacted]	[redacted]

Footnotes: [a]Number (%) of patients with SAEs, sorted by descending frequency of preferred term in the dapagliflozin group. Patients with multiple events in the same preferred term are counted only once in that preferred term. Patients with events in more than one preferred term are counted once in each of those preferred terms. This table includes SAEs with an onset date on or after date of first dose and up to and including 30 days following last dose of study drug, with a frequency ≥0.5% in either treatment group. Percentages are based on the total numbers of patients in the treatment group (N). Refer to Section B.2.10.2 for AEs of special interest (amputation, diabetic ketoacidosis, fracture, renal-related AEs, major hypoglycaemia and volume depletion).
Abbreviations: SAE: serious adverse event.
Source: AstraZeneca Data on File 2020: DAPA-CKD Clinical Study Report Table 28.[94]

B.2.10.2 AEs of special interest

Pre-specified AEs of special interest included amputation, diabetic ketoacidosis, fracture, renal events, major hypoglycaemia and volume depletion.[73] Diabetic ketoacidosis, major hypoglycaemic events, renal events and amputation were all reported by fewer patients in the dapagliflozin group than the placebo group, with no patients in the dapagliflozin group reporting diabetic ketoacidosis.[73] Conversely, events of fracture and symptoms of volume depletion were reported by more patients in the dapagliflozin group than the placebo group.[73] An overview of the reported AEs of special interest for the on- and off- treatment period is presented above in Table 17 and an overview of on- treatment data are presented below in Table 19.

Table 19: AEs of special interest (on- treatment)

AE	Number (%) of patients[a]	
	Dapagliflozin 10 mg (N=2,149)	Placebo (N=2,149)
Amputation[b]	[redacted]	[redacted]
Definite or probable diabetic ketoacidosis[c]	[redacted]	[redacted]
Fracture[d]	[redacted]	[redacted]
Renal-related AE[d]	[redacted]	[redacted]
Major hypoglycaemic event[e]	[redacted]	[redacted]
Volume depletion[d]	[redacted]	[redacted]

Footnotes: The on-treatment period includes events with onset on or after the first dose of randomised study drug and on or before 30 days after the last dose. [a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories. [b]Shown are cases of surgical amputation or spontaneous or nonsurgical amputation, excluding amputation due to trauma. [c]Events adjudicated as definite or probable diabetic ketoacidosis. [d]Based on predefined list of preferred terms. [e]AE with the following criteria confirmed by the investigator: i) Symptoms of severe impairment in consciousness or behaviour ii) need of external assistance iii) intervention to treat hypoglycaemia iv) prompt recovery of acute symptoms following the intervention. [e]Surgical or spontaneous/non-surgical amputation, excluding amputation due to trauma. Refer to Table 17 for AEs of special interest for on- and off- treatment patients.
Abbreviations: AE: adverse event.
Source: AstraZeneca Data on File 2020: DAPA-CKD Clinical Study Report Table 14.3.2.1.[94]

B.2.10.3 Adverse drug reactions reported in the Summary of Product Characteristics

A summary of common and uncommon adverse drug reactions which have been identified in the placebo-controlled clinical studies and post-marketing surveillance of dapagliflozin is provided in Table 20, based on the Summary of Product Characteristics for dapagliflozin.[1]

Table 20: Adverse drug reactions reported in the Summary of Product Characteristics for dapagliflozin in T1DM and T2DM

System organ class	Very common	Common	Uncommon	Rare	Very rare
Infections and infestations	-	Vulvovaginitis, balanitis and related genital infections Urinary tract infection	Fungal infection	-	Necrotising fasciitis of the perineum (Fournier's gangrene)
Metabolism and nutrition disorders	Hypoglycaemia[a]	Diabetic ketoacidosis (when used in T1DM)	Volume depletion Thirst	Diabetic ketoacidosis (when used in T2DM)	-
Nervous system disorders	-	Dizziness	-	-	-
Gastrointestinal disorders	-	-	Constipation Dry mouth	-	-
Skin and subcutaneous tissue disorders	-	Rash	-	-	Angioedema
Musculoskeletal and connective tissue disorders	-	Back pain	-	-	-
Renal and urinary disorders	-	Dysuria Polyuria	Nocturia	-	-
Reproductive system and breast disorders	-	-	Vulvovaginal pruritus Pruritus genital	-	-
Investigations	-	Haematocrit increased Creatinine renal clearance decreased during initial treatment Dyslipidaemia	Blood creatinine increased during initial treatment Blood urea increased Weight decreased	-	-

Footnotes: [a]When used with sulfonylurea or insulin. Frequency categories are defined according to the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥ 1/10,000 to <1/1,000); very rare (<1/10,000), and not known (cannot be estimated from the available data).
Abbreviations: T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.
Source: Dapagliflozin Summary of Product Characteristics.[1]

B.2.11 *Ongoing studies*

Other than DAPA-CKD, there are no ongoing studies relevant to this appraisal.

B.2.12 *Innovation*

CKD is associated with a significant clinical and economic burden

CKD affects approximately 1.9 million adults in England.[42] Premature mortality due to CKD is responsible for 40–45,000 premature deaths in the UK every year.[47] Patients with CKD also have a significantly increased risk of CV events compared to the general population even in early-stage CKD, with an even greater risk in the later stages of disease.[17, 37]

Current SOC is inadequate for many patients with CKD, and is associated with clinically relevant AEs which may limit upward dose titration

No treatments are currently able to reverse CKD. Current SOC includes a combination of treatment strategies individually adapted to a patient's specific characteristics (Section B.1.3.3). Despite the investigation of many novel treatments for CKD over the past two decades, ACE inhibitors and ARBs remain the only treatments to demonstrate efficacy in slowing the progression of CKD to ESKD in a clinical trial, with no clinical development in this area until the development of SGLT2 inhibitors.[23] NICE guidelines for the management of CKD recommend ACE inhibitors or ARBs to slow disease progression for patients in higher uACR categories (i.e. >3 mg/mol in patients with comorbid T2DM, >30 mg/mol in patients with comorbid HTN and ≥70mg/mol in patients without comorbid T2DM or HTN). However, there is currently a lack of disease-modifying treatments for patients in lower uACR categories and no specific pharmacotherapy recommendations are made to minimise disease progression in these patients.

Moreover, as discussed in Section B.1, a proportion of patients with CKD may be unable to tolerate ACE inhibitor or ARB therapy due to the associated risk of hyperkalaemia, hypotension and angioedema, which may necessitate discontinuation or reduced doses of ACE inhibitor/ARB therapy.[82] Patients with CKD in UK clinical practice therefore often receive lower doses of ACE inhibitors and ARBs than those used in clinical trials, and these suboptimal doses of ACE inhibitors or ARBs are associated with increased CV events and mortality compared with higher doses.[67, 105]

In addition, a substantial residual risk of CKD progression remains despite treatment with ACE inhibitors and ARBs: 161/2,152 (7.5%) and 165/2,199 (7.5%) of patients with CKD enrolled in the DAPA-CKD and CREDENCE RCTs respectively progressed to ESKD over a median follow up of 2.4 years and 2.62 years despite background therapy with ACE inhibitors or ARBs for the majority of patients.[72, 73] There is also a paucity of evidence for the effectiveness of ACE inhibitors and ARBs in patients with CKD without comorbid T2DM or CKD patients with normo/microalbuminuria, as the majority of relevant trials have been conducted in patients with diabetic kidney disease and macroalbuminuria only.[75-79]

Dapagliflozin is available as a single-dose, once-daily treatment and does not require dose titration, making it easy to initiate and for patients to adhere to, and is not associated with the hypotension and hyperkalaemia AEs which can limit use of current SOC.[1]

Dapagliflozin offers a substantial treatment benefit above current SOC

Dapagliflozin is an innovative treatment for patients with CKD with or without comorbid T2DM and offers substantial clinical benefit over and above current SOC; an early and sustained treatment benefit compared to current SOC was observed in the pivotal DAPA-CKD trial in both

the primary composite outcome of sustained decline in eGFR ≥50%, ESKD or death from renal or CV causes and a key secondary endpoint of all-cause mortality.[73] Dapagliflozin is the only treatment for CKD that has demonstrated a significant reduction in all-cause mortality in a renal outcomes trial in patients with CKD with and without comorbid T2DM, and the DAPA-CKD trial was stopped early due to evidence of overwhelming efficacy.[73] In light of this evidence, dapagliflozin [redacted] and will be the first SGLT2 inhibitor licensed to treat patients with CKD with or without comorbid T2DM. In addition, optimal management of CKD and reducing CV events aligns with the prevention focussed NHS Long Term Plan; CKD is included in the CVDPREVENT national primary care audit which aims to collate data on diagnosis and management of high-risk conditions that cause stroke, heart attack and dementia in order to identify areas for improvement.[87, 106]

B.2.13 *Interpretation of clinical effectiveness and safety evidence*

B.2.13.1 Principal findings from the clinical evidence highlighting the clinical benefits and harms of the technology

DAPA-CKD is the first SGLT2 inhibitor renal outcomes trial to demonstrate renal efficacy in CKD patients with or without comorbid T2DM

Dapagliflozin is the first SGLT2 inhibitor to be rigorously studied in patients with CKD receiving the maximum tolerated dose of SOC with and without comorbid T2DM.[73] As discussed above in Section B.2.12, current SOC for patients with CKD is inadequate; despite treatment with SOC, many patients progress to ESKD and experience CV events, as well as premature mortality, and there is a paucity of evidence for existing and novel treatments in patients with CKD but without comorbid T2DM.[27] The substantial treatment benefit of dapagliflozin over and above current SOC in the randomised, double-blind DAPA-CKD RCT (n=4,304) demonstrates that dapagliflozin presents a crucial opportunity to significantly improve outcomes for patients with CKD with and without comorbid T2DM.[73]

Dapagliflozin significantly reduced progression of CKD to ESKD and renal/CV death compared with placebo, with a substantial margin of benefit (39% relative risk reduction)

In DAPA-CKD, the risk of the primary composite endpoint of sustained decline in eGFR ≥50%, ESKD or death from renal or CV causes was significantly reduced in patients receiving dapagliflozin compared with those receiving placebo (HR: 0.61; 95% CI: 0.51, 0.72; p<0.001).[73] Moreover, the event rates for each component of the primary endpoint favoured dapagliflozin. Importantly, the risk of the ESKD component (eGFR <15 ml/min/1.73m^2, chronic dialysis or kidney transplantation) was significantly reduced by treatment with dapagliflozin (HR: 0.64; 95% CI: 0.50, 0.82; [redacted]).[73]

The chronic dialysis component of the ESKD component was also significantly reduced in the dapagliflozin group (HR: 0.66; 95% CI: 0.48, 0.90; [redacted]).[73, 94] The substantial treatment effect observed with dapagliflozin offers patients the opportunity to reduce CKD progression and delay the onset of ESKD; [redacted]

[redacted].[107] Furthermore, by reducing the relative risk of dialysis by 34%, dapagliflozin may alleviate the burden of dialysis on patients and healthcare facilities.[73]

The significant reduction in the secondary endpoint of all-cause mortality for dapagliflozin compared with placebo (HR 0.69; 95% CI: 0.53, 0.88; p=0.004) is a highly relevant treatment benefit to patients with CKD, who have a high mortality rate despite treatment with current SOC.[73] Dapagliflozin also represents the first novel therapeutic option to date to demonstrate a reduction in all-cause mortality in a renal outcomes trial in patients with CKD.

The positive renal treatment effect of dapagliflozin compared with placebo was also evident in the significant reduction of secondary renal endpoints, including a 44% relative risk reduction in the kidney-composite secondary endpoint

Dapagliflozin was superior to placebo for all secondary endpoints in DAPA-CKD, including a renal-specific composite of sustained decline in eGFR ≥50%, ESKD and renal death (HR 0.56; 95% CI: 0.45, 0.68; p<0.001).[73] In addition, [redacted] of patients with early-stage CKD at baseline (eGFR >40 ml/min/1.73 m^2) reached stage 4 CKD (eGFR <30 ml/min/1.73 m^2) in the dapagliflozin arm compared with [redacted] of patients in the placebo arm ([redacted]). Finally, dapagliflozin demonstrated a significant reduction in the risk of chronic dialysis, renal transplant and renal death versus placebo ([redacted]).[73, 94] This substantial and highly clinically relevant impact on progression of CKD emphasises the need for early treatment in patients with CKD in order to minimise progression to later stages of disease, which are associated with increased risk of adverse renal and CV outcomes, poorer HRQoL and increased costs, compared with earlier stages.[17, 18, 58]

Consistent with other phase III RCTs of dapagliflozin, a significant reduction in the risk of hospitalisation for HF or CV death was observed for dapagliflozin compared with placebo in DAPA-CKD

An important treatment goal in CKD is effective management of CV risk to reduce the incidence of CV events. In the DAPA-CKD trial, dapagliflozin was associated with a significant 29% reduction in the relative risk of hospitalisation for HF or CV death (HR 0.71; 95% CI: 0.55, 0.92; p=0.009), and this positive treatment effect is consistent with the results of the DAPA-HF and DECLARE-TIMI 58 study (discussed in more detail in Section B.2.13.2).[73, 84, 92] Dapagliflozin therefore enables HCPs treating patients with CKD to manage CV risk effectively.

The efficacy of dapagliflozin was consistent across pre-specified and post hoc subgroups, including patients with and without comorbid T2DM or comorbid CVD

The efficacy of dapagliflozin was consistent across clinically relevant pre-specified and post hoc subgroups, including patients with comorbid T2DM, patients with comorbid CVD and patients without comorbid T2DM and without comorbid CVD.[73, 98] The treatment benefit of dapagliflozin was also observed across the range of included eGFR and uACR measurements, demonstrating the effectiveness of dapagliflozin for CKD regardless of CKD severity.[73]

Dapagliflozin was generally well tolerated, consistent with its known safety profile

Dapagliflozin showed a favourable tolerability profile compared with placebo; SAEs were numerically less frequent with dapagliflozin (29.5%) than with placebo (33.9%) and there was no difference in AEs leading to discontinuation between dapagliflozin (5.5%) and placebo (5.7%).

Rates of AEs of special interest (amputation, diabetic ketoacidosis, fracture, renal events, major hypoglycaemia and volume depletion) were generally low and were balanced between treatment groups.[73]

Dapagliflozin is a vital new treatment option for patients with CKD, with the potential to significantly reduce the burden of CKD on patients and the healthcare system

Overall, the results of the DAPA-CKD study demonstrate that dapagliflozin is an effective and well tolerated treatment across a wide range of patients, including those with and without comorbid T2DM and comorbid CVD. By delaying CKD progression, reducing the risk of chronic dialysis and hospitalisation for HF and reducing all-cause mortality compared with current SOC, dapagliflozin can reduce the burden of CKD to the NHS and improve outcomes for patients with CKD. The impact of dapagliflozin on delaying dialysis is likely to have a particularly significant effect on the healthcare system, as dialysis is associated with a substantial cost burden (Section B.1.3.2). The treatment benefit of dapagliflozin was evident shortly after treatment initiation and continued with prolonged treatment, as demonstrated by the early separation of the KM curves for the primary and secondary endpoints. This supports the initiation of dapagliflozin in primary care, which avoids patients missing out on this early treatment benefit as a result of delays to treatment caused by waiting for an appointment with a specialist.

Given that the most appropriate care setting for the majority of patients with CKD is primary care ([redacted] of patients with stage 3–5 CKD are treated in primary care, as discussed in Section B.1.3.3[68]), treatment with dapagliflozin is highly appropriate in the primary care setting. Initiation in primary care would allow patients to gain the maximum possible treatment benefit to prevent deterioration and prolong time to costly dialysis.

B.2.13.2 Supporting data outside of the DAPA-CKD trial

The efficacy of dapagliflozin in the broader population of patients with CKD, regardless of uACR and eGFR category, is supported by DECLARE-TIMI 58 and DAPA-HF

The DAPA-CKD trial enrolled patients with an eGFR of 25–75 ml/min/1.73 m^2 and a uACR of 200–5,000 mg/g (22.6–565 mg/mmol),[73] [redacted] The extensive clinical trial program for dapagliflozin in T2DM and HFrEF covers patients with a range of renal functions and provides data supporting the efficacy of dapagliflozin in patients who were not eligible for inclusion in DAPA-CKD with respect to uACR and eGFR. Overall, these data demonstrate that dapagliflozin is effective at reducing progression of CKD and the risk of CV events in patients with a broad range of eGFR and uACR measurements.

The phase III DECLARE-TIMI 58 RCT (n=17,160) enrolled patients with T2DM who had or were at risk for atherosclerotic CVD.[84, 101] The phase III DAPA-HF RCT (n=4,744) enrolled patients with heart failure with reduced ejection fraction (HFrEF), regardless of the presence or absence of comorbid T2DM.[92, 100] Both trials enrolled a proportion of patients with comorbid CKD, and are therefore of relevance to this appraisal.

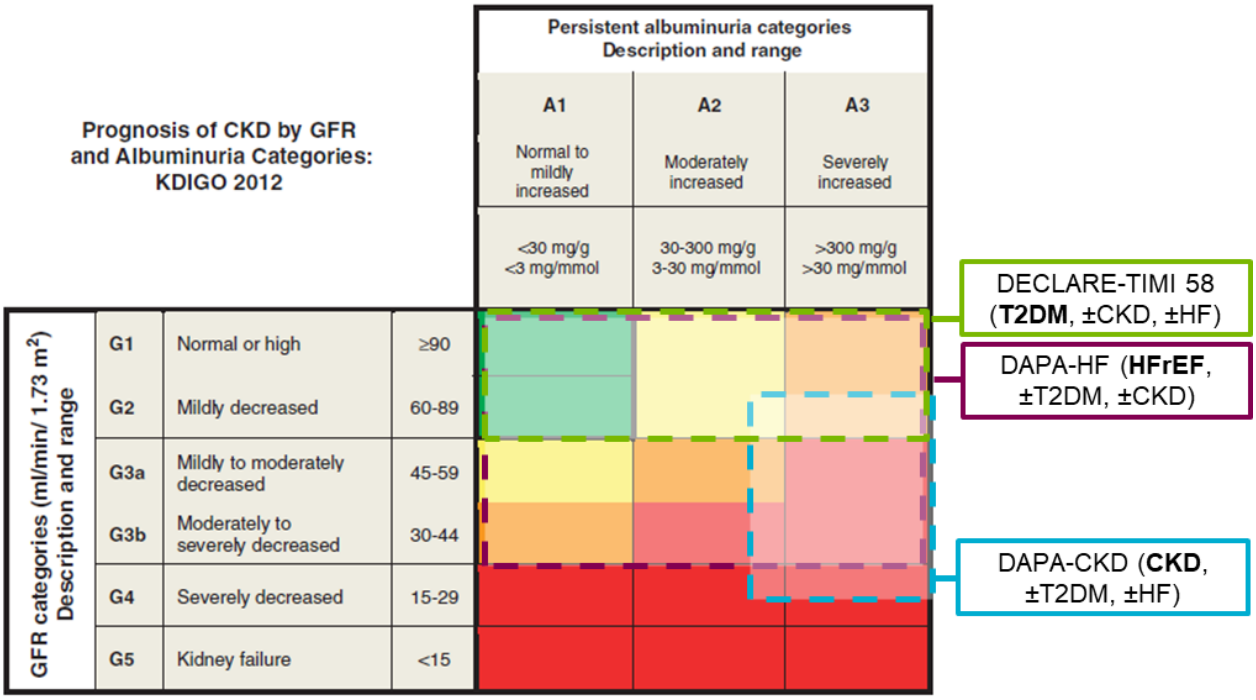
The majority of the DECLARE-TIMI 58 patient population had preserved renal function, but 1,265 patients (7%) had an eGFR of <60 ml/min/1.73m^2 at randomisation (CKD stage 3a–b; patients discontinued treatment with dapagliflozin if creatinine clearance fell below 30 ml/min/1.73m^2).[84,

[101] The DAPA-HF trial enrolled patients with a broad range of eGFR categories, with 41% of patients having an eGFR of <60 ml/min/1.73m^2 (CKD stage 3a and above).[92, 100]

Both trials enrolled patients with a range of albuminuria categories: in DECLARE-TIMI 58 the majority of patients had normoalbuminuria (n=11,644 [69.1%]), but a substantial number of patients had microalbuminuria (n=4,030 [23.9%]) or macroalbuminuria (n=1,169 [6.9%]).[101] uACR was not measured during the DAPA-HF trial, but given the lack of uACR restriction it is likely that the patients enrolled had a wide range of uACR categories.

Figure 16 below depicts the breadth of the patient population covered by these studies in terms of eGFR and uACR ranges and highlights the evidence available for dapagliflozin in the broader CKD population, [redacted]. Further details of specific supporting analyses from these trials are provided in the sections below, and further information on the enrolled patient populations, methodology and overall results of the DECLARE-TIMI 58 and DAPA-HF trials are presented in Appendix L.

Figure 16: Supporting data for the efficacy and safety of dapagliflozin within the full anticipated marketing authorisation



Footnote: Bold indicates primary trial population.
Abbreviations: CKD: chronic kidney disease; GFR: glomerular filtration rate; HFrEF: heart failure with reduced ejection fraction; T2DM: type 2 diabetes mellitus.
Sources: KDIGO 2012a;[13] Heerspink et al. 2020b;[73] McMurray et al. 2019;[92] Wiviott et al. 2018.[84]

The treatment effect observed in DAPA-CKD versus placebo is likely to be generalisable to patients in lower uACR categories

Analyses from both DECLARE-TIMI 58 and DAPA-HF (which would have enrolled patients with a wide range of uACR categories) suggest that the treatment effect observed in DAPA-CKD extends to patients in lower uACR categories than patients enrolled in DAPA-CKD (i.e. with a uACR <200 mg/g [22.6 mg/mmol]: patients with less kidney damage), as summarised in Figure 17.

Firstly, the treatment effect of dapagliflozin observed in the DECLARE-TIMI 58 trial on the co-primary endpoint of hospitalisation for HF or CV death, and the renal endpoint without CV death (eGFR ≥40%, ESKD, or death from renal causes) was consistent between patients with a uACR <200 mg/g (<22.6 mg/mmol) or ≥200 mg/g (≥22.6 mg/mmol) (Figure 17). Although the p-value for interaction fell below 0.05 for the cardiorenal endpoint of ≥40% eGFR decline, ESKD, renal death or CV death endpoint, this is likely to be a chance finding as these analyses have not been adjusted for multiple testing. Regardless of the p value for interaction, a clear treatment benefit was observed for both uACR subgroups, with 95% CIs below one.

Figure 17: Relevant subgroup analyses from the DECLARE-TIMI 58 study

Footnotes: Co-primary endpoint: hospitalisation for HF or CV death. Renal endpoint: ≥40% sustained eGFR decline, ESKD, renal death. Cardiorenal endpoint: ≥40% sustained eGFR decline, renal death, ESKD, CV death.
Abbreviations: CI: confidence interval; CV: cardiovascular; ESKD: end-stage kidney disease; eGFR: estimated glomerular filtration rate; HF: heart failure; HR: hazard ratio; uACR: urine albumin creatinine ratio.
Sources: AstraZeneca Data on File 2021e: Post-hoc subgroup analyses of DECLARE-TIMI 58.[108]

Although the DECLARE-TIMI 58 trial enrolled only patients with T2DM, the results of these subgroup analyses are likely to also apply to patients with CKD without comorbid T2DM; the clinical characteristics of CKD are similar irrespective of the presence of T2DM due to common pathological processes in the kidneys. In addition, dapagliflozin is anticipated to improve renal outcomes via mechanisms independent of blood glucose lowering and also confers benefits to the entire cardiorenal system in the form of reduction of body weight and BP, both in patients with CKD and comorbid T2DM and patients without diabetes.[4, 5] Subgroup analyses of the DAPA-HF trial also support the consistency of the dapagliflozin treatment effect across patients with and without T2DM: dapagliflozin significantly reduced the risk of the primary outcome of worsening HF or CV death independently of diabetes status.[109]

Overall, dapagliflozin was associated with significant reductions in the primary endpoint of worsening HF or CV death (HR: 0.74; 95% CI: 0.65, 0.85; p<0.001) in the DAPA-HF trial, which enrolled patients across a wide range of uACR categories.[92] Overall, the consistent treatment effect of dapagliflozin observed in the subset of patients with lower severity of kidney damage than those enrolled in DAPA-CKD (measured as uACR) indicate that dapagliflozin would be beneficial to these patients in lower uACR categories.

The evidence shows that the treatment benefit of dapagliflozin versus placebo is also generalisable to patients with higher eGFR levels

Analyses from both DECLARE-TIMI 58 and DAPA-HF provide evidence that the treatment effect observed in DAPA-CKD extends to patients within higher eGFR categories (i.e. patients with better kidney function) than patients enrolled in DAPA-CKD, as summarised in Figure 18.

In DECLARE-TIMI 58, the treatment benefit of dapagliflozin on the co-primary endpoint of hospitalisation for HF or CV death was consistent across eGFR categories (≥90 ml/min/1.73 m^2, ≥60 to <90 ml/min/1.73 m^2 or <60 ml/min/1.73 m^2; p value for interaction=0.37; Figure 18).[84] The positive treatment effect of dapagliflozin on the renal-specific composite endpoint of a sustained decline in eGFR ≥40%, ESKD, or death from renal causes was also consistent across eGFR categories (p value for interaction=0.87), as was the reduction in the cardiorenal composite endpoint of a sustained decline in eGFR ≥40%, ESKD, or death from renal or CV causes (p value for interaction=0.97).[101] These results demonstrate that the treatment benefit of dapagliflozin on renal and CV events extends to patients in higher eGFR categories than those enrolled in DAPA-CKD.

Figure 18: Relevant subgroup analyses from the DECLARE-TIMI 58 study

Patient subgroup	Dapagliflozin n/N	Placebo n/N	HR (95% CI)	p-value (interaction)
Co-primary endpoint				
eGFR ≥ 90 ml/min/1.73m²	163/4137	163/4025	0.96 (0.77-1.19)	
eGFR ≥60 to <90 ml/min/1.73m²	199/3838	252/3894	0.79 (0.66-0.95)	0.37
eGFR < 60 ml/min/1.73m²	55/606	81/659	0.78 (0.55-1.09)	
Overall	**417/8581**	**496/8578**	**0.84 (0.74-0.96)**	
Renal endpoint				
eGFR ≥ 90 ml/min/1.73m²	41/4137	79/4025	0.50 (0.34-0.73)	
eGFR ≥60 to <90 ml/min/1.73m²	65/3838	121/3894	0.54 (0.40-0.73)	0.87
eGFR < 60 ml/min/1.73m²	21/606	38/659	0.60 (0.35-1.02)	
Overall	**127/8581**	**238/8578**	**0.53 (0.43-0.66)**	
Cardiorenal endpoint				
eGFR ≥ 90 ml/min/1.73m²	135/4137	164/4025	0.79 (0.63-0.99)	
eGFR ≥60 to <90 ml/min/1.73m²	182/3838	240/3894	0.76 (0.63-0.93)	0.97
eGFR < 60 ml/min/1.73m²	53/606	76/659	0.77 (0.54-1.09)	
Overall	**370/8581**	**480/8578**	**0.77 (0.68-0.89)**	

Footnotes: Co-primary endpoint: hospitalisation for HF or CV death. Renal endpoint: ≥40% sustained eGFR decline, ESKD, renal death. Cardiorenal endpoint: ≥40% sustained eGFR decline, renal death, ESKD, CV death.
Abbreviations: CI: confidence interval; CV: cardiovascular; ESKD: end-stage kidney disease; eGFR: estimated glomerular filtration rate; HF: heart failure; HR: hazard ratio.
Sources: Mosenzon et al. 2019;[101] Wiviott et al. 2018.[84]

Subgroup analyses of the DAPA-HF trial also demonstrate the consistency of the treatment effect of dapagliflozin across eGFR categories (p value for interaction=[redacted]). The significant reduction in the secondary endpoint of hospitalisation for HF or CV death observed in the overall population was consistent across eGFR categories, with point estimates indicating treatment benefit in all subgroups (Figure 19). This provides further evidence of the positive CV treatment effect of dapagliflozin across a wide range of eGFR levels.

Figure 19: Subgroup analyses by eGFR classification from the DAPA-HF study

Footnotes: Primary endpoint: hospitalisation for HF, urgent HF visit or CV death.
Abbreviations: CI: confidence interval; CV: cardiovascular; eGFR: estimated glomerular filtration rate; HF: heart failure; HR: hazard ratio.
Sources: AstraZeneca Data on File 2021f: Post-hoc subgroup analysis of DAPA-HF.[110]

The treatment effect of dapagliflozin is consistent regardless of background therapy

The DAPA-CKD trial enrolled patients who were receiving an optimised dose of an ACE inhibitor or ARB unless contraindicated (at randomisation, 3.0% of patients were not receiving an ACE inhibitor or an ARB).[96] In clinical practice, dapagliflozin is expected to be used in addition to optimised SOC, which may or may not include an ACE inhibitor or ARB, as these medications are not recommended in all patients with CKD and may not be tolerated by some patients.[67] Given that the haemodynamic mechanisms by which SGLT2 inhibitors act are thought to be both distinct and complementary to ACE inhibitors or ARBs (i.e. RAAS inhibition), the treatment effect of dapagliflozin is likely to be similar irrespective of background therapy with ACE inhibitors or ARBs.[7] The significant treatment benefit observed in the DAPA-CKD trial is therefore expected to extend to patients who are not receiving ACE inhibitor or ARB therapy, and this is supported by subgroup analyses of the DECLARE-TIMI 58 and DAPA-HF trials.

In DECLARE-TIMI 58, the treatment effect of dapagliflozin on the co-primary endpoint, renal-specific composite endpoint and cardiorenal composite endpoint was consistent in patients receiving or not receiving ACE inhibitor or ARB therapy at baseline, as shown in Figure 20.

Figure 20: Relevant subgroup analyses from the DECLARE-TIMI 58 study

Footnotes: Co-primary endpoint: hospitalisation for HF or CV death. Renal endpoint: ≥40% sustained eGFR decline, ESKD, renal death. Cardiorenal endpoint: ≥40% sustained eGFR decline, renal death, ESKD, CV death.

Abbreviations: ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker; CV: cardiovascular; ESKD: end-stage kidney disease; eGFR: estimated glomerular filtration rate; HF: heart failure; HR: hazard ratio.
Sources: AstraZeneca Data on File 2021e: Post-hoc subgroup analyses of DECLARE-TIMI 58[108]

The positive treatment effect of dapagliflozin versus placebo observed in the DAPA-HF trial on the secondary composite endpoint of hospitalisation for HF or CV death was also consistent regardless of background therapy. Treatment benefit was observed in subgroups of patients receiving or not receiving ACE inhibitor or ARB therapy at baseline (Figure 21; p value for interaction=[redacted]).[110]

Figure 21: Subgroup analyses by background therapy from the DAPA-HF study

Footnotes: Primary endpoint: hospitalisation for HF, urgent HF visit or CV death.
Abbreviations: ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker; CV: cardiovascular; ESKD: end-stage kidney disease; eGFR: estimated glomerular filtration rate; HF: heart failure; HR: hazard ratio.
Source: AstraZeneca Data on File 2021f: Post-hoc subgroup analysis of DAPA-HF.[110]

There is a wealth of evidence that supports the use of dapagliflozin in the full population specified by the expected marketing authorisation: adults with CKD

In summary, there is considerable evidence for the effectiveness of dapagliflozin in reducing progression of CKD, hospitalisation for HF and CV and renal mortality in patients with CKD outside of the DAPA-CKD study eligibility criteria. Treatment with dapagliflozin is likely to benefit patients with CKD across a broad range of eGFR and uACR categories, and regardless of ACE inhibitor or ARB background therapy, [redacted].

B.2.13.3 Strengths and limitations of the clinical evidence base for the technology

DAPA-CKD was a well-conducted trial which enrolled patients with a range of comorbidities

DAPA-CKD was a large (n=4,304), phase III, double-blind, placebo-controlled RCT which enrolled a patient population with a broad range of comorbidities (including patients with and without comorbid T2DM). Patient characteristics were generally balanced between treatment groups for demographics, disease severity and background therapy.[73]

The outcome measures selected were those most relevant to CKD, including CKD progression, CV and renal death, with a composite of these outcomes selected as the primary efficacy measure. This composite primary outcome was based on guidance from the EMA, who have previously described a composite endpoint of a sustained decline of ≥50% in eGFR, onset of ESKD and death from renal causes as an acceptable outcome measure. CV mortality was also included in the primary endpoint due to the high risk of CV death in this population and the correlation between CV death and risk of developing ESKD; CV mortality is therefore a

competitive risk component and dapagliflozin was expected to have a beneficial effect on both CV death and renal outcomes.[97, 111]

The trial was stopped early due to overwhelming efficacy associated with dapagliflozin

As discussed in Section B.2.3.7, the DAPA-CKD trial was stopped early based on a determination of overwhelming efficacy by the independent data monitoring committee. This may have reduced the power of the trial; there were a total of 509 primary endpoint events versus the originally planned 681 primary endpoint events. However, the treatment effect of dapagliflozin on the primary endpoint was unequivocal and had clearly been established over a period of time; a post hoc sensitivity analysis of the primary endpoint using an earlier censoring date (26th February 2020, compared with 3rd April 2020 for the primary analysis) demonstrated consistent results with the primary analysis (HR: [redacted]).
[redacted].[94]

Differences between background therapies administered during the DAPA-CKD trial compared with UK clinical practice are unlikely to influence the generalisability of the trial results

As discussed in Section B.2.5.1 and Section B.2.13.2, the higher proportion of patients enrolled in the DAPA-CKD trial receiving ACE inhibitor or ARB background therapy compared with UK clinical practice is not anticipated to affect the generalisability of the DAPA-CKD trial results. SGLT2 inhibition acts through distinct and complementary mechanisms to ACE inhibitors or ARBs (i.e. RAAS inhibition), and as such the treatment effect of dapagliflozin is likely to be similar irrespective of background therapy with ACE inhibitors or ARBs.[7] This is supported by subgroup analyses of the DECLARE-TIMI 58 and DAPA-HF trials, which indicate that the treatment effect of dapagliflozin is consistent regardless of ACE inhibitor or ARB background therapy.[84, 112] Dapagliflozin may be associated with an even greater absolute treatment benefit over and above SOC in clinical practice compared with the DAPA-CKD trial, as lower rates of ACE inhibitor and ARB use may result in higher overall event rates than were observed in the DAPA-CKD trial population (Section B.2.5.1).

In addition, UK clinical GPs and nephrologists also indicated that the higher proportion of patients in DAPA-CKD receiving an ARB rather than an ACE inhibitor compared with UK clinical practice is unlikely to affect the generalisability of the results, as the efficacy of these therapies is seen as interchangeable between classes (Section B.2.5.1). The use of statins and antiplatelets in DAPA-CKD was generally aligned to that seen in UK clinical practice.[34, 96]

The efficacy of dapagliflozin is not expected to differ in populations of different ethnicities

Analysis of the UK CPRD found that amongst patients with CKD in the UK, [redacted]% were White, [redacted]% were Black or African American, and [redacted]% were listed as “Other” ethnicity.[34] Feedback from UK clinical GPs and nephrologists indicated that the proportion of the DAPA-CKD trial population that was Black or South Asian (Indian) was smaller than would be expected in UK clinical practice (4.0–4.8% and [redacted]%, respectively).[67] However subgroup analyses of DAPA-CKD by race demonstrated a consistent treatment effect for dapagliflozin across ethnicities, and feedback from UK clinical experts indicates that this would not result in a significantly different treatment effect in clinical practice, as discussed in Section B.2.5.1.[67, 73]

Considerable evidence outside of the DAPA-CKD trial population supports the use of dapagliflozin [redacted]

The DAPA-CKD trial provides strong evidence that patients with CKD with an eGFR of 25–75 ml/min/1.73 m^2 and a uACR of 200–5,000 mg/g (22.6–565 mg/mmol) receiving a stable dose of an ACE inhibitor or ARB (unless contraindicated) would receive a significant treatment benefit from dapagliflozin. There is also considerable evidence that a broader population of patients with CKD who fall outside of these criteria would benefit from treatment with dapagliflozin (please refer to Section B.2.13.2). The evidence available to support the use of dapagliflozin is therefore aligned with the anticipated [redacted].

B.3 Cost effectiveness

Summary of cost-effectiveness

- A cost-utility model was developed to estimate the cost-effectiveness of dapagliflozin in addition to SOC versus SOC alone for the treatment of adult patients with CKD
- The model was a Markov cohort model with health states based on CKD stages 1, 2, 3a, 3b, 4 and 5 and need for dialysis or kidney transplant (renal replacement therapy)
- Baseline characteristics were informed by data from the CPRD to reflect the CKD population in UK clinical practice. Clinical evidence for the efficacy of dapagliflozin plus SOC and placebo plus SOC were derived directly from the DAPA-CKD trial, and applied in the cost-effectiveness model as transition probabilities, survival equations and risk equations
- Health state utility values and clinical event disutility values were predominantly derived from the DAPA-CKD trial and supplemented with values from the literature
- The analysis was consistent with the NICE reference case and took a National Health Service (NHS) and Personal Social Services (PSS) perspective. Costs and benefits were discounted at a rate of 3.5% and a lifetime time horizon was adopted
- In the deterministic base case economic analysis, treatment with dapagliflozin, compared with placebo, as an add-on therapy to SOC was associated with increased life years (+1.007 per patient), increased QALYs (+0.769 per patient), at an incremental cost of £5,118 per patient. As a result, dapagliflozin as add-on therapy to SOC was highly cost-effective compared with placebo, with an ICER of £6,655/QALY gained
- The probabilistic cost-effectiveness analysis results were similar to the deterministic base case results, demonstrating that the cost-effectiveness of dapagliflozin is robust to any uncertainties associated with model input parameters. The probabilistic sensitivity analysis (PSA) showed that the probabilities of cost-effectiveness for dapagliflozin at willingness-to-pay thresholds of £20,000/QALY and £30,000/QALY gained were 99.9% and 100%, respectively
- The key drivers of the deterministic sensitivity analysis were the model time horizon and the discount factor for costs, but overall dapagliflozin remained highly cost-effective compared with placebo with ICERs below £11,000/QALY gained in all deterministic sensitivity analysis scenarios
- The scenario analyses also demonstrated the cost-effectiveness analysis to be robust and dapagliflozin consistently remained highly cost-effective in all scenarios. Specifically, scenario analyses in patient subgroups with comorbid T2DM, with comorbid CVD, and without comorbid T2DM and without comorbid CVD, and patient subgroups by uACR levels showed the cost-effectiveness of dapagliflozin to be consistent across all subgroups, with the ICERs in all subgroups and scenario analyses remaining below £7,000/QALY gained
- In summary, the cost-effectiveness analysis showed dapagliflozin to represent a highly cost-effective use of NHS resources, as an add-on therapy to SOC for the treatment of adults with CKD

B.3.1 *Published cost-effectiveness studies*

An SLR was conducted in October 2020 to identify published UK economic evaluations assessing the cost-effectiveness of CKD treatments for stage 2–4 CKD. A PRISMA flow diagram detailing studies that were included and excluded at each stage of the SLR is provided in Figure 6 in Appendix G. Full details of the SLR search strategy, study selection process and results are presented in Appendix G.

MEDLINE, Embase, the Health Technology Assessment Database (HTAD), and NHS Economic Evaluation Database (NHS EED) were searched, in addition to hand searching of relevant Health Technology Assessment (HTA) body websites, economic websites and conference records. Records were eligible for inclusion if they reported a novel economic evaluation assessing the cost-effectiveness of a treatment for stage 2–4 CKD, or the cost-effectiveness of treatment for a complication of CKD, in which the economic evaluation also modelled the progression of CKD. All included economic evaluations took a UK payer perspective.

Overall, 5,592 unique records were identified in the SLR database searches, of which 5,501 were excluded following abstract review and a further 82 records were excluded following full text review. Hand-searching found an additional 3,502 records, of which 3,494 records were excluded following review, meaning 8 records were ultimately included from hand-search results. A total of 17 publications reporting on 16 unique economic evaluations were ultimately included in the SLR as relevant to UK clinical practice.

B.3.1.1 Summary of the cost-effectiveness studies relevant to UK clinical practice

A full list of the included economic evaluations studies can be found in Tables 28 and 30 of Appendix G. Of the 16 economic evaluations included in the SLR as relevant to UK clinical practice, eight were Markov models,[113-120] four were patient simulation models,[121-125] three were decision trees followed by Markov models,[126-128] and in one study the model type was not reported.[129] Seven studies included in the SLR directly assessed the cost-effectiveness of a treatment for stages 2–4 CKD, including one assessing dapagliflozin for the treatment of patients with CKD,[113] and another assessing canagliflozin for the treatment of patients with diabetic kidney disease.[121] Two further studies identified assessed the use of tolvaptan in patients with autosomal dominant polycystic kidney disease and CKD.[114, 124] One identified study assessed the value of enabling the use of RAAS inhibitor therapy by maintaining normokalaemia in CKD patients.[123] Additionally, two of the identified studies assessed the cost-effectiveness of hypertensive therapies in patients with nephropathy and hypertension, including losartan-based regimens, irbesartan, and amlodipine, assessing how the use of these therapies may delay progression to ESKD.[117, 129]

The remaining nine studies included in the SLR modelled CKD progression, but assessed the cost-effectiveness of treatments for complications of CKD. These studies are of relevance to this submission, although the evaluations do not consider the full population of the decision problem. Three included studies assessed a treatment for hyperkalaemia in patients with CKD, evaluating the enablement of RAAS inhibitor therapy through the use of potassium binders.[115, 118, 125] Three of the identified studies assessed the cost-effectiveness of a treatment for hyperphosphataemia, with two evaluating lanthanum carbonate, and one assessing sevelamer.[120, 127, 128]

A further study included in the SLR assessed the cost-effectiveness of the DyeVert™ PLUS EZ system to avoid AKI in patients with stage 3 or 4 CKD, undergoing diagnostic coronary angiography (DAG) and/or percutaneous coronary intervention (PCI).[126] Another study assessed the costs of cholesterol lowering agents statin/ezetimibe in patients with CKD,[119]; and finally one study compared the cost-effectiveness of paricalcitol to alfacalcidol in patients with CKD and secondary hyperparathyroidism.[116, 119]

As mentioned above, only one economic evaluation identified by the SLR evaluated the cost-effectiveness of dapagliflozin in patients with CKD in the UK.[113] This model was developed by AstraZeneca and was therefore further adapted to address the decision problem of the current appraisal, as described in Sections B.3.2–B.3.6.

B.3.2 *Economic analysis*

As described above, the economic evaluation of dapagliflozin in patients with CKD identified in the SLR and originally developed by AstraZeneca was adapted to address the decision problem of the current appraisal.[113] The modelling approach and model structures of other previously published cost-effectiveness models, the majority of which were Markov models, were considered during the adaptation of the dapagliflozin cost-effectiveness model for this appraisal.

A Markov model approach was considered appropriate for this appraisal, as a Markov model is able to sufficiently account for the patient heterogeneity of CKD patients using mutually exclusive health states. The decision to use a Markov model for this appraisal is in line with the ISPOR State-Transition Modelling Task Force report, which states that Markov cohort models are preferred over individual patient simulation models for their transparency, efficiency, ease of debugging, and the ability to conduct value-of-information analyses, when a manageable number of health states are able to incorporate all the characteristics relevant to the decision problem.[130]

A model validation exercise was carried out by independent health economists to critically appraise the model conceptualisation, alignment with the NICE reference case, and the transparency of the model.[131] As part of this model validation, a model replication exercise was carried out, which concluded that a Markov model was sufficient to account for patient heterogeneity and generated results that were comparable to a microsimulation model.[131]

Finally, the model was conceptualised and developed in close collaboration with [redacted], who provided clinical expert input on the model design and modelled outcomes (see Section B.3.10.1). [redacted] provided health economic guidance on the model design.

B.3.2.1 Patient population

The base case cost-effectiveness analysis evaluated the cost-effectiveness of dapagliflozin in adult patients with CKD, [redacted] in line with the NICE final scope of this appraisal. Subgroup analyses were also conducted, including subgroups of patients with comorbid T2DM at baseline, with comorbid CVD at baseline, without comorbid T2DM and without comorbid CVD at baseline, and subgroups by uACR levels at baseline (see Section B.3.8.3), to demonstrate the consistency in cost-effectiveness of dapagliflozin across the full CKD population.

B.3.2.2 Model structure

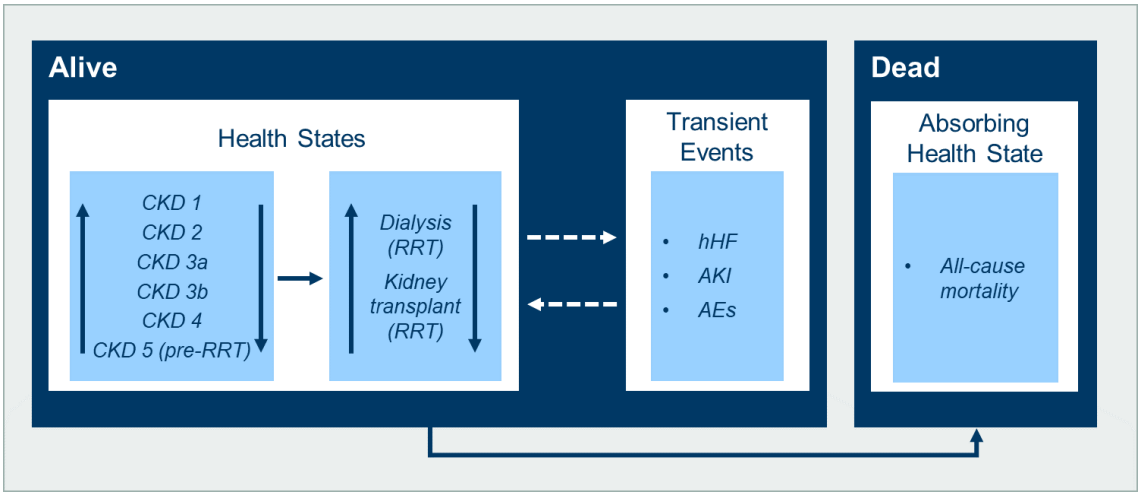
The dapagliflozin cost-effectiveness model is a cohort Markov model (Figure 22), with disease progression modelled as transitions between mutually exclusive and exhaustive health states based on CKD stage and need for dialysis or kidney transplant (collectively termed renal replacement therapy). The CKD stages 1, 2, 3a, 3b, 4 and 5 were defined by eGFR levels, using the same thresholds as in NICE clinical guidelines for the management of CKD (see Table 3 in Section B.1.3.1).[14, 16] Time-variant transitions between CKD stages were derived from DAPA-CKD, the pivotal trial for dapagliflozin in this indication, and supplemented by transition probabilities from the literature for transitions between dialysis and kidney transplant (see Section B.3.3.1.2).

The model captured the incidence of hospitalisation for HF and AKI in each of the health states as transient clinical events, using generalised estimated equations derived from individual patient-level data (IPD) from DAPA-CKD (see Sections B.3.3.1.4 and B.3.3.1.5). All-cause mortality in each of the health states was estimated using a parametric survival equation, derived from IPD from DAPA-CKD (see Section B.3.3.1.3). Annual probabilities of AEs were applied to estimate the number of AEs in the model.

Patients receiving dapagliflozin within the model had a per-cycle probability of discontinuing treatment with dapagliflozin due to tolerability or other reasons, based on rates of treatment discontinuation observed in the DAPA-CKD trial (see Section B.3.3.1.7). Patients discontinuing treatment with dapagliflozin experienced the same transient clinical event rates, AE rates, mortality rates and transition probabilities as patients receiving placebo.

CKD is a chronic disease associated with an increased risk of mortality. As such, the model incorporated a lifetime time horizon in line with the NICE Methods Guide, in order to capture all relevant costs and outcomes. The cycle length of the model was 1 month, to provide sufficient granularity to capture all relevant costs and outcomes, and a half-cycle correction was applied.

Figure 22: Markov model structure, health states and events



Abbreviations: AE: adverse event; AKI: acute kidney injury; CKD: chronic kidney disease; hHF: hospitalisation for, heart failure; RRT: renal replacement therapy.

The key features of the cost-effectiveness analysis are summarised in Table 21. As NICE have not previously conducted any appraisals in CKD, Table 21 summarises the economic analysis for dapagliflozin only.

Table 21: Features of the economic analysis

Factor	Current appraisal	
	Chosen approach	Justification
Model structure	Cohort Markov model, with health states by CKD stages	Cohort Markov models have frequently been used in previous CKD cost-effectiveness studies.[113-120] The mutually exclusive health states are sufficient in capturing the heterogeneity between CKD patients as distinct health states. Cohort Markov models also have the advantage of being more transparent and having short run-times compared to individual patient simulations.
Time horizon	Lifetime	CKD is a chronic disease; treatments for CKD have an impact on costs and outcomes over a patient's lifetime.
Treatment waning effect?	No	No treatment waning effect was identified in the DAPA-CKD trial and a sustained treatment effect is supported by the continual separation of the KM curves from the trial. Similarly, no treatment waning effect has been identified in previous trials of dapagliflozin for the treatment of T2DM, T1DM and HF.
Source of utilities	DAPA-CKD trial	As per NICE Methods Guide
Source of costs	Costs related to NHS and PSS resources were valued using prices relevant to the NHS and PSS; other cost inputs were informed by systematic and targeted literature reviews	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; HF: heart failure; KM: Kaplan Meier; NHS: National Health Service; NICE: National Institute For Health And Care Excellence; T1DM: type 1 diabetes mellitus; T2DM: type 2 diabetes mellitus; PSS: personal social services; QALY: quality adjusted life-year.

B.3.2.3 Intervention technology and comparators

This cost-effectiveness model evaluates the use of dapagliflozin in addition to optimised SOC for the treatment of patients with CKD, [redacted] in line with the NICE final scope. The relevant comparator to dapagliflozin as add-on therapy to SOC is established clinical management without dapagliflozin (i.e. optimised SOC alone) in line with the NICE final scope and based on the DAPA-CKD trial design where dapagliflozin was compared with placebo as add-on therapy to SOC.

As discussed in Section B.1.3.3, canagliflozin is not widely used for the treatment of CKD in patients with comorbid T2DM in UK clinical practice.[67, 71] As such, canagliflozin has not been included as a comparator in the base case cost-effectiveness analysis. This approach is in line with the NICE final scope, which does not include canagliflozin as a comparator. However, for completeness, canagliflozin has been included as a comparator in a scenario analysis (see Section B.3.8.3).

B.3.3 *Clinical parameters and variables*

B.3.3.1 Incorporation of clinical data into the model

B.3.3.1.1 Baseline characteristics

As discussed in Section B.2.5.1, UK GPs and nephrologists stated that the DAPA-CKD trial was generally representative of UK clinical practice, with the exception of the proportion of Black/African American and South Asian (Indian) patients in the study, which was considered to be lower than in UK clinical practice in certain regions.[67] However, the clinical experts did not expect the relative treatment effect of dapagliflozin versus placebo to be different in these patients, based on the subgroup analysis by ethnicity. Moreover, the UK clinical experts explained that Afro-Caribbean and Southern Asian patients typically have faster disease progression and higher clinical event rates compared to Caucasian patients.[67] This means that the absolute risk reduction associated with dapagliflozin in these patients is likely to be greater. Some clinical experts also commented on the slightly younger age and better controlled blood pressure in the DAPA-CKD trial compared with UK clinical practice.[67] This also suggests that the clinical event rates in UK clinical practice are likely to be higher than those observed in the DAPA-CKD trial, further supporting a greater absolute risk reduction in clinical practice.

To improve the generalisability of the cost-effectiveness results to UK clinical practice, the baseline characteristics of the base case analysis were based on patient characteristics from patients with stage 1–4 CKD in the CPRD (Table 22).[34] The use of these baseline characteristics with the fully adjusted survival and risk equations, which incorporate patient characteristics as covariables, aims to address the slight discrepancies in baseline characteristics between the DAPA-CKD trial and UK clinical practice, as identified by UK clinical GPs and nephrologists, and to ensure the modelled events rates are representative of CKD patients in UK clinical practice.

The baseline characteristics include the proportion of patients in each of the CKD, dialysis and transplant health states, and therefore determined the initial distribution of patients in the Markov model.

Scenario analyses were conducted using alternative baseline characteristics, including those from the DAPA-CKD overall population, subgroups of DAPA-CKD, and subgroups of the CPRD dataset. The baseline characteristics used for these scenario analyses are presented in Section B.3.8.3.

Table 22: Patient baseline characteristics

Characteristic	Overall CKD population (CPRD)	
	Mean	SE
Patient characteristics		
Age (years)	[redacted]	[redacted]

Female	[redacted]	[redacted]
BMI (kg/m^2)	[redacted]	[redacted]
Race: White	[redacted]	[redacted]
Race: Black or African American	[redacted]	[redacted]
Race: Other	[redacted]	[redacted]
Smoker	[redacted]	[redacted]
Clinical characteristics		
CKD 1	[redacted]	[redacted]
CKD 2	[redacted]	[redacted]
CKD 3a	[redacted]	[redacted]
CKD 3b	[redacted]	[redacted]
CKD 4	[redacted]	[redacted]
CKD 5 (pre-RRT)	[redacted]	[redacted]
Dialysis	[redacted]	[redacted]
Transplant	[redacted]	[redacted]
uACR: <30 mg/g (3.39 mg/mmol)	[redacted]	[redacted]
uACR: 30–300 mg/g (3.39–33.9 mg/mmol)	[redacted]	[redacted]
uACR: ≥300 mg/g (33.9 mg/mmol)	[redacted]	[redacted]
T2DM	[redacted]	[redacted]
Glomerulonephritis	[redacted]	[redacted]
ACE inhibitor	[redacted]	[redacted]
ARB	[redacted]	[redacted]
MRA	[redacted]	[redacted]
Diuretic	[redacted]	[redacted]
Potassium (mmol/L)	[redacted]	[redacted]
Systolic blood pressure (mmHg)	[redacted]	[redacted]
Haemoglobin (g/dL)	[redacted]	[redacted]
History		
Prior HF	[redacted]	[redacted]
Prior MI	[redacted]	[redacted]
Prior stroke	[redacted]	[redacted]

Footnote: Variables reported in the table are proportions unless otherwise stated.
Abbreviations: ACE: angiotensin converting enzyme; ARB: angiotensin II receptor blocker; BMI: body mass index; CKD: chronic kidney disease; CPRD: clinical practice research datalink; HF: heart failure; MI: myocardial infarction; MRA: mineralocorticoid receptor antagonist; RRT: renal replacement therapy; uACR: urine albumin creatinine ratio; SE: standard error; T2DM: type 2 diabetes mellitus.
Source: AstraZeneca Data on File 2021b: REF-109687 (CPRD Analysis).[34]

B.3.3.1.2 Health state transitions

Treatment-specific transition probabilities between CKD stages and progression from CKD stages to dialysis or kidney transplant were derived from the DAPA-CKD trial, using monthly transition count data, assuming last observation carried forward (i.e. patients were assumed to remain in a CKD stage until an observation indicating that they had moved). The use of treatment-specific transition probabilities is justified by the statistically significant difference in the endpoint of sustained decline in eGFR of ≥50% (component of primary endpoint) between the

dapagliflozin arm and the placebo arm of the DAPA-CKD trial, which provides direct evidence on the treatment effect of dapagliflozin on disease progression (see Section B.2.6.1).

Based on the eGFR trajectories observed in the DAPA-CKD trial, two sets of treatment-specific transition probability matrices were derived per treatment arm to represent the initial eGFR drop followed by a nominal increase in eGFR associated with dapagliflozin initiation (see Section B.2.6.3.1 for details), and to represent the long-term eGFR trajectory with a roughly linear eGFR decline over time (Figure 11). The initial set of transition probability matrices were applied to cycles 0 to 4 in the model, and the long-term set of transition probability matrices were applied from cycle 5 onwards in the model.

The transition probabilities between dialysis and kidney transplant were sourced from Sugrue et al. 2019 as there were not enough observed events in the DAPA-CKD trial to reliably derive these transition probabilities *de novo*.[132]

The transition probabilities used for dapagliflozin and placebo are shown in Table 23 and Table 24, respectively.

Table 23: Health state transition matrix – dapagliflozin

Mean (SE)		To								Reference
		CKD 1	CKD 2	CKD 3a	CKD 3b	CKD 4	CKD 5	Dialysis	Kidney transplant	
Months 0-4										
From	CKD 1	0.586 (0.076)	0.219 (0.064)	0.049 (0.033)	0.049 (0.033)	0.024 (0.024)	0.024 (0.024)	0.024 (0.024)	0.025 (0.024)	DAPA-CKD[94]
	CKD 2	0.018 (0.005)	0.709 (0.016)	0.246 (0.015)	0.019 (0.005)	0.003 (0.002)	0.003 (0.002)	0.001 (0.001)	0.001 (0.001)	
	CKD 3a	0.001 (0.001)	0.079 (0.006)	0.749 (0.009)	0.162 (0.008)	0.008 (0.002)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	
	CKD 3b	0.001 (0.000)	0.005 (0.001)	0.079 (0.004)	0.812 (0.006)	0.102 (0.005)	0.001 (0.000)	0.000 (0.000)	0.000 (0.000)	
	CKD 4	0.001 (0.001)	0.003 (0.001)	0.006 (0.002)	0.143 (0.008)	0.843 (0.008)	0.004 (0.001)	0.001 (0.001)	0.001 (0.000)	
	CKD 5	0.063 (0.060)	0.125 (0.080)	0.062 (0.058)	0.124 (0.080)	0.375 (0.118)	0.125 (0.080)	0.063 (0.059)	0.062 (0.059)	
	Dialysis	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.995 (0.100)	0.005 (0.000)	Sugrue et al. 2019[132]
	Kidney transplant	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.007 (0.001)	0.993 (0.099)	
Months 5 and onwards										
From	CKD 1	0.891 (0.017)	0.070 (0.014)	0.009 (0.005)	0.015 (0.007)	0.006 (0.004)	0.003 (0.003)	0.003 (0.003)	0.003 (0.003)	DAPA-CKD[94]
	CKD 2	0.005 (0.001)	0.909 (0.004)	0.078 (0.004)	0.006 (0.001)	0.002 (0.001)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	
	CKD 3a	0.001 (0.000)	0.025 (0.001)	0.913 (0.003)	0.059 (0.002)	0.002 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	
	CKD 3b	0.000 (0.000)	0.001 (0.000)	0.025 (0.001)	0.938 (0.002)	0.035 (0.001)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	
	CKD 4	0.000 (0.000)	0.000 (0.000)	0.001 (0.000)	0.035 (0.002)	0.952 (0.002)	0.010 (0.001)	0.001 (0.000)	0.000 (0.000)	
	CKD 5	0.001 (0.001)	0.002 (0.001)	0.002 (0.001)	0.001 (0.001)	0.027 (0.005)	0.920 (0.008)	0.045 (0.006)	0.002 (0.001)	
	Dialysis	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.995 (0.100)	0.005 (0.000)	Sugrue et al. 2019[132]
	Kidney transplant	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.007 (0.001)	0.993 (0.099)	

Abbreviations: CKD: chronic kidney disease; SE: standard error.

Table 24: Health state transition matrix – placebo

Mean (SE)		To								Reference
		CKD 1	CKD 2	CKD 3a	CKD 3b	CKD 4	CKD 5	Dialysis	Kidney transplant	
Months 0-4										
From	CKD 1	0.375 (0.084)	0.313 (0.081)	0.156 (0.064)	0.031 (0.030)	0.031 (0.030)	0.031 (0.030)	0.031 (0.030)	0.031 (0.030)	DAPA-CKD[94]
	CKD 2	0.009 (0.003)	0.770 (0.014)	0.195 (0.013)	0.016 (0.004)	0.004 (0.002)	0.002 (0.002)	0.002 (0.002)	0.001 (0.001)	
	CKD 3a	0.002 (0.001)	0.070 (0.005)	0.774 (0.009)	0.149 (0.007)	0.004 (0.001)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	
	CKD 3b	0.002 (0.001)	0.004 (0.001)	0.084 (0.005)	0.826 (0.006)	0.082 (0.005)	0.001 (0.001)	0.001 (0.000)	0.000 (0.000)	
	CKD 4	0.001 (0.001)	0.002 (0.001)	0.005 (0.002)	0.127 (0.008)	0.856 (0.009)	0.007 (0.002)	0.001 (0.001)	0.001 (0.001)	
	CKD 5	0.043 (0.041)	0.174 (0.077)	0.043 (0.042)	0.044 (0.042)	0.175 (0.077)	0.348 (0.097)	0.130 (0.068)	0.043 (0.041)	
	Dialysis	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.995 (0.100)	0.005 (0.000)	Sugrue et al. 2019[132]
	Kidney transplant	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.007 (0.001)	0.993 (0.099)	
Months 5 and onwards										
From	CKD 1	0.884 (0.020)	0.075 (0.016)	0.015 (0.007)	0.011 (0.006)	0.004 (0.004)	0.004 (0.004)	0.004 (0.004)	0.004 (0.004)	DAPA-CKD[94]
	CKD 2	0.004 (0.001)	0.915 (0.004)	0.072 (0.004)	0.008 (0.001)	0.002 (0.001)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	
	CKD 3a	0.000 (0.000)	0.023 (0.001)	0.910 (0.003)	0.064 (0.002)	0.003 (0.001)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	
	CKD 3b	0.000 (0.000)	0.001 (0.000)	0.026 (0.001)	0.931 (0.002)	0.041 (0.001)	0.000 (0.000)	0.001 (0.000)	0.000 (0.000)	
	CKD 4	0.000 (0.000)	0.001 (0.000)	0.001 (0.000)	0.028 (0.001)	0.954 (0.002)	0.014 (0.001)	0.002 (0.000)	0.000 (0.000)	
	CKD 5	0.001 (0.001)	0.001 (0.001)	0.001 (0.001)	0.002 (0.001)	0.038 (0.005)	0.910 (0.008)	0.044 (0.005)	0.003 (0.002)	
	Dialysis	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.995 (0.100)	0.005 (0.000)	Sugrue et al. 2019[132]
	Kidney transplant	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.007 (0.001)	0.993 (0.099)	

Abbreviations: CKD: chronic kidney disease; SE: standard error.

B.3.3.1.3 All-cause mortality

All-cause mortality was modelled based on methods advocated by NICE for the analysis of survival data alongside clinical trials and equation fitting and selection was carried out in line with published guidelines.[133-136] The exponential, Weibull, log-logistic, log-normal, Gompertz, generalised gamma and gamma distributions were explored.

Pre-defined subgroups of DAPA-CKD (see Section B.2.3.6 for a full list of pre-specified subgroups) were selected as candidate covariables and tested in univariable analyses to identify covariables that were likely to be predictive of all-cause mortality in the DAPA-CKD overall population. Multivariable analysis was then carried out using all covariables to assess which covariables were still influential after multivariable adjustment, the effect size of each covariable, and the clinical face validity of the directionality of the effects. Following these assessments, stepwise backward elimination based on Akaike information criterion (AIC) and p values was used to remove covariables from the fully-adjusted model that did not improve model fit. CKD stages 3a and 3b (eGFR 30–60 mL/min/1.73m^2) were pooled for analysis to increase statistical power, as there was little differentiation observed in mortality outcomes between patients with stage 3a and 3b CKD in the DAPA-CKD trial.

The survival estimates based on the Gompertz distribution had the most plausible estimates of long-term survival (Figure 23) based on clinical expert opinion and when compared with published life expectancy tables for patients with CKD from a widely-cited study in a large population-based registry in Canada.[137, 138] The goodness of fit of all survival distributions evaluated were comparable based on AIC and BIC, with the exception of the gamma distribution which had higher AIC and BIC values (Table 25). Therefore, the choice of the survival distribution for all-cause mortality was guided by long-term plausibility, and as such the Gompertz distribution was used to extrapolate long-term all-cause mortality in the base case cost-effectiveness analysis. The parameterisation of the adjusted Gompertz survival equation is summarised in Table 26.

The adjusted all-cause mortality survival equation was applied to each of the health states at the end of each model cycle to estimate the proportion of patients from each health state that transition to the absorbing dead health state.

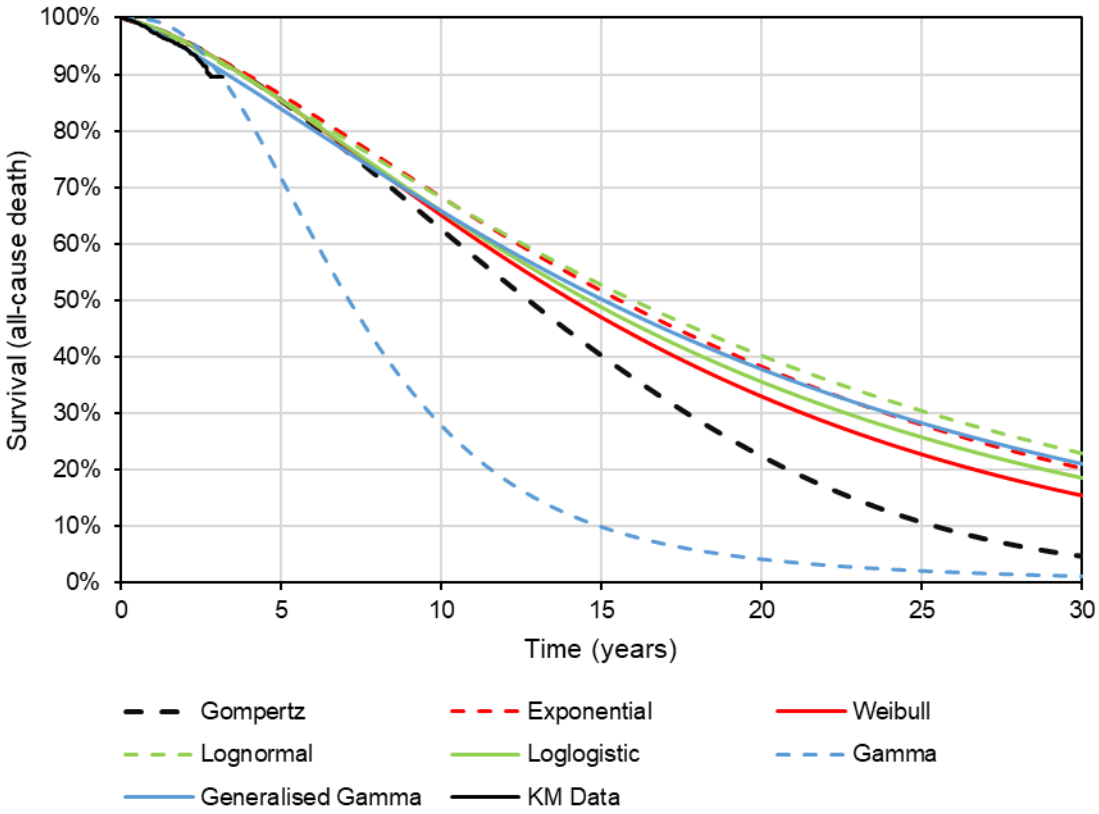
The impact of applying the exponential, Weibull, log-logistic, log-normal and generalised gamma distributions based on the extrapolation of data from DAPA-CKD were explored in scenario analyses and the parameters for these alternative survival equations are presented in Section B.3.8.3. The gamma distribution was not explored as it had a much worse goodness of fit to the trial data compared to the other survival distributions evaluated (Table 25).

Table 25: All-cause mortality survival equations goodness of fit

Distribution	AIC	BIC
Exponential	5061.10	5,236.01
Weibull	5057.33	5,241.96
Gompertz	5061.78	5,246.42
Log-logistic	5056.32	5,240.96
Log-normal	5066.77	5,251.40
Generalised gamma	5144.07	5,338.42
Gamma	5495.05	5,679.69

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion.

Figure 23: KM curve from DAPA-CKD and survival equation distributions explored



Footnote: The effect of disease progression, including the increased mortality associated with progression to dialysis and renal transplant have been captured in the survival plots above, by using CKD progression rates from the trial and mortality estimates from the literature for patients who progress to dialysis and renal transplant.
Abbreviations: KM: Kaplan Meier.

Table 26: Parameterisations of adjusted all-cause mortality survival equation – Gompertz distribution (base case)

Covariate	Coefficient	SE	p value
Shape	0.00026	0.00	0.216
Rate	0.00069	0.00	0.357
Dapagliflozin	-0.36597	0.13	0.005
Age	0.03436	0.01	<0.001
Female	-0.36049	0.14	0.012
Race: Black or African American	0.63375	0.34	0.064
Race: White	0.81962	0.20	<0.001
Race: Other	0.84351	0.25	0.001
BMI (kg/m^2)	-0.02235	0.01	0.065
eGFR <15 ml/min/1.73 m^2	1.47894	0.37	<0.001
eGFR 15–30 ml/min/1.73 m^2	0.53771	0.30	0.069
eGFR 30–60 ml/min/1.73 m^2	0.28160	0.28	0.322
Haemoglobin (g/dL)	-0.22982	0.04	<0.001
Glomerulonephritis	-0.45994	0.29	0.112

Systolic blood pressure (mmHg)	-0.00930	0.00	0.011
Potassium (mmol/L)	-0.16838	0.11	0.136
Prior HF	0.81752	0.16	<0.001
Prior MI	0.37557	0.17	0.031
Prior stroke	0.47429	0.20	0.018

Footnote: Reference category for eGFR was ≥60 ml/min/1.73m^2.
Abbreviations: BMI: body mass index; eGFR: estimated glomerular filtration rate; HF: heart failure; MI: myocardial infarction; SE: standard error.

B.3.3.1.4 Hospitalisation for heart failure

The incidence of hospitalisation for HF events were modelled using generalised estimating equations assuming that these events were Poisson-distributed in order to capture first and recurrent hospitalisation for HF events.

Pre-defined subgroups of DAPA-CKD (see Section B.2.3.6 for a full list of pre-specified subgroups) were selected as candidate covariables and tested in univariable analyses to identify covariables that were likely to be predictive of hospitalisation for HF events. Multivariable analysis was then carried out using all covariables to assess which covariables were still influential after multivariable adjustment, the effect size of each covariable, and the clinical face validity of the directionality of the effects. Following these assessments, stepwise backward elimination based on quasi-information criterion (QIC) and p values was used to remove covariables from the fully-adjusted model that did not improve model fit. As for the incorporation of all-cause mortality, CKD stages 3a and 3b (eGFR 30–60 mL/min/1.73m^2) were pooled for analysis to increase statistical power, as there was little differentiation observed in hospitalisation for HF outcomes between patients with stage 3a and 3b CKD in the DAPA-CKD trial.

The parameterisation of the adjusted generalised estimating equation for hospitalisation for HF applied in model is summarised in Table 27.

Table 27: Adjusted generalised estimating equations predicting hospitalisation for HF events

Covariate	Coefficient	SE	p value
Intercept	-11.41542	1.76	<0.001
Dapagliflozin	-0.64716	0.21	0.002
Age	0.04654	0.01	<0.001
T2DM	0.81195	0.33	0.013
BMI (kg/m^2)	0.05873	0.02	0.001
Race: Black or African American	0.41411	0.50	0.405
Race: White	0.65848	0.33	0.047
Race: Other	-0.35959	0.58	0.536
Smoking	0.48239	0.15	0.002
eGFR <15 ml/min/1.73 m^2	0.87720	0.77	0.257
eGFR 15–30 ml/min/1.73 m^2	0.85811	0.62	0.166
eGFR 30–60 ml/min/1.73 m^2	0.33567	0.59	0.573
uACR 30–300 mg/g (3.39–33.9 mg/mmol)	1.32207	1.03	0.199

uACR ≥300 mg/g (33.9 mg/mmol)	1.63788	1.01	0.106
Potassium	-0.43026	0.17	0.012
Haemoglobin	-0.15531	0.07	0.032
Prior HF	1.75096	0.23	<0.001

Footnote: Reference category for eGFR was ≥60 ml/min/1.73m^2; reference category for uACR was <30 mg/g (3.39 mg/mmol).
Abbreviations: BMI: body mass index; eGFR: estimated glomerular filtration rate; HF: heart failure; T2DM: type 2 diabetes mellitus; uACR: urine albumin creatinine ratio.

B.3.3.1.5 Acute kidney injury

The effect of dapagliflozin on AKI was evaluated in the DAPA-CKD trial as an exploratory endpoint, based on adjudicated doubling of serum creatinine compared to the most recent central laboratory measurement (see Section B.2.6.3.5). The incidence of AKI events in the cost-effectiveness model were modelled using generalised estimating equations assuming that these events were Poisson-distributed in order to capture first and recurrent AKI events.

Pre-defined subgroups of DAPA-CKD (see Section B.2.3.6 for a full list of pre-specified subgroups) were selected as candidate covariables and tested in univariable analyses to identify covariables that were likely to be predictive of AKI. Multivariable analysis was then carried out using all covariables to assess which covariables were still influential after multivariable adjustment, the effect size of each covariable, and the clinical face validity of the directionality of the effects. Following these assessments, stepwise backward elimination based on QIC and p values was used to remove covariables from the fully-adjusted model that did not improve model fit. As for all-cause mortality and hospitalisation for HF, stage 3a and 3b CKD (eGFR 30–60 mL/min/1.73m^2) were pooled for analysis to increase statistical power, as there was little differentiation observed in AKI outcomes between patients with stage 3a and 3b CKD in the DAPA-CKD trial.

The parameterisation of the adjusted generalised estimating equation for AKI applied to the model is summarised in Table 28.

Table 28: Adjusted generalised estimating equations predicting AKI events

Covariate	Coefficient	SE	p value
Intercept	-6.81785	1.10	<0.001
Dapagliflozin	-0.30783	0.16	0.054
Race: Black or African American	0.55403	0.37	0.136
Race: White	0.54789	0.21	0.010
Race: Other	0.32357	0.30	0.277
eGFR <15 ml/min/1.73 m^2	2.12615	0.40	<0.001
eGFR 15–30 ml/min/1.73 m^2	0.61858	0.37	0.091
eGFR 30–60 ml/min/1.73 m^2	0.01084	0.35	0.976
Glomerulonephritis	-0.59022	0.30	0.050
Prior MI	0.32089	0.22	0.143
Potassium	0.25111	0.14	0.081
Haemoglobin	-0.14558	0.05	0.006
Prior HF	0.76177	0.19	<0.001

Footnote: Reference category for eGFR was ≥60 ml/min/1.73m$^{2.}$
Abbreviations: eGFR: estimated glomerular filtration rate; HF: heart failure; MI: myocardial infarction.

B.3.3.1.6 Adverse events

The modelled probability of AEs were informed by the most common serious AEs reported in the DAPA-CKD trial and by the genital infections and urinary tract infections (UTIs) reported in DECLARE-TIMI 58 trial.[73, 84] Genital infection and UTI occurrences were not routinely collected in the DAPA-CKD trial, as genital infections and UTIs were not an AE of special interest. However, the incidences of genital infection and UTI were nevertheless included in the cost-effectiveness model for the proportion of patients with comorbid T2DM at baseline, based on the incidences of these AEs observed in the dapagliflozin and placebo arms of the cardiovascular outcomes trial of dapagliflozin in T2DM patients (DECLARE-TIMI 58).[84]

The annual probability of AEs modelled is summarised in Table 29. These annual probabilities were converted to monthly probabilities in the model before being applied to the monthly model cycles.

Table 29: Annual probability of AEs

AE	Mean	SE	
Dapagliflozin			
Volume depletion	[redacted]	[redacted]	DAPA-CKD[94]
Major hypoglycaemic events	[redacted]	[redacted]	
Bone fractures	[redacted]	[redacted]	
Diabetic ketoacidosis	[redacted]	[redacted]	
Amputation	[redacted]	[redacted]	
Genital infections	[redacted]	[redacted]	Calculated based on the event incidence rate in DECLARE-TIMI 58 and proportion of patients with comorbid T2DM in the base case[34, 139]
UTI	[redacted]	[redacted]	
Placebo			
Volume depletion	[redacted]	[redacted]	DAPA-CKD[94]
Major hypoglycaemic events	[redacted]	[redacted]	
Bone fractures	[redacted]	[redacted]	
Diabetic ketoacidosis	[redacted]	[redacted]	
Amputation	[redacted]	[redacted]	
Genital infections	[redacted]	[redacted]	Calculated based on the event incidence rate in DECLARE-TIMI 58 and proportion of patients with comorbid T2DM in the base case[34, 139]
UTI	[redacted]	[redacted]	

Footnote: The annual probabilities presented in this table were converted to monthly probabilities in the model before being applied to the monthly model cycles.
Abbreviations: SE: standard error; T2DM: type 2 diabetes mellitus; UTI: urinary tract infection.

B.3.3.1.7 Treatment discontinuation

The modelled rate of treatment discontinuation was derived from the DAPA-CKD trial, with a constant rate of discontinuation applied to all patients receiving treatment with dapagliflozin in each modelled cycle. Following discontinuation of dapagliflozin, patients were modelled as per

placebo-treated patients i.e. discontinued patients were subject to the same transition probabilities, event risks, mortality, costs, and utility decrements as patients in the control arm. The default annual probability of dapagliflozin treatment discontinuation was [redacted]). This annual probability of discontinuation was converted to a monthly probability in the model before being applied to the monthly cycles. Additionally, it was assumed that patients discontinued dapagliflozin when they received a kidney transplant. Once a patient discontinued dapagliflozin, it was assumed that they would not re-initiate treatment with dapagliflozin and therefore they would continue to be modelled as per placebo-treated patients until death. In the base case cost-effectiveness analysis, patients continued to receive dapagliflozin in the dialysis health state, in line with the DAPA-CKD trial protocol which allowed the use of dapagliflozin to continue after initiation of dialysis. A scenario analysis was conducted with the alternative assumption that patients discontinue dapagliflozin when they move to the dialysis health state (see Section B.3.8.3). No treatment discontinuation was modelled in the SOC arm.

B.3.4 *Measurement and valuation of health effects*

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

Health-state utility values and disutilities associated with AEs and clinical events were derived from a pooled analysis of IPD from patients in both arms of the DAPA-CKD trial.

Linear mixed effects regression models were fitted to predict patient-reported utility values derived from EQ-5D-5L questionnaires, which were collected at randomisation, Day 120, Day 240, Day 360 and thereafter every 12 months and at study closure visit or a premature treatment discontinuation visit.

Mixed effects models were used to account for repeated measures and within-patient correlation adjusted for age, sex, T2DM status, CKD stage, uACR category, hospitalisation for HF (event and history), hyperkalaemia, AKI, volume depletion, hypoglycaemia, fracture, amputation, genital infection and UTI. EQ-5D-5L responses were mapped to EQ-5D-3L applying the mapping function developed by van Hout et al. 2012,[140] in line with the NICE position statement,[141] and assuming that reported domain scores within individual questionnaires were uncorrelated. Responses were then converted to utility index scores using published UK utility values for EQ-5D health states, derived using the time trade-off method described in Dolan 1997.[142] The utility model used to inform the base case health state utilities and utility decrements associated with AEs and clinical events is presented in Table 30.

Table 30: Summary of mixed effects model used to derive patient utility decrements from DAPA-CKD

Variable	Coefficient	SE	p value
Intercept	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]
Sex: Male	[redacted]	[redacted]	[redacted]
T2DM	[redacted]	[redacted]	[redacted]
CKD stage 3	[redacted]	[redacted]	[redacted]
CKD stage 4	[redacted]	[redacted]	[redacted]
CKD stage 5	[redacted]	[redacted]	[redacted]
Dialysis	[redacted]	[redacted]	[redacted]
uACR >1,000 mg/g (113 mg/mmol)	[redacted]	[redacted]	[redacted]
Hospitalisation for HF event	[redacted]	[redacted]	[redacted]
Hospitalisation for HF history	[redacted]	[redacted]	[redacted]
Hyperkalaemia	[redacted]	[redacted]	[redacted]
AKI	[redacted]	[redacted]	[redacted]
Volume depletion	[redacted]	[redacted]	[redacted]
Hypoglycaemia	[redacted]	[redacted]	[redacted]
Fracture	[redacted]	[redacted]	[redacted]
Amputation	[redacted]	[redacted]	[redacted]
Genital infection	[redacted]	[redacted]	[redacted]
UTI	[redacted]	[redacted]	[redacted]

Footnote: The coefficients represent utility decrements, therefore, a value >0 represents and deterioration in HRQoL, and a value <0 represent an improvement in HRQoL.
Abbreviations: AKI: acute kidney injury; CKD: chronic kidney disease; HF: heart failure; HRQoL: health-related quality of life; SE: standard error; T2DM: type 2 diabetes mellitus; uACR: urine albumin creatinine ratio; UTI: urinary tract infection.
Source: AstraZeneca Data on File; DAPA-CKD Clinical Study Report.[94]

B.3.4.2 Mapping

As described above, EQ-5D-5L responses from the DAPA-CKD trial were mapped to EQ-5D-3L by applying the mapping function developed by van Hout et al. 2012,[140] in line with the NICE position statement,[141] and assuming that reported domain scores within individual questionnaires were uncorrelated.

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

An SLR was conducted in October 2020 to identify published studies reporting health state utility values for adult patients with any stage of CKD, with or without T2DM. Full details of the SLR search strategy, study selection process and results are presented in Appendix H.

MEDLINE, Embase, the HTAD, and NHS EED were searched, in addition to hand searching of relevant HTA body websites, economic websites and conference records. Records were eligible for inclusion if they reported novel health state utility data in patients with CKD, using the EQ-5D questionnaire, and used a UK value set or were set in the UK.

A total of 32 publications representing 30 unique studies and reporting health state utility values for adult patients with any stage of CKD, with or without T2DM, were ultimately included in the SLR. A full list of the included heath-state utility studies can be found in Table 36 in Appendix H. Health state utility values for the dialysis and transplant health states in the cost-effectiveness model were informed by Lee et al. 2005[55] which was identified in the SLR. Utility values identified in the SLR for pre-RRT health states were broadly in line with the health state utility values derived from DAPA-CKD, supporting the use of the health state utility values from DAPA-CKD to inform the cost-effectiveness analysis.

B.3.4.4 Adverse reactions

The DAPA-CKD trial collected data on serious AEs, AEs resulting in discontinuation of dapagliflozin and AEs of special interest, which included symptoms of volume depletion, renal events, major hypoglycaemia, bone fractures, amputations and potential DKA.[73] There were fewer renal events in the dapagliflozin arm (7.2%) compared to the placebo arm (8.7%);[73] as a conservative approach with respect to dapagliflozin, these differences in renal AEs were not modelled, to avoid double-counting with the renal efficacy endpoints and AKI endpoint already modelled.

In the base case cost-effectiveness analysis, the proportion of the cohort that was modelled to experience an AE in any given cycle incurred the relevant AE-related utility decrements. AE-related utility decrements were applied to health state utilities multiplicatively in accordance with NICE technical support document (TSD) 12.[143]

B.3.4.4.1 Volume depletion

The results from the mixed effect model of patient utilities from the DAPA-CKD trial suggested volume depletion to be associated with improved HRQoL (Table 30). Given the lack of face validity of these results, the impact of volume depletion on HRQoL in the cost-effectiveness model was instead based on the disutility of volume depletion derived from the dapagliflozin trial in patients with HFrEF (DAPA-HF, disutility: 0.051).[144] No disutility value for volume depletion could be identified from the literature. Volume depletion is the sustained reduction of extracellular volume. The impact on HRQoL is likely to be limited with mild volume depletion, as clinical symptoms only become evident with large fluid losses, potentially leading to postural dizziness, postural hypotension, fatigue, confusion, muscle cramps and chest pain.[145]

B.3.4.4.2 Major hypoglycaemic events

The results from the mixed effect model of patient utilities from the DAPA-CKD trial also suggested hypoglycaemic events to be associated with improved HRQoL (Table 30). Given the lack of face validity of these results, disutility values from the literature were used to inform the disutility associated with hypoglycaemic events in the base case cost-effectiveness analysis.

An SLR of utility values for economic modelling in T2DM by Beaudet et al. 2014[146] identified a study by Currie et al. 2006,[147] which provided disutility estimates for hypoglycaemia events. Using this study, the impact of major hypoglycaemic events was captured in the base case cost-effectiveness analysis as the disutility associated with symptomatic hypoglycaemia from Currie et al. 2006.[147] This study used a multivariate model to predict the impact of severity and frequency of hypoglycaemic events on utility values as measured by EQ-5D. The analysis was from a UK population of 1,305 patients with diabetes and a symptomatic hypoglycaemic episode was found to be associated with a 0.014 utility decrement.

Exploratory analyses in Currie et al. 2006 revealed the Hypoglycaemia Fear Survey (HFS) score to be a major predictor of EQ-5D, and the number of prior hypoglycaemic events was found to be a predictor of the HFS score. As such, as a scenario analysis (see Section B.3.8.3), the disutility associated with a change in the HFS score corresponding to a severe hypoglycaemic event (0.047) was applied to test the impact of taking fear-related disutilities for hypoglycaemia into account.

B.3.4.4.3 Bone fractures

The HRQoL decrement associated with bone fracture ([redacted]) from the mixed effect model of patient utility from the DAPA-CKD trial was applied in the base case analysis. This value is aligned with the disutility for bone fractures in the literature of 0.078 from Sullivan et al. 2016.[148] This publication provided a catalogue of disutility values for the UK, based on EQ-5D scores for diabetes-related chronic conditions, derived from a nationally representative SF-12 survey response (n=20,705) from the US which were mapped to EQ-5D-3L, and subsequently valued using UK-specific EQ-5D tariffs. The multivariate regression model included all diabetes-related comorbidities as independent variables and was controlled for two comorbidity indexes, region, age, sex, race, ethnicity, education, insurance coverage, family income and body mass index (BMI) category.

B.3.4.4.4 Diabetic ketoacidosis

There were too few DKA events in the DAPA-CKD trial for a disutility value associated with DKA events to be derived from the mixed effect model of patient utility. Instead, the literature was searched in an attempt to find an estimate of the disutility associated with DKA.

No disutility value could be identified for DKA in patients with CKD or patients with T2DM in the literature. Therefore, no disutility was applied in the base case cost-effectiveness analysis for DKA. This approach was also taken by NICE in the cost-effectiveness model informing the T1DM clinical guideline (NG17).[149]

As a scenario analysis (see Section B.3.8.3), a disutility of 0.0091 was applied for DKA, based on a study by Peasgood et al. 2016 (random-effects model).[150] This disutility value was not applied in the base case cost-effectiveness analysis, because the study did not find DKA to be a statistically significant predictor of EQ-5D in either the fixed- or random-effects models and the study reported a positive coefficient in the fixed-effects model (i.e. DKA was found to be associated with a numerical improvement in EQ-5D).

B.3.4.4.5 Amputation

The HRQoL decrement associated with amputation ([redacted]) from the mixed effect model of patient utility from the DAPA-CKD trial was applied to the base case cost-effectiveness analysis. This disutility value for amputation is comparable to the disutility for amputation in the literature. An SLR of utility values for economic modelling in T2DM by Beaudet et al. 2014[146] identified the United Kingdom Prospective Diabetes Study Group 62 (UKPDS 62) publication (Clarke et al. 2002) to provide disutility estimates for complications.[151] Data from 3,192 UKPDS respondents to the EQ-5D questionnaire were analysed using Tobit and censored least absolute deviations regression analyses to estimate the utility impact of major complications. Amputation was found to be associated with a 0.28 utility decrement. The alternative disutility value from Clarke et al. 2002 was applied to the cost-effectiveness analysis in a scenario analysis (see Section B.3.8.3).

B.3.4.4.6 Genital infections

The disutility associated with genital infection as derived from the DAPA-CKD trial was [redacted], however, this coefficient was not significant in the mixed effect model. Therefore, the literature was searched and Sullivan et al. 2016[148] (see description of study above) was identified to report a disutility value associated with genital infections of 0.049. As such, this value was used to inform the disutility associated with genital infections in the base case cost-effectiveness analysis.

B.3.4.4.7 Urinary tract infection

The disutility associated with UTI as derived from the DAPA-CKD mixed effect model ([redacted]) was applied in the base case cost-effectiveness analysis. In previous NICE appraisals of dapagliflozin in HF, T2DM and T1DM,[149, 152-156] a disutility value for UTI of 0.003 was applied based on a published economic evaluation of interventions for UTIs in women, by Barry et al. 1997.[157] As such, this alternative disutility value from Barry et al. 1997 was applied in a scenario analysis (see Section B.3.8.3).

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

B.3.4.5.1 HRQoL experienced in each health state and HRQoL decrements associated with event incidence

In the base case cost-effectiveness analysis, each of the CKD stage health states and each of the dialysis or transplant health states were associated with a utility weighting. The proportion of patients residing within each heath state in each cycle informed the accrual of QALYs over time. The impacts of hospitalisation for HF and AKI events were captured as one-off utility decrements to the proportion of patients who experienced the event, and the decrement was multiplicatively applied to the relevant CKD stage or dialysis or transplant health state utility value. Similarly, the impact of AEs was captured as one-off utility decrements to the proportion of patients who experienced the AE, in a multiplicative manner in line with NICE TSD 12.[143]

The CKD stage health state utility values were derived using a mixed effect model of patient utilities from DAPA-CKD (Table 30). It was not possible to derive health state utility values for the dialysis and transplant health states from any of the dapagliflozin clinical trials due to the small numbers of patients reaching dialysis or kidney transplant, and therefore these health state utility values were sourced from the literature. Lee et al. 2005 was identified in the HRQoL SLR (see Section B.3.4.3 and Appendix H) to provide health state utility values for peritoneal dialysis patients (0.53), haemodialysis patients (0.44), and kidney transplant patients (0.71).[55] Using these values, a weighted average health state utility value for dialysis (0.46) was calculated based on the estimated proportions of dialysis patients on peritoneal dialysis (24%) and haemodialysis (76%), and applied in the base case cost-effectiveness analysis.[158]

The disutilities associated with hospitalisation for HF ([redacted]) and AKI ([redacted]) events in the base case cost-effectiveness analysis were informed by disutility values derived from the DAPA-CKD mixed effect model of patient utilities.

B.3.4.5.2 Health effects excluded from the analysis

The base case cost-effectiveness analysis included the impact of hospitalisation for HF, AKI and AEs. No disutility value could be identified for DKA, and therefore no disutility value was included for DKA in the base case cost-effectiveness analysis. Scenario analyses were conducted with assumed disutility values for DKA, to test the sensitivity of the model to this AE disutility assumption. In addition, renal AEs were not directly modelled to avoid potential double-counting with renal efficacy endpoints and the AKI endpoint modelled, as a conservative approach with respect to dapagliflozin.

B.3.4.5.3 Cost-effectiveness model inputs

The health state utility values and the clinical event disutilities applied in the base case cost-effectiveness analysis are summarised in Table 31 alongside the source for each value.

Table 31: Summary of utility values applied to the cost-effectiveness model

	Mean	SE	Source	Reference in submission
Health state utility values				
CKD 1	[redacted]	[redacted]	DAPA-CKD[94]	B.3.4.5.1
CKD 2	[redacted]	[redacted]		B.3.4.5.1
CKD 3a	[redacted]	[redacted]		B.3.4.5.1
CKD 3b	[redacted]	[redacted]		B.3.4.5.1
CKD 4	[redacted]	[redacted]		B.3.4.5.1
CKD 5 (pre-RRT)	[redacted]	[redacted]		B.3.4.5.1
Dialysis	0.462	0.046[a]	Lee et al. 2005.[55] –NHS Blood and Transplant 2009[158]	B.3.4.5.1
Transplant	0.710	0.071[a]	Lee et al. 2005.[55]	B.3.4.5.1
Event disutility				
Hospitalisation for HF	[redacted]	[redacted]	DAPA-CKD[94]	B.3.4.5.1
AKI	[redacted]	[redacted]	DAPA-CKD[94]	B.3.4.5.1
AEs				
Volume depletion	0.051	0.012	DAPA-HF[144]	B.3.4.4.1
Major hypoglycaemic events	0.014	0.001[a]	Currie et al. 2006[147]	B.3.4.4.2
Bone fractures	[redacted]	[redacted]	DAPA-CKD[94]	B.3.4.4.3
DKA	0	0	Assumed; no evidence identified	B.3.4.4.4
Amputation	[redacted]	[redacted]	DAPA-CKD[94]	B.3.4.4.5
Genital infection	[redacted]	[redacted]		B.3.4.4.6
UTI	[redacted]	[redacted]		B.3.4.4.7

Footnote: [a]SE assumed to be 10% of the mean value.
Abbreviations: AKI: acute kidney injury; DKA: diabetic ketoacidosis; CKD: chronic kidney disease; HF: heart failure; RRT: renal replacement therapy; SE: standard error; UTI: urinary tract infection.

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

An SLR was conducted in October 2020 to identify published UK studies reporting cost and resource use data for adult patients with any stage of CKD, with or without T2DM. Full details of the SLR search strategy, study selection process and results are presented in Appendix I.

MEDLINE, Embase, the HTAD, and NHS EED were searched, in addition to hand searching of relevant HTA bodies, economic websites and conference records. Records were eligible for inclusion if they reported direct cost or resource use data relevant to a model of dapagliflozin in CKD, were published since 2015, and presented cost data specific to the UK.

A total of 34 publications on 29 unique studies were ultimately included in the SLR. A full list of the included heath-state utility studies can be found in Table 43 in Appendix I. Kent et al. 2015 was identified in the SLR and used to inform the health state costs in the cost-effectiveness analysis, as this was the only study that reported CKD management costs for CKD stages 1–5 (pre-RRT).[57]

All costs applied in the model were inflated to a 2019/20 cost-year, based on the Hospital and Community Health Services (HCHS) pay and price inflation index (up to and including 2007/08), the HCHS index (between 2008/09 and 2013/14), the New Health Services index using the consumer price index (2014/15), and the NHS Cost Inflation Index (from 2015/2016 onwards), as reported in the relevant Personal Social Services Research Unit (PSSRU) publications (Unit Costs of Health and Social Care).[159] Please see Appendix M for details of the inflation indices used.

B.3.5.1 Intervention and comparators' costs and resource use

In the base case cost-effectiveness analysis, dapagliflozin was compared with placebo as add-on therapy to SOC. As discussed in Section B.1.3.3, SOC for CKD differs by patient characteristics and comprises a range of therapies, with ACE inhibitors/ARBs recommended for patients with uACR >70 mg/mmol regardless of underlying comorbidities, and for patients with lower levels of albuminuria who have comorbidities such as HTN (recommended if uACR is >30 mg/mmol) or T2DM (recommended if uACR is >3 mg/mmol) (see Section B.1.3.3 for details).

The average annual cost for background SOC applied to the model was estimated based on data from CPRD, clinician opinion of most commonly used ACE inhibitors and ARBs, and costs from eMIT. Analyses of the UK CPRD were used to inform the proportion of patients with CKD treated with each drug class (ACE inhibitors, ARBs, statins, antiplatelets) in clinical practice.[34] The annual costs of ACE inhibitors and ARBs were calculated based on clinician opinion of the most frequently used ACE inhibitor (ramipril) and ARBs (irbesartan and losartan) in clinical practice.[67] The cost of atorvastatin was used as a representative cost for statins to calculate the annual cost of statins, and the cost of aspirin was used to calculate the annual cost of antiplatelets, as aspirin is the most commonly used antiplatelet.

The annual costs of dapagliflozin, placebo and background SOC are summarised in Table 32 and Table 33. The annual cost of canagliflozin is also included in Table 33, as canagliflozin was considered as a comparator in one of the scenario analyses.

Table 32: Calculation of weighted average cost for SOC

Therapy	Maximum daily dose, mg[a]	Pack size	Pack cost	Annual cost	% patients with CKD treated with this therapy	Weighted annual cost[b]
Ramipril	10	10 mg, 28 tablets	£0.33	£4.30	[redacted]	*Weighted average cost: £15.28*
Losartan	100	100 mg, 28 tablets	£0.72	£9.39	[redacted]	
Irbesartan	300	300 mg, 28 tablets	£2.65	£34.54		
Atorvastatin	80	40 mg, 28 tablets	£0.57	£14.86	[redacted]	
Aspirin	150	75 mg, 100 tablets	£0.47	£3.43	[redacted]	

Footnotes: [a]Based on the respective Summary of Product Characteristics. [b] Assumes a 50/50 split for irbesartan and losartan.
Abbreviations: CKD: chronic kidney disease; SOC: standard of care.
Sources: Ramipril SmPC,[24] losartan SmPC,[25] irbesartan SmPC,[26] atorvastatin SmPC,[160] aspirin SmPC,[161] eMIT 2021,[162] AstraZeneca Data on File 2021b: REF-109687 (CPRD Analysis),[34] AstraZeneca Data on File: Clinical Expert Opinion.[67]

Table 33: Annual drug costs of intervention, comparator and background SOC

Items	Annual cost	Source
Dapagliflozin (intervention)	£476.98	MIMS[12]
Placebo (comparator)	£0	Assumption
Background SOC	£15.28	See Table 32
Canagliflozin (comparator in scenario analysis)	£476.98	MIMS[163]

Footnote: The annual drug costs were converted to monthly costs in the model before being applied to the monthly model cycles.
Abbreviations: CKD: chronic kidney disease; MIMS: Monthly Index of Medical Specialities; SOC: standard of care.

B.3.5.2 Health-state unit costs and resource use

The annual health state costs and per-clinical event costs applied in the cost-effectiveness model are summarised in Table 34. These annual costs were converted to monthly costs in the model before being applied to the monthly model cycles.

The annual health state costs of each of the CKD stages were sourced from Kent et al. 2015, which evaluated the impact of CKD stage on the annual cost of hospital care.[57] The annual cost per patient was estimated by CKD stage (1-3b, stage 4 and stage 5 [pre-dialysis]).

The annual cost of dialysis was sourced from the health economics report of NICE guideline NG107 for renal replacement therapy and conservative management, which estimated the cost of dialysis to be £30,591 per patient in 2016/17.[60]

The costs associated with a kidney transplant in the first year following transplant were based on NHS reference costs 2018/19. The sum of the weighted average costs for the total Healthcare Resource Groups (HRG) for pre-transplant workup, transplant and post-transplant examination was used as the initial cost of kidney transplant. A maintenance cost for kidney transplant in

subsequent years was applied based on the cost for immune suppression reported by the NHS Blood and Transplant factsheet.[158]

The per-clinical event costs for hospitalisation for HF and AKI were calculated based on relevant NHS reference costs 2018/19.[164]

Based on interviews with UK nephrologists and GPs, the initiation and use of dapagliflozin for the treatment of CKD are not expected to require any additional appointments or tests beyond those already associated with the current management of CKD.[67] Therefore, no additional tests or appointment costs for dapagliflozin were modelled.

Table 34: Annual health state costs and per-event costs

	Mean	SE	Source
Annual health state cost			
CKD 1	£1,211.41	£52.82	Kent et al. 2015[57]
CKD 2	£1,211.41	£52.82	
CKD 3a	£1,211.41	£52.82	
CKD 3b	£1,211.41	£52.82	
CKD 4	£4,241.65	£96.45	
CKD 5 (pre-RRT)	£14,872.17	£212.43	
Dialysis	£32,360.41	£3,236.04[a]	NICE NG107[60]
Transplant (initial cost)	£27,032.64	£2,703.26 [a]	NHS Reference Costs 2018/19:[164] *Total HRG LA01A, LA02A, LA03A, LA12A, LA13A, LA11Z, LA14Z*
Transplant (maintenance cost)	£5,948.98	£594.90	NHS Blood and Transplant fact sheet 7[158]
Per-clinical event costs			
Hospitalisation for HF	£2,005.28	£200.53[a]	National Schedule of NHS Costs Year 2018/19:[164] *Non-Elective Long Stay and Non-Elective Short Stay: EB03A-E*
AKI	£1,875.63	£187.56[a]	National Schedule of NHS Costs Year 2018/19:[164] *Total HRG: LA07H/J/K/L/M/N/P, LE01A/B, LE02A/B*

Footnote: The annual costs were converted to monthly costs in the model before being applied to the monthly model cycles. [a]Where SEs were not reported in the literature, SEs were assumed to be 10% of the mean value
Abbreviations: AKI: acute kidney injury; CKD: chronic kidney disease; HF: heart failure; NHS: National Health Service; RRT: renal replacement therapy; SE: standard error.

B.3.5.3 Adverse reaction unit costs and resource use

The per-event costs applied for AEs in the base case cost-effectiveness analysis are summarised in Table 35.

The costs of treating volume depletion, UTI, and genital infection were represented by the cost of a GP visit, as it was assumed the majority of these AEs could be treated by oral rehydration therapy, antibiotics, and topical antifungals, respectively.

The cost of hypoglycaemic events was informed by Hammer et al. 2009, which surveyed the healthcare resource used by patients with T1DM and T2DM who had experienced a severe hypoglycaemic event. In UK patients with T2DM, the estimated average cost per serious hypoglycaemic event was €537. This value was converted to pounds using a conversion rate of £1.00 = €1.473 provided in the paper.[165]

The cost of bone fractures was estimated by calculating the weighted average NHS national reference cost, total HRG, for fractures in various parts of the body (HE11, HE21, HE41, HE31, HE51, and HE71).

The cost of a DKA event was estimated from Dhatariya et al. 2017, a costing study based on a national survey of UK hospitals on aspects of their care during acute hospital admissions of DKA.[166] The total cost per DKA estimated by Dhatariya et al. 2017 included costs for diagnostic and laboratory assessments, nurse and physician contacts, drug usage during the acute phase of DKA admission, and daily ward costs following resolution of DKA.[166]

The cost of amputation was informed by Alva et al. 2015, which accounted for inpatient care costs and outpatient care costs associated with amputation in the UKPDS T2DM study.[167] The study found amputation to be associated with inpatient and outpatient care costs of £9,546 and £2,699, respectively. The inpatient and outpatient care costs were summed to inform the cost of amputation in the base case cost-effectiveness analysis.[167]

Table 35: AE per-event costs

AE	Mean	SE	Source
Volume depletion	£40.10	£4.01[a]	PSSRU 2020[b] *Assume one GP visit*
Major hypoglycaemic events	£450.67	£45.07[a]	Hammer et al. (2009)[165] *Severe hypoglycaemic events, €537, conversion to Euros at rate of 1.473, uplifted from 2007 cost year to 2019/20*
Bone fractures	£2,362.87	£236.29[a]	NHS Reference Costs[164] *Total HRG, weighted average of HE11, HE21, HE41, HE31, HE51 and HE71*
DKA	£2,237.47	£211.00	Dhatariya et al. 2017[166] *£2,064 in 2014, uplifted to 2019/20 cost year*
Amputation	£13,540.96	£2,130.61	Alva et al. 2015[167] *Inpatient care cost and outpatient care cost, uplifted to 2019/20 cost year*
Genital infections	£40.10	£4.01[a]	PSSRU 2020[159] *Assume one GP visit*
UTI	£40.10	£4.01[a]	PSSRU 2020[159] *Assume one GP visit*

Footnote: [a]Where SEs were not reported in the literature, SEs were assumed to be 10% of the mean value.

Abbreviations: DKA: diabetic ketoacidosis; PSSRU: Personal Social Services Research Unit; UTI: urinary tract infection; SE: standard error.

B.3.5.4 Miscellaneous unit costs and resource use

All relevant costs have been captured in the above sections.

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

B.3.6.1 Summary of base case analysis inputs

An overview of the base case cost-effectiveness analysis inputs is provided in Table 36.

Table 36: Base case model inputs

Variable	Mean	SE	Distribution	Reference
Baseline characteristics				
Age (years)	[redacted]	[redacted]	Normal	Table 22
Female	[redacted]	[redacted]	Beta	
BMI (kg/m^2)	[redacted]	[redacted]	Normal	
Race: White	[redacted]	[redacted]	Beta	
Race: Black or African American	[redacted]	[redacted]	Beta	
Race: Other	[redacted]	[redacted]	Beta	
Smoker	[redacted]	[redacted]	Beta	
CKD 1	[redacted]	[redacted]	Beta	
CKD 2	[redacted]	[redacted]	Beta	
CKD 3a	[redacted]	[redacted]	Beta	
CKD 3b	[redacted]	[redacted]	Beta	
CKD 4	[redacted]	[redacted]	Beta	
CKD 5 (pre-RRT)	[redacted]	[redacted]	Beta	
Dialysis	[redacted]	[redacted]	Beta	
Transplant	[redacted]	[redacted]	Beta	
uACR: 30-300 mg/g (3.39–33.9 mg/mmol)	[redacted]	[redacted]	Beta	
uACR: ≥ 300 mg/g (33.9 mg/mmol)	[redacted]	[redacted]	Beta	
T2DM	[redacted]	[redacted]	Beta	
Glomerulonephritis	[redacted]	[redacted]	Beta	
ACE inhibitor	[redacted]	[redacted]	Beta	
ARB	[redacted]	[redacted]	Beta	
MRA	[redacted]	[redacted]	Beta	
Diuretic	[redacted]	[redacted]	Beta	
Potassium (mmol/L)	[redacted]	[redacted]	Normal	
Systolic blood pressure (mmHg)	[redacted]	[redacted]	Normal	
Haemoglobin (g/dL)	[redacted]	[redacted]	Normal	

Prior HF	[redacted]	[redacted]	Beta	
Prior MI	[redacted]	[redacted]	Beta	
Prior Stroke	[redacted]	[redacted]	Beta	
Health state transition probabilities – dapagliflozin (months 0–4)				
CKD 1 ->CKD 1	0.586	0.076	Beta	Table 23
CKD 1 ->CKD 2	0.219	0.064	Beta	
CKD 1 ->CKD 3a	0.049	0.033	Beta	
CKD 1 ->CKD 3b	0.049	0.033	Beta	
CKD 1 ->CKD 4	0.024	0.024	Beta	
CKD 1 ->CKD 5	0.024	0.024	Beta	
CKD 1 ->Dialysis	0.024	0.024	Beta	
CKD 1 ->Transplant	0.025	0.024	Beta	
CKD 2 ->CKD 1	0.018	0.005	Beta	
CKD 2 ->CKD 2	0.709	0.016	Beta	
CKD 2 ->CKD 3a	0.246	0.015	Beta	
CKD 2 ->CKD 3b	0.019	0.005	Beta	
CKD 2 ->CKD 4	0.003	0.002	Beta	
CKD 2 ->CKD 5	0.003	0.002	Beta	
CKD 2 ->Dialysis	0.001	0.001	Beta	
CKD 2 ->Transplant	0.001	0.001	Beta	
CKD 3a ->CKD 1	0.001	0.001	Beta	
CKD 3a ->CKD 2	0.079	0.006	Beta	
CKD 3a ->CKD 3a	0.749	0.009	Beta	
CKD 3a ->CKD 3b	0.162	0.008	Beta	
CKD 3a ->CKD 4	0.008	0.002	Beta	
CKD 3a ->CKD 5	0.000	0.000	Beta	
CKD 3a ->Dialysis	0.000	0.000	Beta	
CKD 3a ->Transplant	0.000	0.000	Beta	
CKD 3b ->CKD 1	0.001	0.000	Beta	
CKD 3b ->CKD 2	0.005	0.001	Beta	
CKD 3b ->CKD 3a	0.079	0.004	Beta	
CKD 3b ->CKD 3b	0.812	0.006	Beta	
CKD 3b ->CKD 4	0.102	0.005	Beta	
CKD 3b ->CKD 5	0.001	0.000	Beta	
CKD 3b ->Dialysis	0.000	0.000	Beta	
CKD 3b ->Transplant	0.000	0.000	Beta	
CKD 4 ->CKD 1	0.001	0.001	Beta	
CKD 4 ->CKD 2	0.003	0.001	Beta	

CKD 4 ->CKD 3a	0.006	0.002	Beta	
CKD 4->CKD 3b	0.143	0.008	Beta	
CKD 4 ->CKD 4	0.843	0.008	Beta	
CKD 4 ->CKD 5	0.004	0.001	Beta	
CKD 4 ->Dialysis	0.001	0.001	Beta	
CKD 4 ->Transplant	0.001	0.000	Beta	
CKD 5 ->CKD 1	0.063	0.060	Beta	
CKD 5 ->CKD 2	0.125	0.080	Beta	
CKD 5 ->CKD 3a	0.062	0.058	Beta	
CKD 5 ->CKD 3b	0.124	0.080	Beta	
CKD 5 ->CKD 4	0.375	0.118	Beta	
CKD 5 ->CKD 5	0.125	0.080	Beta	
CKD 5 ->Dialysis	0.063	0.059	Beta	
CKD 5 ->Transplant	0.062	0.059	Beta	
Dialysis ->CKD 1	0.000	0.000	Beta	
Dialysis ->CKD 2	0.000	0.000	Beta	
Dialysis ->CKD 3a	0.000	0.000	Beta	
Dialysis->CKD 3b	0.000	0.000	Beta	
Dialysis ->CKD 4	0.000	0.000	Beta	
Dialysis ->CKD 5	0.000	0.000	Beta	
Dialysis ->Dialysis	0.995	0.100	Beta	
Dialysis ->Transplant	0.005	0.000	Beta	
Transplant ->CKD 1	0.000	0.000	Beta	
Transplant ->CKD 2	0.000	0.000	Beta	
Transplant ->CKD 3a	0.000	0.000	Beta	
Transplant ->CKD 3b	0.000	0.000	Beta	
Transplant ->CKD 4	0.000	0.000	Beta	
Transplant ->CKD 5	0.000	0.000	Beta	
Transplant ->Dialysis	0.007	0.001	Beta	
Transplant ->Transplant	0.993	0.099	Beta	
Health state transition probabilities – placebo (months 0–4)				
CKD 1 ->CKD 1	0.375	0.084	Beta	Table 24
CKD 1 ->CKD 2	0.313	0.081	Beta	
CKD 1 ->CKD 3a	0.156	0.064	Beta	
CKD 1 ->CKD 3b	0.031	0.030	Beta	
CKD 1 ->CKD 4	0.031	0.030	Beta	
CKD 1 ->CKD 5	0.031	0.030	Beta	
CKD 1 ->Dialysis	0.031	0.030	Beta	

CKD 1 ->Transplant	0.031	0.030	Beta	
CKD 2 ->CKD 1	0.009	0.003	Beta	
CKD 2 ->CKD 2	0.770	0.014	Beta	
CKD 2 ->CKD 3a	0.195	0.013	Beta	
CKD 2 ->CKD 3b	0.016	0.004	Beta	
CKD 2 ->CKD 4	0.004	0.002	Beta	
CKD 2 ->CKD 5	0.002	0.002	Beta	
CKD 2 ->Dialysis	0.002	0.002	Beta	
CKD 2 ->Transplant	0.001	0.001	Beta	
CKD 3a ->CKD 1	0.002	0.001	Beta	
CKD 3a ->CKD 2	0.070	0.005	Beta	
CKD 3a ->CKD 3a	0.774	0.009	Beta	
CKD 3a ->CKD 3b	0.149	0.007	Beta	
CKD 3a ->CKD 4	0.004	0.001	Beta	
CKD 3a ->CKD 5	0.000	0.000	Beta	
CKD 3a ->Dialysis	0.000	0.000	Beta	
CKD 3a ->Transplant	0.000	0.000	Beta	
CKD 3b ->CKD 1	0.002	0.001	Beta	
CKD 3b ->CKD 2	0.004	0.001	Beta	
CKD 3b ->CKD 3a	0.084	0.005	Beta	
CKD 3b ->CKD 3b	0.826	0.006	Beta	
CKD 3b ->CKD 4	0.082	0.005	Beta	
CKD 3b ->CKD 5	0.001	0.001	Beta	
CKD 3b ->Dialysis	0.001	0.000	Beta	
CKD 3b ->Transplant	0.000	0.000	Beta	
CKD 4 ->CKD 1	0.001	0.001	Beta	
CKD 4 ->CKD 2	0.002	0.001	Beta	
CKD 4 ->CKD 3a	0.005	0.002	Beta	
CKD 4->CKD 3b	0.127	0.008	Beta	
CKD 4 ->CKD 4	0.856	0.009	Beta	
CKD 4 ->CKD 5	0.007	0.002	Beta	
CKD 4 ->Dialysis	0.001	0.001	Beta	
CKD 4 ->Transplant	0.001	0.001	Beta	
CKD 5 ->CKD 1	0.043	0.041	Beta	
CKD 5 ->CKD 2	0.174	0.077	Beta	
CKD 5 ->CKD 3a	0.043	0.042	Beta	
CKD 5 ->CKD 3b	0.044	0.042	Beta	
CKD 5 ->CKD 4	0.175	0.077	Beta	

CKD 5 ->CKD 5	0.348	0.097	Beta	
CKD 5 ->Dialysis	0.130	0.068	Beta	
CKD 5 ->Transplant	0.043	0.041	Beta	
Dialysis ->CKD 1	0.000	0.000	Beta	
Dialysis ->CKD 2	0.000	0.000	Beta	
Dialysis ->CKD 3a	0.000	0.000	Beta	
Dialysis->CKD 3b	0.000	0.000	Beta	
Dialysis ->CKD 4	0.000	0.000	Beta	
Dialysis ->CKD 5	0.000	0.000	Beta	
Dialysis ->Dialysis	0.995	0.100	Beta	
Dialysis ->Transplant	0.005	0.000	Beta	
Transplant ->CKD 1	0.000	0.000	Beta	
Transplant ->CKD 2	0.000	0.000	Beta	
Transplant ->CKD 3a	0.000	0.000	Beta	
Transplant ->CKD 3b	0.000	0.000	Beta	
Transplant ->CKD 4	0.000	0.000	Beta	
Transplant ->CKD 5	0.000	0.000	Beta	
Transplant ->Dialysis	0.007	0.001	Beta	
Transplant ->Transplant	0.993	0.099	Beta	
Health state transition probabilities – dapagliflozin (month 5 onwards)				
CKD 1 ->CKD 1	0.891	0.017	Beta	Table 23
CKD 1 ->CKD 2	0.070	0.014	Beta	
CKD 1 ->CKD 3a	0.009	0.005	Beta	
CKD 1 ->CKD 3b	0.015	0.007	Beta	
CKD 1 ->CKD 4	0.006	0.004	Beta	
CKD 1 ->CKD 5	0.003	0.003	Beta	
CKD 1 ->Dialysis	0.003	0.003	Beta	
CKD 1 ->Transplant	0.003	0.003	Beta	
CKD 2 ->CKD 1	0.005	0.001	Beta	
CKD 2 ->CKD 2	0.909	0.004	Beta	
CKD 2 ->CKD 3a	0.078	0.004	Beta	
CKD 2 ->CKD 3b	0.006	0.001	Beta	
CKD 2 ->CKD 4	0.002	0.001	Beta	
CKD 2 ->CKD 5	0.000	0.000	Beta	
CKD 2 ->Dialysis	0.000	0.000	Beta	
CKD 2 ->Transplant	0.000	0.000	Beta	
CKD 3a ->CKD 1	0.001	0.000	Beta	
CKD 3a ->CKD 2	0.025	0.001	Beta	
CKD 3a ->CKD 3a	0.913	0.003	Beta	
CKD 3a ->CKD 3b	0.059	0.002	Beta	

CKD 3a ->CKD 4	0.002	0.000	Beta	
CKD 3a ->CKD 5	0.000	0.000	Beta	
CKD 3a ->Dialysis	0.000	0.000	Beta	
CKD 3a ->Transplant	0.000	0.000	Beta	
CKD 3b ->CKD 1	0.000	0.000	Beta	
CKD 3b ->CKD 2	0.001	0.000	Beta	
CKD 3b ->CKD 3a	0.025	0.001	Beta	
CKD 3b ->CKD 3b	0.938	0.002	Beta	
CKD 3b ->CKD 4	0.035	0.001	Beta	
CKD 3b ->CKD 5	0.000	0.000	Beta	
CKD 3b ->Dialysis	0.000	0.000	Beta	
CKD 3b ->Transplant	0.000	0.000	Beta	
CKD 4 ->CKD 1	0.000	0.000	Beta	
CKD 4 ->CKD 2	0.000	0.000	Beta	
CKD 4 ->CKD 3a	0.001	0.000	Beta	
CKD 4->CKD 3b	0.035	0.002	Beta	
CKD 4 ->CKD 4	0.952	0.002	Beta	
CKD 4 ->CKD 5	0.010	0.001	Beta	
CKD 4 ->Dialysis	0.001	0.000	Beta	
CKD 4 ->Transplant	0.000	0.000	Beta	
CKD 5 ->CKD 1	0.001	0.001	Beta	
CKD 5 ->CKD 2	0.002	0.001	Beta	
CKD 5 ->CKD 3a	0.002	0.001	Beta	
CKD 5 ->CKD 3b	0.001	0.001	Beta	
CKD 5 ->CKD 4	0.027	0.005	Beta	
CKD 5 ->CKD 5	0.920	0.008	Beta	
CKD 5 ->Dialysis	0.045	0.006	Beta	
CKD 5 ->Transplant	0.002	0.001	Beta	
Dialysis ->CKD 1	0.000	0.000	Beta	
Dialysis ->CKD 2	0.000	0.000	Beta	
Dialysis ->CKD 3a	0.000	0.000	Beta	
Dialysis->CKD 3b	0.000	0.000	Beta	
Dialysis ->CKD 4	0.000	0.000	Beta	
Dialysis ->CKD 5	0.000	0.000	Beta	
Dialysis ->Dialysis	0.995	0.100	Beta	
Dialysis ->Transplant	0.005	0.000	Beta	
Transplant ->CKD 1	0.000	0.000	Beta	
Transplant ->CKD 2	0.000	0.000	Beta	
Transplant ->CKD 3a	0.000	0.000	Beta	
Transplant ->CKD 3b	0.000	0.000	Beta	
Transplant ->CKD 4	0.000	0.000	Beta	
Transplant ->CKD 5	0.000	0.000	Beta	
Transplant ->Dialysis	0.007	0.001	Beta	

Transplant ->Transplant	0.993	0.099	Beta	
Health state transition probabilities – placebo (month 5 onwards)				
CKD 1 ->CKD 1	0.884	0.020	Beta	Table 24
CKD 1 ->CKD 2	0.075	0.016	Beta	
CKD 1 ->CKD 3a	0.015	0.007	Beta	
CKD 1 ->CKD 3b	0.011	0.006	Beta	
CKD 1 ->CKD 4	0.004	0.004	Beta	
CKD 1 ->CKD 5	0.004	0.004	Beta	
CKD 1 ->Dialysis	0.004	0.004	Beta	
CKD 1 ->Transplant	0.004	0.004	Beta	
CKD 2 ->CKD 1	0.004	0.001	Beta	
CKD 2 ->CKD 2	0.915	0.004	Beta	
CKD 2 ->CKD 3a	0.072	0.004	Beta	
CKD 2 ->CKD 3b	0.008	0.001	Beta	
CKD 2 ->CKD 4	0.002	0.001	Beta	
CKD 2 ->CKD 5	0.000	0.000	Beta	
CKD 2 ->Dialysis	0.000	0.000	Beta	
CKD 2 ->Transplant	0.000	0.000	Beta	
CKD 3a ->CKD 1	0.000	0.000	Beta	
CKD 3a ->CKD 2	0.023	0.001	Beta	
CKD 3a ->CKD 3a	0.910	0.003	Beta	
CKD 3a ->CKD 3b	0.064	0.002	Beta	
CKD 3a ->CKD 4	0.003	0.001	Beta	
CKD 3a ->CKD 5	0.000	0.000	Beta	
CKD 3a ->Dialysis	0.000	0.000	Beta	
CKD 3a ->Transplant	0.000	0.000	Beta	
CKD 3b ->CKD 1	0.000	0.000	Beta	
CKD 3b ->CKD 2	0.001	0.000	Beta	
CKD 3b ->CKD 3a	0.026	0.001	Beta	
CKD 3b ->CKD 3b	0.931	0.002	Beta	
CKD 3b ->CKD 4	0.041	0.001	Beta	
CKD 3b ->CKD 5	0.000	0.000	Beta	
CKD 3b ->Dialysis	0.001	0.000	Beta	
CKD 3b ->Transplant	0.000	0.000	Beta	
CKD 4 ->CKD 1	0.000	0.000	Beta	
CKD 4 ->CKD 2	0.001	0.000	Beta	
CKD 4 ->CKD 3a	0.001	0.000	Beta	
CKD 4->CKD 3b	0.028	0.001	Beta	
CKD 4 ->CKD 4	0.954	0.002	Beta	
CKD 4 ->CKD 5	0.014	0.001	Beta	
CKD 4 ->Dialysis	0.002	0.000	Beta	
CKD 4 ->Transplant	0.000	0.000	Beta	
CKD 5 ->CKD 1	0.001	0.001	Beta	

CKD 5 ->CKD 2	0.001	0.001	Beta	
CKD 5 ->CKD 3a	0.001	0.001	Beta	
CKD 5 ->CKD 3b	0.002	0.001	Beta	
CKD 5 ->CKD 4	0.038	0.005	Beta	
CKD 5 ->CKD 5	0.910	0.008	Beta	
CKD 5 ->Dialysis	0.044	0.005	Beta	
CKD 5 ->Transplant	0.003	0.002	Beta	
Dialysis ->CKD 1	0.000	0.000	Beta	
Dialysis ->CKD 2	0.000	0.000	Beta	
Dialysis ->CKD 3a	0.000	0.000	Beta	
Dialysis->CKD 3b	0.000	0.000	Beta	
Dialysis ->CKD 4	0.000	0.000	Beta	
Dialysis ->CKD 5	0.000	0.000	Beta	
Dialysis ->Dialysis	0.995	0.100	Beta	
Dialysis ->Transplant	0.005	0.000	Beta	
Transplant ->CKD 1	0.000	0.000	Beta	
Transplant ->CKD 2	0.000	0.000	Beta	
Transplant ->CKD 3a	0.000	0.000	Beta	
Transplant ->CKD 3b	0.000	0.000	Beta	
Transplant ->CKD 4	0.000	0.000	Beta	
Transplant ->CKD 5	0.000	0.000	Beta	
Transplant ->Dialysis	0.007	0.001	Beta	
Transplant ->Transplant	0.993	0.099	Beta	
Annual probability of discontinuation				
Dapagliflozin	[redacted]	[redacted]	Beta	Section B.3.3.1.7
All-cause mortality survival equation – Gompertz				
Shape	0.00026	0.00	Normal	Table 26
Rate	0.00069	0.00	Normal	
Dapagliflozin	-0.36597	0.13	Normal	
Age	0.03436	0.01	Normal	
Female	-0.36049	0.14	Normal	
Race: Black or African American	0.63375	0.34	Normal	
Race: White	0.81962	0.20	Normal	
Race: Other	0.84351	0.25	Normal	
BMI (kg/m^2)	-0.02235	0.01	Normal	
eGFR <15 ml/min/1.73 m^2	1.47894	0.37	Normal	
eGFR 15–30 ml/min/1.73 m^2	0.53771	0.30	Normal	
eGFR 30–60 ml/min/1.73 m^2	0.28160	0.28	Normal	
Haemoglobin (g/dL)	-0.22982	0.04	Normal	
Glomerulonephritis	-0.45994	0.29	Normal	

Systolic blood pressure (mmHg)	-0.00930	0.00	Normal	
Potassium (mmol/L)	-0.16838	0.11	Normal	
Prior HF	0.81752	0.16	Normal	
Prior MI	0.37557	0.17	Normal	
Prior Stroke	0.47429	0.20	Normal	
Hospitalisation for HF risk equation – generalised estimating equation				
Intercept	-11.41542	1.76	Normal	Table 27
Dapagliflozin	-0.64716	0.21	Normal	
Age	0.04654	0.01	Normal	
T2DM	0.81195	0.33	Normal	
BMI (kg/m^2)	0.05873	0.02	Normal	
Race: Black or African American	0.41411	0.50	Normal	
Race: White	0.65848	0.33	Normal	
Race: Other	-0.35959	0.58	Normal	
Smoking	0.48239	0.15	Normal	
eGFR <15 ml/min/1.73 m^2	0.87720	0.77	Normal	
eGFR 15–30 ml/min/1.73 m^2	0.85811	0.62	Normal	
eGFR 30–60 ml/min/1.73 m^2	0.33567	0.59	Normal	
uACR: 30–300 mg/g (3.39–33.9 mg/mmol)	1.32207	1.03	Normal	
uACR: ≥300 mg/g (33.9 mg/mmol)	1.63788	1.01	Normal	
Potassium	-0.43026	0.17	Normal	
Haemoglobin	-0.15531	0.07	Normal	
Prior HF	1.75096	0.23	Normal	
AKI risk equation – generalised estimating equation				
Intercept	-6.81785	1.10	Normal	Table 28
Dapagliflozin	-0.30783	0.16	Normal	
Race: Black or African American	0.55403	0.37	Normal	
Race: White	0.54789	0.21	Normal	
Race: Other	0.32357	0.30	Normal	
eGFR <15 ml/min/1.73 m^2	2.12615	0.40	Normal	
eGFR 15–30 ml/min/1.73 m^2	0.61858	0.37	Normal	
eGFR 30–60 ml/min/1.73 m^2	0.01084	0.35	Normal	
Glomerulonephritis	-0.59022	0.30	Normal	
Prior MI	0.32089	0.22	Normal	
Potassium	0.25111	0.14	Normal	
Haemoglobin	-0.14558	0.05	Normal	

Prior HF	0.76177	0.19	Normal	
Annual probability of AEs – dapagliflozin				
Volume depletion	[redacted]	[redacted]	Beta	Table 29
Major hypoglycaemic events	[redacted]	[redacted]	Beta	
Bone fractures	[redacted]	[redacted]	Beta	
Diabetic ketoacidosis	[redacted]	[redacted]	Beta	
Amputation	[redacted]	[redacted]	Beta	
Genital infections	[redacted]	[redacted]	Beta	
UTI	[redacted]	[redacted]	Beta	
Annual probability of AEs – placebo				
Volume depletion	[redacted]	[redacted]	Beta	Table 29
Major hypoglycaemic events	[redacted]	[redacted]	Beta	
Bone fractures	[redacted]	[redacted]	Beta	
Diabetic ketoacidosis	[redacted]	[redacted]	Beta	
Amputation	[redacted]	[redacted]	Beta	
Genital infections	[redacted]	[redacted]	Beta	
UTI	[redacted]	[redacted]	Beta	
Health states utility values				
CKD 1	[redacted]	[redacted]	Beta	Table 31
CKD 2	[redacted]	[redacted]	Beta	
CKD 3a	[redacted]	[redacted]	Beta	
CKD 3b	[redacted]	[redacted]	Beta	
CKD 4	[redacted]	[redacted]	Beta	
CKD 5 (pre-RRT)	[redacted]	[redacted]	Beta	
Dialysis	0.462	0.046	Beta	
Transplant	0.710	0.071	Beta	
Event disutility				
Hospitalisation for HF	[redacted]	[redacted]	Beta	Table 31
AKI	[redacted]	[redacted]	Beta	
Adverse event disutility				
Volume depletion	0.051	0.012	Beta	Table 31
Major hypoglycaemic events	0.014	0.001	Beta	
Bone fractures	[redacted]	[redacted]	Beta	
DKA	0	0	Beta	
Amputation	[redacted]	[redacted]	Beta	
Genital infection	[redacted]	[redacted]	Beta	
UTI	[redacted]	[redacted]	Beta	
Annual drug costs				
Annual cost of dapagliflozin	£476.98	N/A	N/A	Table 33
Placebo (comparator)	£0	N/A	N/A	

Background SOC	£15.28	£1.53	Gamma	
Canagliflozin (comparator in scenario analysis)	£476.98	N/A	N/A	
Annual health state cost				
CKD 1	£1,211.41	£52.82	Gamma	Table 34
CKD 2	£1,211.41	£52.82	Gamma	
CKD 3a	£1,211.41	£52.82	Gamma	
CKD 3b	£1,211.41	£52.82	Gamma	
CKD 4	£4,241.65	£96.45	Gamma	
CKD 5 (pre-RRT)	£14,872.17	£212.43	Gamma	
Dialysis	£32,360.41	£3,236.04	Gamma	
Transplant (initial cost)	£27,032.64	£2,703.26	Gamma	
Transplant (maintenance cost)	£5,948.98	£594.90	Gamma	
Per event costs				
Hospitalisation for HF	£2,005.28	£200.53	Gamma	Table 34
AKI	£1,875.63	£187.56	Gamma	
AE per event costs				
Volume depletion	£40.10	£4.01	Gamma	Table 34
Major hypoglycaemic events	£450.67	£45.07	Gamma	
Bone fractures	£2,362.87	£236.29	Gamma	
DKA	£2,237.47	£211.00	Gamma	
Amputation	£13,540.96	£2,130.61	Gamma	
Genital infections	£40.10	£4.01	Gamma	
UTI	£40.10	£4.01	Gamma	

Footnote: All annual probabilities and costs were converted to monthly probabilities and costs in the model before being applied to the monthly model cycles.
Abbreviations: ACE: angiotensin converting enzyme; AE: adverse event; AKI: acute kidney injury; ARB: angiotensin II receptor blocker; BMI: body mass index; CKD: chronic kidney disease; DKA: diabetic ketoacidosis; eGFR: estimated glomerular filtration rate; HF: heart failure; MI: myocardial infarction; MRA: mineralocorticoid receptor antagonist; RRT: renal replacement therapy; T2DM: type 2 diabetes mellitus; uACR: urine albumin creatinine ratio; UTI: urinary tract infection.

B.3.6.2 Assumptions

The base case cost-effectiveness analysis estimates the cost-effectiveness of dapagliflozin versus placebo as add-on therapy to SOC in patients with CKD, based on transition probabilities, adjusted survival equations and adjusted risk equations derived from the DAPA-CKD trial.

The endpoint of ≥50% sustained eGFR decline which was a component of the composite primary endpoint was captured through treatment-specific transition probabilities. These transition probabilities were derived from IPD from DAPA-CKD, based on eGFR measurements from the trial. Similarly, the treatment effect of dapagliflozin on time to ESKD and dialysis (also components of the primary endpoint) were captured through these treatment-specific transition probabilities which results in a delayed progression to ESKD and dialysis in the dapagliflozin arm compared with placebo.

Changes in uACR were not captured in the model, and as such uACR could not be modelled as a time-updated covariable for the survival equations and risk equations in the model, despite the prognostic value of uACR.[17] Change from baseline uACR was observed in the DAPA-CKD trial as an exploratory endpoint [redacted] B.2.6.3.6 [redacted].[94] As such, the omission of explicit uACR modelling is likely to be conservative with respect to dapagliflozin, as consequences of uACR improvements beyond the trial duration would not be accounted for by the clinical endpoints modelled from the trial data, and therefore these benefits of dapagliflozin would not be captured in the current model.

Changes in patients' T2DM status overtime were not modelled, and therefore, any benefits of dapagliflozin on new onset T2DM could not be captured. Exploratory analyses of the DAPA-CKD trial show dapagliflozin [redacted].[94] Similarly, the well-established benefit of dapagliflozin on glycaemic control in patients with comorbid T2DM is not captured in the current model.[152, 154, 155]

The model assumed health state utility values to be constant with age. The coefficient for age in the mixed effects model of patient utilities from DAPA-CKD was very small ([redacted] decrement per additional year of age), and therefore was considered unlikely to have an impact on the cost-effectiveness results, especially given the relatively few total life years modelled.

The cost-effectiveness model assumed that patients continue to receive dapagliflozin as they progress to dialysis. This is in line with the DAPA-CKD trial protocol, which allowed the use of dapagliflozin to continue after initiation of dialysis. This may not be fully representative of clinical practice, as a proportion of patients may discontinue dapagliflozin at dialysis, despite the CV benefits associated with dapagliflozin. A scenario analysis was conducted to test the impact on cost-effectiveness of dapagliflozin whereby the model assumes patients discontinue dapagliflozin at initiation of dialysis.

The cost-effectiveness analysis does not model the conservative management of CKD, whereby ESKD is managed without dialysis or transplant, with the primary objective of optimising HRQoL. In UK clinical practice, only a small proportion of patients with ESKD (approximately 5%) choose conservative management.[47] Therefore, the impact of omitting conservative management from the model is unlikely to have a substantial impact on the cost-effectiveness results.

Finally, genital infections and UTIs were only modelled for the proportion of patients in the cost-effectiveness model with comorbid T2DM. This modelling approach was taken because patients with T2DM are more susceptible to these AEs, due to glucosuria and hyperglycaemia-related impairment of the immune response, leading to higher prevalence and recurrence of genital infections and UTIs in adults with T2DM compared to those without T2DM.[168, 169] Genital infections and UTIs have a negligible impact on the cost-effectiveness results, and the ICER is not expected to substantially change, even if these AEs are applied to the whole CKD patient population including those without T2DM.

B.3.7 *Base case results*

The deterministic base case cost-effectiveness analysis results of dapagliflozin compared with placebo over a lifetime horizon are summarised in Table 37. Dapagliflozin as an add-on therapy

to SOC was associated with 6.8 total QALYs and £56,526 total costs. In comparison, placebo as an add-on therapy to SOC was associated with 6.0 total QALYs and £51,408 total costs. Treatment with dapagliflozin, compared with placebo, as an add-on therapy to SOC was associated with increased life years (+1.007 per patient), increased QALYs (+0.769 per patient), at an incremental cost of £5,118 per patient. Dapagliflozin as add-on therapy to SOC was highly cost-effective compared with placebo, with an ICER of £6,655/QALY gained.

The incremental QALYs were driven by increased life years and longer duration spent in the earlier stages of CKD (stages 1–4) (Table 38). The reduction in hospitalisation for HF and AKI incidence associated with dapagliflozin versus placebo did not have a substantial impact on the incremental QALYs.

The additional costs associated with the dapagliflozin plus SOC arm were due to additional costs associated with dapagliflozin treatment (these were the main driver of the difference in costs), and additional CKD background SOC and dialysis costs due to increased life years (Table 39). There was also a small incremental cost associated with AEs with dapagliflozin. However, these additional costs were partially offset by cost-savings from reduced transplant, hospitalisation for HF and AKI costs.

Details of clinical outcomes from the base case analysis and the health state distribution over time are provided in Appendix J.

Table 37: Base case deterministic results

	Dapagliflozin + SOC (intervention)	Placebo + SOC (comparator)	Incremental	ICER (£/QALY)
Life years	9.260	8.254	1.007	£6,655
QALYs	6.800	6.031	0.769	
Costs (£)	£56,526	£51,408	£5,118	

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years; SOC: standard of care.

Table 38: Base case deterministic results – disaggregated QALYs

	Dapagliflozin + SOC (intervention)	Placebo + SOC (comparator)	Incremental
QALYs from health states			
CKD 1	0.041	0.026	0.015
CKD 2	0.524	0.470	0.054
CKD 3a	1.433	1.250	0.183
CKD 3b	2.277	1.852	0.424
CKD 4	1.690	1.593	0.097
CKD 5 (pre-RRT)	0.185	0.194	-0.009
Dialysis	0.405	0.397	0.008
Transplant	0.252	0.254	-0.003
Event disutility			
Hospitalisation for HF	0.000	0.000	0.000
AKI	-0.002	-0.003	0.000

	Dapagliflozin + SOC (intervention)	Placebo + SOC (comparator)	Incremental
AE related disutility	-0.004	-0.003	-0.001
Total QALYs			
Total QALYs	6.800	6.031	0.769

Abbreviations: AE: adverse event; AKI: acute kidney injury; CKD: chronic kidney disease; HF: heart failure; QALY: quality-adjusted life year; RRT: renal replacement therapy; SOC: standard of care.

Table 39: Base case deterministic results – disaggregated costs

	Dapagliflozin + SOC (intervention)	Placebo + SOC (comparator)	Incremental
Management costs			
Drug acquisition costs	£3,212	£126	£3,086
Disease management costs (excluding RRT)	£19,926	£18,498	£1,428
Clinical event costs			
Dialysis	£28,395	£27,858	£537
Transplant	£2,932	£2,939	-£7
Hospitalisation for HF	£41	£54	-£13
AKI	£382	£424	-£42
AEs	£1,637	£1,509	£128
Total costs			
Total costs	£56,526	£51,408	£5,118

Abbreviations: AE: adverse event; AKI: acute kidney injury; HF: heart failure; RRT: renal replacement therapy; SOC: standard of care.

B.3.8 *Sensitivity analyses*

B.3.8.1 Probabilistic sensitivity analysis

A PSA was performed to explore the effect of uncertainty associated with all model inputs. One thousand PSA iterations were run to obtain stable estimates of the mean model results, and the mean total costs and mean total QALYs were calculated to estimate the probabilistic ICER.

In the PSA, all values were drawn from a distribution at the beginning of each simulated cohort in order to vary parameters that would otherwise remain fixed in the deterministic base case. Model input values were sampled from distributions around the mean (used in the deterministic analysis), based on the SE associated with the input parameter. In general, beta distributions were used for utilities, proportions and probability estimates, gamma distributions were used for costs, and normal distributions were used for the other parameters. Details on the parameters, SEs, and assumptions are provided throughout Section B.3 and summarised in Section B.3.6.1.

The probabilistic results (Table 40) were highly comparable with the deterministic results (see Section B.3.7). The incremental life years, QALYs and costs in the probabilistic analysis results were 1.001 life years, 0.764 QALYs and £5,134, compared to 1.007 life years, 0.769 QALYs and £5,118 in the deterministic analysis results. The ICER in the probabilistic analysis remained highly cost-effective at £6,717/QALY gained. The probabilities of cost-effectiveness at

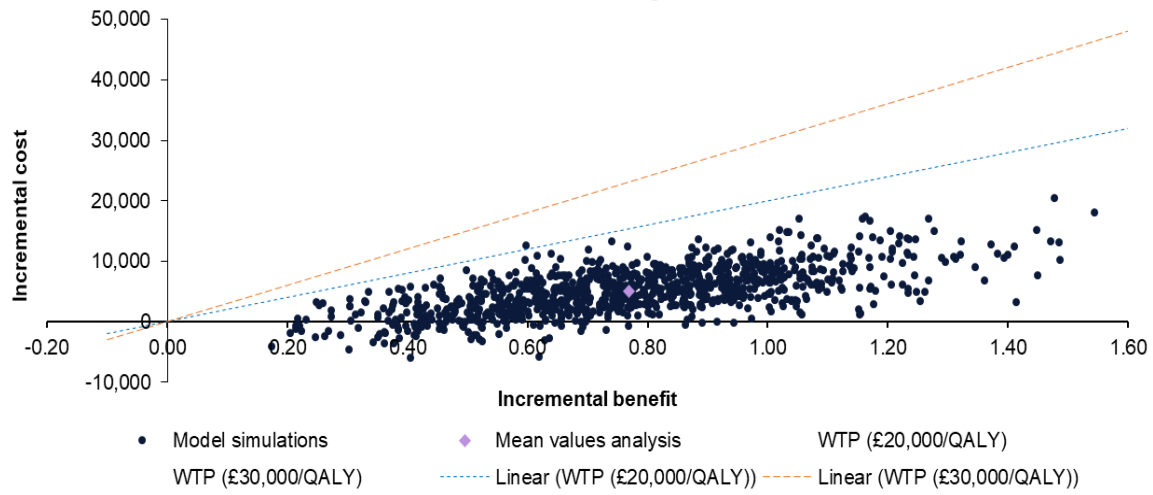
willingness-to-pay thresholds of £20,000/QALY and £30,000/QALY were 99.9% and 100%, respectively (Figure 24). The PSA scatterplot, cost-effectiveness acceptability curve and the ICER convergence curve from the PSA are shown in Figure 24–Figure 26.

Table 40: Base case probabilistic results

	Dapagliflozin + SOC (intervention)	Placebo + SOC (comparator)	Incremental	ICER (£/QALY)
Life years	9.305	8.304	1.001	£6,717
QALYs	6.832	6.068	0.764	
Costs (£)	£56,839	£51,706	£5,134	

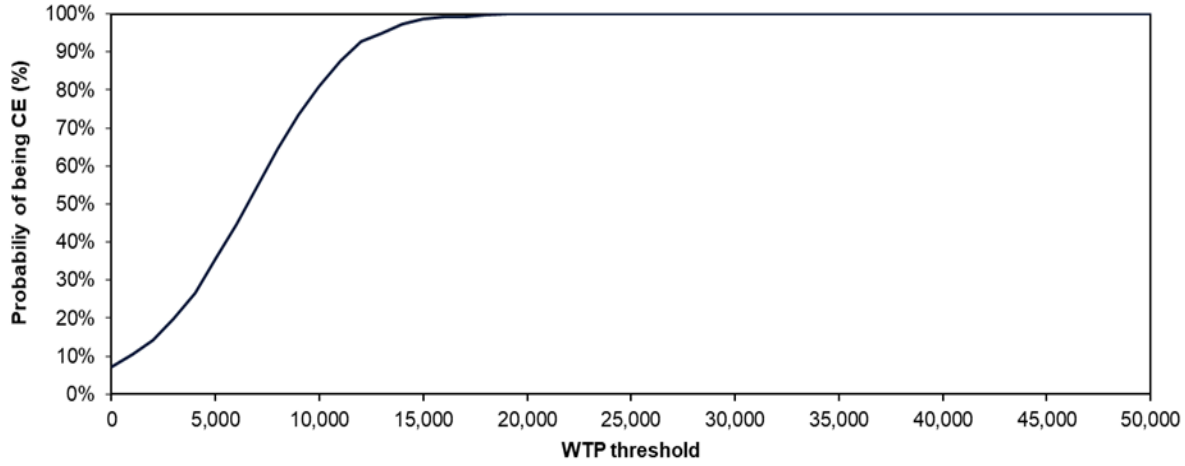
Abbreviations: ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years: SOC, standard of care.

Figure 24: Cost-effectiveness scatter plot from PSA



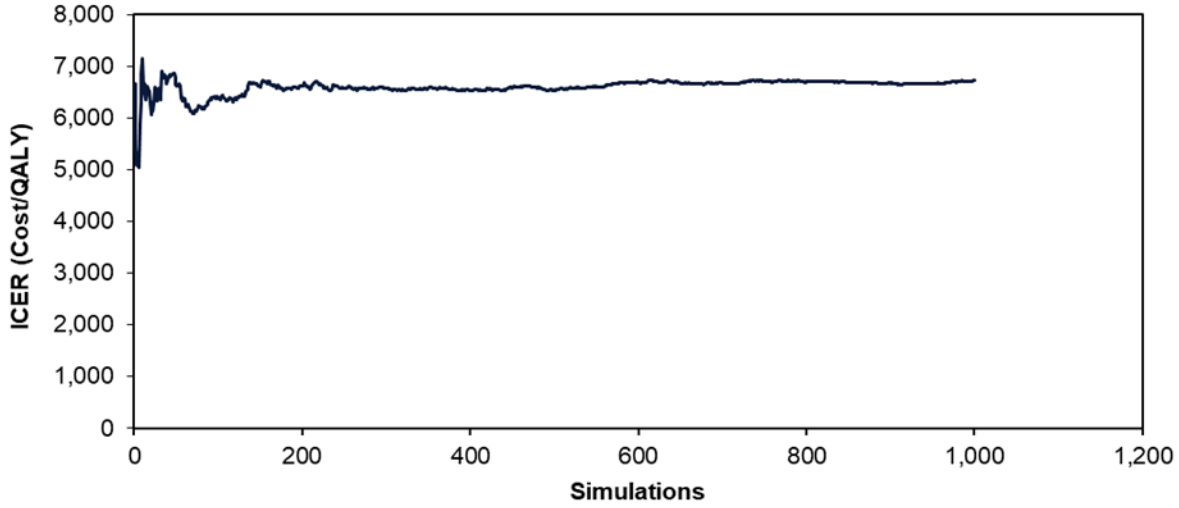
Abbreviations: CE: cost-effectiveness; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life year; WTP: willingness to pay.

Figure 25: Cost-effectiveness acceptability curve from PSA



Abbreviations: CE: cost-effectiveness; PSA: probabilistic sensitivity analysis; WTP: willingness to pay.

Figure 26: ICER convergence curve from PSA



Abbreviations: ICER: incremental cost-effectiveness ratio; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life year.

B.3.8.2 Deterministic sensitivity analysis

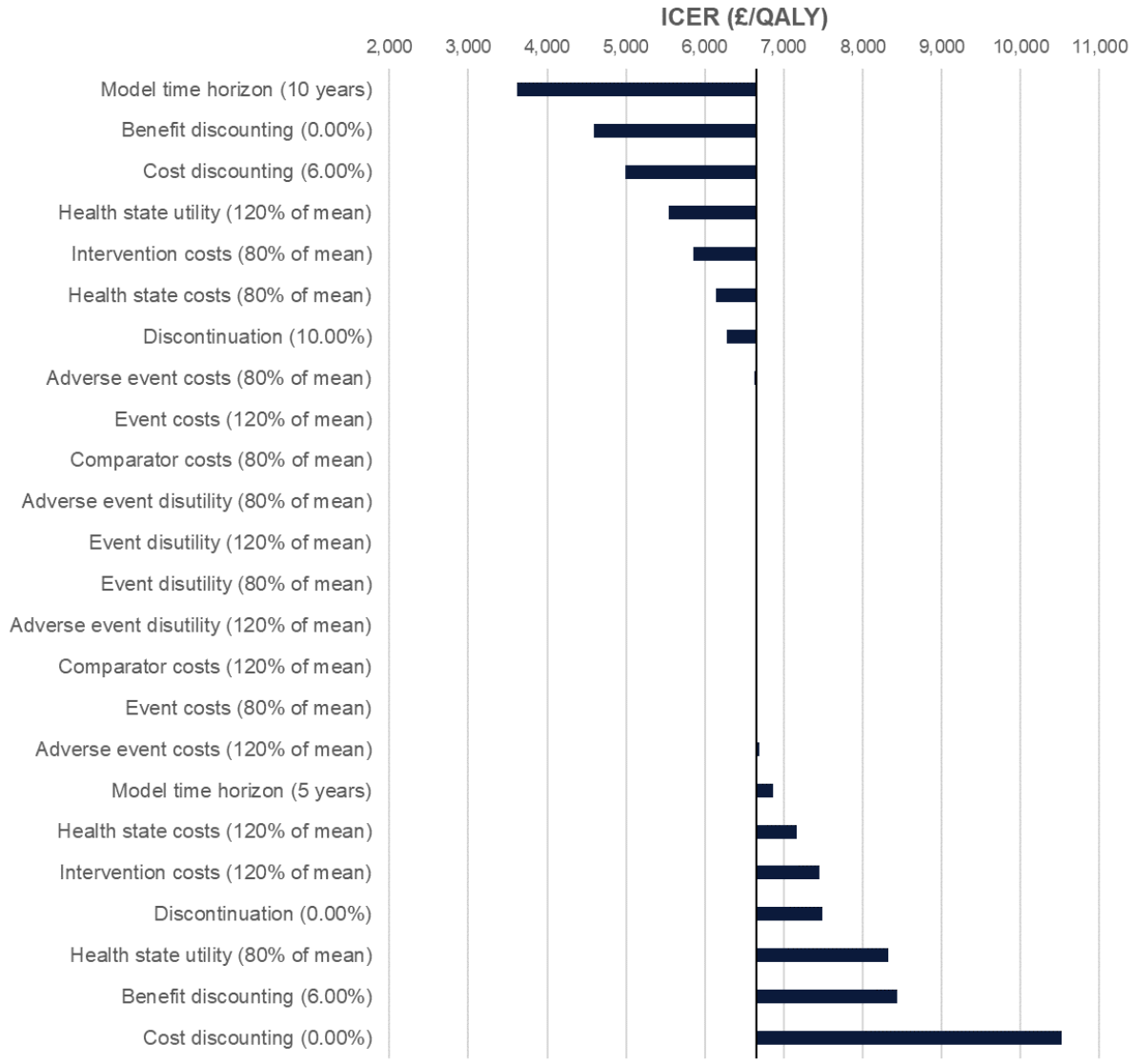
Deterministic sensitivity analyses were performed to explore the effect of uncertainty associated with varying individual model inputs or groups of individual model inputs. Model inputs were varied by 20% from baseline, or to 0% or 6% for the discounting factor, or to 5 years and 10 years for the time horizon. The results are presented as a tornado plot in Figure 27.

In the deterministic sensitivity analyses, a reduction in the time horizon to 10 years had the largest impact on reducing the ICER (by -£3,039/QALY gained to an ICER of £3,616/QALY gained), whereas a decrease in the discount factor for costs to 0% had the largest impact on increasing the ICER (by +£3,873/QALY gained to an ICER of £10,527/QALY gained).

These results can be explained by the longer duration patients in the dapagliflozin arm spend in the dialysis health state versus the placebo arm, which is associated with low HRQoL and high costs towards the end of a patient's life. The truncation of the time horizon from lifetime to 10 years, means that some of the longer-term dialysis costs are excluded from the analysis, which decreases the total costs, more so in the dapagliflozin arm than in the placebo arm, and makes dapagliflozin more cost-effective (lower ICER) compared with the base case. On the other hand, a reduction in the discount factor for costs has the effect of increasing the total costs, more so in the dapagliflozin arm than in the placebo arm, which in turn makes dapagliflozin less cost-effective (higher ICER) compared with the base case.

Dapagliflozin remained highly cost-effective compared with placebo with ICERs below £11,000/QALY gained in all scenarios of the deterministic sensitivity analysis.

Figure 27: Tornado plot of deterministic sensitivity analysis results



Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

B.3.8.3 Scenario analyses

B.3.8.3.1 Overview

A range of scenario analyses were conducted to test the robustness of the model to alternative model inputs and assumptions. The scenarios are summarised in Table 41, with details of model inputs provided in Section B.3.8.3.1.

Table 41: Summary of scenario analyses

Scenario	Base case input/assumption	Scenario input/assumption
#1.	Baseline characteristics:	DAPA-CKD overall trial population
#2.		Subgroup of CPRD patients with comorbid T2DM
#3.		Subgroup of CPRD patients without comorbid T2DM

#4.	CPRD CKD overall patients	Subgroup of CPRD patients with uACR <200 mg/g (22.6 mg/mmol)
#5.		Subgroup of CPRD patients with uACR ≥200 mg/g (22.6 mg/mmol)
#6.		Subgroup of DAPA-CKD patients with comorbid T2DM (dapagliflozin versus placebo)
#7.		Subgroup of DAPA-CKD patients with comorbid T2DM (dapagliflozin versus canagliflozin)
#8.		Subgroup of DAPA-CKD patients without comorbid T2DM
#9.		Subgroup of DAPA-CKD patients with comorbid CVD
#10.		Subgroup of DAPA-CKD patients without comorbid CVD
#11.		Subgroup of DAPA-CKD patients without comorbid T2DM and without comorbid CVD
#12.	All-cause mortality survival distribution: Gompertz	Exponential
#13.		Weibull
#14.		Lognormal
#15.		Log-logistic
#16.		Generalised gamma
#17.	Patient continue dapagliflozin following initiation of dialysis	Patients discontinue dapagliflozin following initiation of dialysis
#18.	Patients continue to be modelled after RRT	Patients exit model at RRT
#19.	Disutility values as per Table 31	Alternative disutility values for major hypoglycaemic event (to include impact of fear Currie et al. 2006[147]), DKA (Peasgood et al. 2016[150]) and amputation (Clarke et al. 2002[151]), see Section B.3.4.4

Abbreviations: CKD: chronic kidney disease;; CPRD: Clinical Practice Research Datalink; CVD: cardiovascular disease; DKA: diabetic ketoacidosis; RRT: renal replacement therapy; T2DM: type 2 diabetes mellitus; uACR: urine albumin creatinine ratio.

B.3.8.3.2 Scenario analyses inputs

Baseline characteristics

Table 42: Patient baseline characteristics – scenario analyses (1/2)

Characteristic	DAPA-CKD (scenario #1)		CPRD subgroup with comorbid T2DM (scenario #2)		CPRD subgroup without comorbid T2DM (scenario #3)		CPRD subgroup with uACR <200 mg/g[a] (scenario #4)		CPRD subgroup with uACR ≥200 mg/g[a] (scenario #5)	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Patient characteristics										
Age (years)	61.841	0.184	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female	0.331	0.007	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI (kg/m^2)	29.518	0.094	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race: White	0.532	0.008	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race: Black or African American	0.044	0.003	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race: Other	0.083	0.004	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Smoker	0.136	0.005	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical characteristics										
CKD 1	0.000	0.000	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CKD 2	0.105	0.005	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CKD 3a	0.309	0.007	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CKD 3b	0.441	0.008	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CKD 4	0.145	0.005	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CKD 5 (pre-RRT)	0.000	0.000	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dialysis	0.000	0.000	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Transplant	0.000	0.000	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
uACR: <30 mg/g (3.39 mg/mmol)	0.000	0.000	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Characteristic	DAPA-CKD (scenario #1)		CPRD subgroup with comorbid T2DM (scenario #2)		CPRD subgroup without comorbid T2DM (scenario #3)		CPRD subgroup with uACR <200 mg/g[a] (scenario #4)		CPRD subgroup with uACR ≥200 mg/g[a] (scenario #5)	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
uACR: 30–300 mg/g (3.39–33.9 mg/mmol)	0.103	0.005	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
uACR: ≥300 mg/g (33.9 mg/mmol)	0.897	0.005	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T2DM	0.675	0.007	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glomerulonephritis	0.161	0.006	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ACE inhibitor	0.274	0.007	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARB	0.556	0.008	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MRA	0.045	0.003	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diuretic	0.371	0.007	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Potassium (mmol/L)	4.647	0.008	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Systolic blood pressure (mmHg)	137.083	0.265	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Haemoglobin (g/dL)	12.825	0.028	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
History										
Prior HF	0.109	0.005	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior MI	0.091	0.004	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior stroke	0.069	0.004	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnote: Variables reported in the table are proportions unless otherwise stated. [a]uACR of 200 mg/g = 22.6 mg/mmol.
Abbreviations: ACE: angiotensin converting enzyme; ARB: angiotensin II receptor blocker; BMI: body mass index; CKD: chronic kidney disease; CPRD: clinical practice research datalink; HF: heart failure, MI: myocardial infarction; MRA: mineralocorticoid receptor antagonist; RRT: renal replacement therapy; uACR: urine albumin creatinine ratio; SE: standard error; T2DM: type 2 diabetes mellitus.

Table 43: Patient baseline characteristics – scenario analyses (2/2)

Characteristic	DAPA-CKD subgroup with comorbid T2DM (scenario #6 and #7)		DAPA-CKD subgroup without comorbid T2DM (scenario #8)		DAPA-CKD subgroup with comorbid CVD (scenario #9)		DAPA-CKD subgroup without comorbid CVD (scenario #10)		DAPA-CKD subgroup without comorbid T2DM and without comorbid CVD (scenario #11)	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Patient characteristics										
Age (years)	64.436	0.180	56.447	0.390	66.350	0.239	59.263	0.242	53.766	0.435
Female	0.332	0.009	0.329	0.013	0.292	0.011	0.354	0.009	0.352	0.015
BMI (kg/m^2)	30.296	0.116	27.904	0.149	30.708	0.160	28.837	0.113	27.469	0.166
Race: White	0.530	0.009	0.536	0.013	0.670	0.012	0.453	0.010	0.480	0.015
Race: Black or African American	0.047	0.004	0.039	0.005	0.052	0.006	0.040	0.004	0.040	0.006
Race: Other	0.102	0.006	0.043	0.005	0.072	0.007	0.089	0.005	0.044	0.006
Smoker	0.136	0.006	0.135	0.009	0.130	0.009	0.139	0.007	0.137	0.010
Clinical characteristics										
CKD 1	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
CKD 2	0.120	0.006	0.076	0.007	0.115	0.008	0.100	0.006	0.081	0.008
CKD 3a	0.316	0.009	0.293	0.012	0.300	0.012	0.313	0.009	0.302	0.014
CKD 3b	0.426	0.009	0.471	0.013	0.442	0.013	0.440	0.009	0.458	0.015
CKD 4	0.138	0.006	0.160	0.010	0.143	0.009	0.146	0.007	0.159	0.011
CKD 5 (pre-RRT)	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Dialysis	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Transplant	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
uACR: 30–300 mg/g (3.39–33.9 mg/mmol)	0.106	0.006	0.097	0.008	0.107	0.008	0.101	0.006	0.094	0.009
uACR: ≥300 mg/g (33.9 mg/mmol)	0.894	0.006	0.903	0.008	0.893	0.008	0.899	0.006	0.906	0.009

Characteristic	DAPA-CKD subgroup with comorbid T2DM (scenario #6 and #7)		DAPA-CKD subgroup without comorbid T2DM (scenario #8)		DAPA-CKD subgroup with comorbid CVD (scenario #9)		DAPA-CKD subgroup without comorbid CVD (scenario #10)		DAPA-CKD subgroup without comorbid T2DM and without comorbid CVD (scenario #11)	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
T2DM	1.000	0.000	0.000	0.000	0.793	0.010	0.608	0.009	0.000	0.000
Glomerulonephritis	0.033	0.003	0.428	0.013	0.060	0.006	0.220	0.008	0.490	0.015
ACE inhibitor	0.269	0.008	0.285	0.012	0.333	0.012	0.240	0.008	0.277	0.014
ARB	0.554	0.009	0.558	0.013	0.513	0.013	0.580	0.009	0.564	0.015
MRA	0.050	0.004	0.036	0.005	0.078	0.007	0.026	0.003	0.023	0.005
Diuretic	0.426	0.009	0.255	0.012	0.482	0.013	0.307	0.009	0.209	0.012
Potassium (mmol/L)	4.674	0.011	4.591	0.014	4.651	0.014	4.645	0.010	4.581	0.015
Systolic blood pressure (mmHg)	139.227	0.322	132.625	0.445	139.160	0.443	135.894	0.329	131.331	0.504
Haemoglobin (g/dL)	12.594	0.033	13.307	0.047	12.921	0.046	12.770	0.034	13.220	0.053
History										
Prior HF	0.124	0.006	0.077	0.007	0.299	0.012	0.000	0.000	0.000	0.000
Prior MI	0.110	0.006	0.051	0.006	0.250	0.011	0.000	0.000	0.000	0.000
Prior stroke	0.079	0.005	0.049	0.006	0.190	0.010	0.000	0.000	0.000	0.000

Footnote: Variables reported in the table are proportions unless otherwise stated.
Abbreviations: ACE: angiotensin converting enzyme; ARB: angiotensin II receptor blocker; BMI: body mass index; CKD: chronic kidney disease; CPRD: clinical practice research datalink; HF: heart failure; MI: myocardial infarction; MRA: mineralocorticoid receptor antagonist; RRT: renal replacement therapy; uACR: urine albumin creatinine ratio; SE: standard error; T2DM: type 2 diabetes mellitus.

Alternative survival distributions

Table 44: Parameterisations of adjusted all-cause mortality survival equation from DAPA-CKD

Covariate	Exponential			Weibull		
	Coeff	SE	p value	Coeff	SE	p value
Shape	0.00074	0.00	0.357	1.17351	0.08	<0.001
Scale	-	-	-	1,168.70559	1083.92	0.281
Dapagliflozin	-0.36422	0.13	0.005	0.31282	0.11	0.006
Age	0.03422	0.01	<0.001	-0.02935	0.01	<0.001
Female	-0.35585	0.14	0.014	0.31055	0.12	0.012
Race: Black or African American	0.64387	0.34	0.06	-0.53414	0.29	0.069
Race: White	0.82620	0.20	<0.001	-0.69485	0.17	<0.001
Race: Other	0.85086	0.25	0.001	-0.71578	0.22	0.001
BMI (kg/m^2)	-0.02231	0.01	0.066	0.01900	0.01	0.068
eGFR <15 ml/min/1.73 m^2 [c]	1.54779	0.36	<0.001	-1.21826	0.33	<0.001
eGFR 15–30 ml/min/1.73 m^2 [a]	0.55027	0.30	0.063	-0.44659	0.25	0.08
eGFR 30–60 ml/min/1.73 m^2 [a]	0.27684	0.28	0.331	-0.24227	0.24	0.318
Haemoglobin (g/dL)	-0.22637	0.04	<0.001	0.19797	0.04	<0.001
Glomerulonephritis	-0.46686	0.29	0.106	0.38809	0.25	0.117
Systolic blood pressure (mmHg)	-0.00927	0.00	0.011	0.00795	0.00	0.011
Potassium (mmol/L)	-0.16721	0.11	0.139	0.14672	0.10	0.128
Prior HF	0.81223	0.16	<0.001	-0.70021	0.14	<0.001
Prior MI	0.37464	0.17	0.031	-0.32012	0.15	0.033
Prior stroke	0.47554	0.20	0.018	-0.40348	0.17	0.019

Footnote: [a]Reference category for eGFR was ≥60 ml/min/1.73m^2
Abbreviations: BM: body mass index; coeff: coefficient; eGFR: estimated glomerular filtration rate; HF: heart failure; MI: myocardial infarction; SE: standard error.

Table 45: Parameterisations of adjusted all-cause mortality survival equation from DAPA-CKD

Covariate	Lognormal			Log-logistic		
	Coeff	SE	p value	Coeff	SE	p value
Shape	7.24036	1.05	<0.001	1.21378	0.08	<0.001
Scale	1.91192	0.11	<0.001	974.81048	929.14	0.294
Dapagliflozin	0.35851	0.13	0.006	0.31486	0.12	0.007
Age	-0.03168	0.01	<0.001	-0.03054	0.01	<0.001
Female	0.30453	0.14	0.033	0.30871	0.13	0.016
Race: Black or African American	-0.53588	0.33	0.105	-0.53281	0.30	0.078
Race: White	-0.67939	0.18	<0.001	-0.70185	0.18	<0.001

Race: Other	-0.72118	0.25	0.003	-0.71081	0.22	0.001
BMI (kg/m^2)	0.01156	0.01	0.301	0.01654	0.01	0.117
eGFR <15 ml/min/1.73 m^2 [a]	-1.91609	0.46	<0.001	-1.40696	0.37	<0.001
eGFR 15–30 ml/min/1.73 m^2 [a]	-0.43705	0.27	0.105	-0.42351	0.26	0.099
eGFR 30–60 ml/min/1.73 m^2 [a]	-0.19079	0.25	0.449	-0.21699	0.24	0.373
Haemoglobin (g/dL)	0.22121	0.04	<0.001	0.20575	0.04	<0.001
Glomerulonephritis	0.33756	0.25	0.17	0.39785	0.25	0.107
Systolic blood pressure (mmHg)	0.01046	0.00	0.005	0.00854	0.00	0.009
Potassium (mmol/L)	0.16731	0.11	0.124	0.15359	0.10	0.118
Prior HF	-0.79404	0.17	<0.001	-0.71206	0.15	<0.001
Prior MI	-0.42197	0.19	0.024	-0.31924	0.16	0.045
Prior stroke	-0.49814	0.21	0.019	-0.45348	0.18	0.013

Footnote: [a]Reference category for eGFR was ≥60 ml/min/1.73m^2
Abbreviations: BMI: body mass index; coeff: coefficient; eGFR: estimated glomerular filtration rate; HF: heart failure; MI: myocardial infarction; SE: standard error.

Table 46: Parameterisations of adjusted all-cause mortality survival equation from DAPA-CKD

Covariate	Generalised gamma		
	Coeff	SE	p value
Mu	9.76631	1.17	<0.001
Sigma	1.75932	0.40	<0.001
Q	0.14190	0.29	0.620
Dapagliflozin	0.41133	0.13	0.001
Age	-0.00376	0.01	0.553
Female	-0.12457	0.15	0.397
Race: Black or African American	-0.18891	0.33	0.564
Race: White	-0.42463	0.17	0.012
Race: Other	-0.17745	0.25	0.470
BMI (kg/m^2)	0.01269	0.01	0.240
eGFR <15 ml/min/1.73 m^2 [a]	-0.99549	0.40	0.012
eGFR 15–30 ml/min/1.73 m^2 [a]	0.17715	0.24	0.455
eGFR 30–60 ml/min/1.73 m^2 [a]	0.36236	0.22	0.105
Haemoglobin (g/dL)	0.02997	0.04	0.463
Glomerulonephritis	0.76796	0.26	0.003
Systolic blood pressure (mmHg)	0.00017	0.00	0.962
Potassium (mmol/L)	-0.11880	0.11	0.284
Prior HF	-0.65073	0.17	<0.001
Prior MI	-0.56307	0.19	0.003
Prior stroke	-0.19508	0.21	0.362

Footnote: [a] Reference category for eGFR was ≥60 ml/min/1.73m^2

Abbreviations: BMI: body mass index; coeff: coefficient; eGFR: estimated glomerular filtration rate; HF: heart failure; MI: myocardial infarction; SE: standard error.

B.3.8.3.3 Scenario analysis results

Table 47: Summary of scenario analyses results

Scenario	Scenario input/assumption	ΔCosts (£)	ΔQALYs	ICER
-	Base case	£5,118	0.769	£6,655
#1.	DAPA-CKD overall trial population	£4,563	0.836	£5,457
#2.	Subgroup of CPRD patients with comorbid T2DM	£5,110	0.766	£6,671
#3.	Subgroup of CPRD patients without comorbid T2DM	£5,096	0.770	£6,619
#4.	Subgroup of CPRD patients with uACR <200 mg/g (22.6 mg/mmol)	£5,054	0.765	£6,608
#5.	Subgroup of CPRD patients with uACR ≥200 mg/g (22.6 mg/mmol)	£5,137	0.783	£6,558
#6.	Subgroup of DAPA-CKD patients with comorbid T2DM (dapagliflozin versus placebo)	£4,675	0.828	£5,648
#7.	Subgroup of DAPA-CKD patients with comorbid T2DM (dapagliflozin versus canagliflozin)	£0	0.000	Parity
#8.	Subgroup of DAPA-CKD patients without comorbid T2DM	£4,357	0.855	£5,098
#9.	Subgroup of DAPA-CKD patients with comorbid CVD	£4,891	0.819	£5,971
#10.	Subgroup of DAPA-CKD patients without comorbid CVD	£4,405	0.845	£5,213
#11.	Subgroup of DAPA-CKD patients without comorbid T2DM and without comorbid CVD	£4,287	0.861	£4,979
#12.	All-cause mortality survival distribution: exponential	£5,864	0.910	£6,447
#13.	All-cause mortality survival distribution: Weibull	-£519	0.765	Dominant
#14.	All-cause mortality survival distribution: log-normal	-£3,087	0.675	Dominant
#15.	All-cause mortality survival distribution: log-logistic	-£1,540	0.715	Dominant
#16.	All-cause mortality survival distribution: generalised gamma	-£3,675	0.708	Dominant
#17.	Patients discontinue dapagliflozin following initiation of dialysis	£1,672	0.708	£2,361
#18.	Patients exit model at RRT	£4,398	0.764	£5,756
#19.	Alternative disutility values for major hypoglycaemic event (to include impact of fear Currie et al. 2006[147]), DKA (Peasgood et al. 2016[150]) and amputation (Clarke et al. 2002[151]), see Section B.3.4.4	£5,118	0.769	£6,655

Abbreviations: CPRD: Clinical Practice Research Datalink; CVD: cardiovascular disease; DKA: diabetic ketoacidosis; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; RRT: renal replacement therapy; T2DM: type 2 diabetes mellitus; uACR: urine albumin creatinine ratio.

B.3.8.4 Summary of sensitivity analyses results

The probabilistic cost-effectiveness analysis results were similar to the deterministic base case results, showing the deterministic ICER to be an appropriate estimate of the cost-effectiveness of dapagliflozin as an add-on therapy to SOC for the treatment of CKD in UK clinical practice. The PSA showed that the probabilities of cost-effectiveness for dapagliflozin at willingness-to-pay thresholds of £20,000/QALY and £30,000/QALY gained were 99.8% and 100%, respectively, demonstrating that the cost-effectiveness of dapagliflozin is robust to any uncertainties associated with model input parameters. Additionally, the cost-effectiveness conclusions of the base case analysis remained unchanged in the deterministic sensitivity analyses and scenario analyses, further demonstrating the robustness of the base case cost-effectiveness results to variations in model inputs and assumptions.

The scenario analyses showed that the cost-effectiveness analysis is very robust and dapagliflozin consistently remained highly cost-effective in all patient subgroups, regardless of patients' uACR levels or comorbidities, with all ICERs remaining below £6,671/QALY gained.

The results from scenario analysis #17 (discontinuation of dapagliflozin following initiation of dialysis) and #18 (patients exit the model at dialysis or kidney transplant [RRT]) can be explained by the dynamics in the model involving the treatment effect of dapagliflozin on delayed progression to dialysis, the treatment effect of dapagliflozin on all-cause mortality pre-dialysis (influencing the competing risks of all-cause mortality and dialysis initiation), and the treatment effect of dapagliflozin on all-cause mortality in the dialysis health state. In the base case analysis, the balance of these three factors means the total costs of dialysis are similar in the two treatment arms (incremental dialysis costs in the dapagliflozin arm versus placebo arm: +£537). In scenario analysis #17, patients are assumed to discontinue dapagliflozin following the initiation of dialysis, which means that there is no longer a treatment effect on all-cause mortality in the dialysis health state. This leads to an overall decrease in the duration of dialysis in the dapagliflozin arm, compared with the base case, which substantially decreases the costs associated with dialysis (incremental dialysis costs in the dapagliflozin arm versus placebo arm: -£2,469). In scenario analysis #18, when all patients exit the model at entry to the dialysis or kidney transplant health states, all dialysis costs are removed, with slightly more dialysis costs removed (vs the base case) from the dapagliflozin arm compared with the placebo arm (incremental dialysis costs in the dapagliflozin arm versus placebo arm: £0).

Dapagliflozin remained cost-effective versus placebo or became dominant over placebo when alternative survival distributions were used to model all-cause mortality. The shift between highly cost-effective and dominant results with the different survival distributions is also a result of the competing risks between dialysis initiation and all-cause mortality. When the overall life-expectancy is longer due to the survival distribution chosen, a larger proportion of patients progress to dialysis, more so in the placebo arm than in the dapagliflozin arm, leading to higher total costs in the placebo arm compared with the dapagliflozin arm.

B.3.9 *Subgroup analysis*

Please see scenario analyses in Section B.3.8.3. No further exploration of subgroups was considered in the cost-effectiveness analysis.

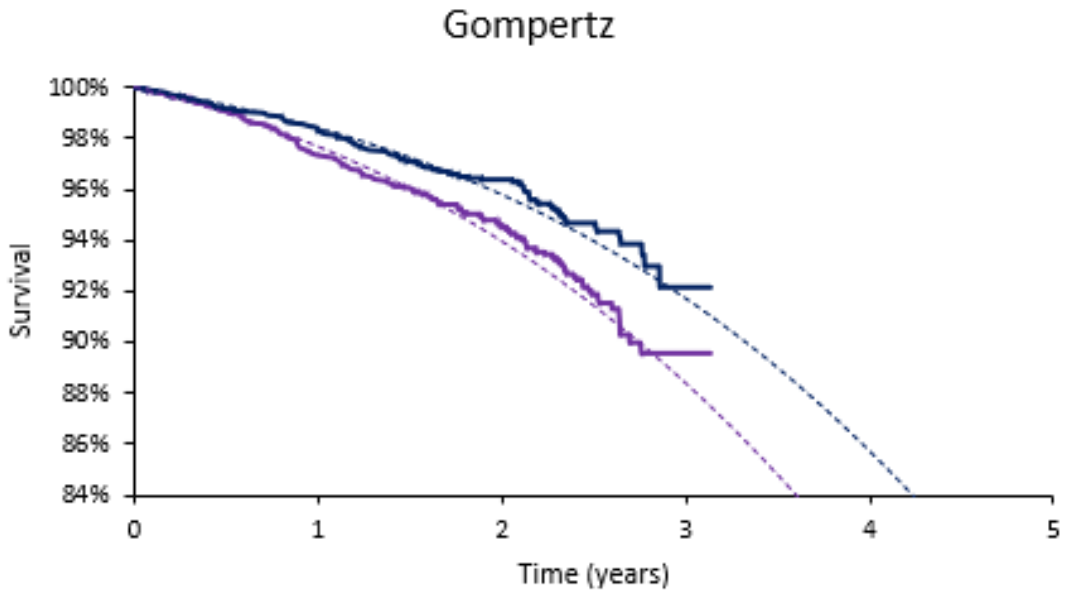
B.3.10 *Validation*

B.3.10.1 Validation of cost-effectiveness analysis

[redacted] provided clinical expert input throughout the model development process and provided external validation of the modelled outcomes.

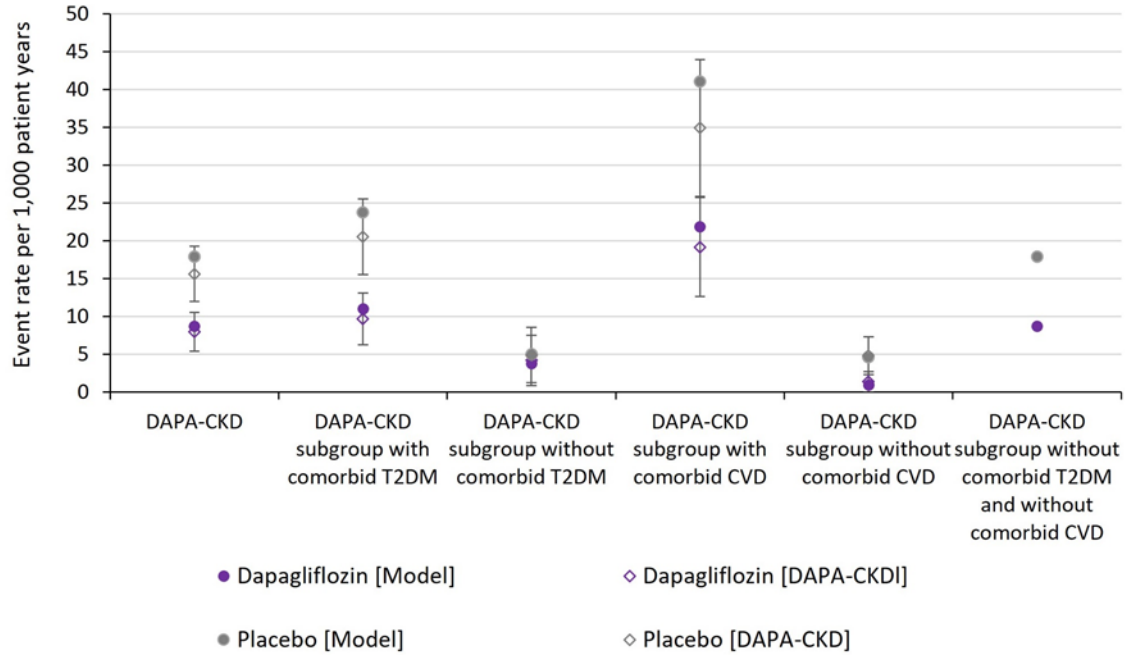
Internal validation of the model was carried out to ensure the model was able to reproduce the results of the trial. The predicted incidence of all-cause mortality and clinical events for the DAPA-CKD overall population was compared with the observed incidence from the DAPA-CKD trial, with model performance assessed statistically and by inspection. Validation plots showing the observed and predicted outcomes from the unadjusted model results are presented for all-cause mortality, and AKI and hospitalisation for HF event incidence in Figure 28–Figure 30. The modelled incidences of clinical events, AEs and mortality at 27 months in a DAPA-CKD-like population (scenario #1) were compared versus the incidence of events observed in DAPA-CKD (median follow-up of 27 months) (Appendix J, Table 48). These results show that the model generally predicts a smaller incremental reduction in clinical event incidences, and a slightly larger incremental increase in AEs incidences, associated with dapagliflozin, when compared to the incremental incidences observed in the DAPA-CKD trial, suggesting that the model is conservative with respect to dapagliflozin. In particular, the incremental reduction in ESKD at 27 months is underestimated in the model (-2.0% in model vs -2.4% in trial), which means that additional cost-savings from mitigated dialysis would be expected in clinical practice beyond the cost-savings predicted by the cost-effectiveness model.

Figure 28: Observed and predicted incidence of all-cause mortality



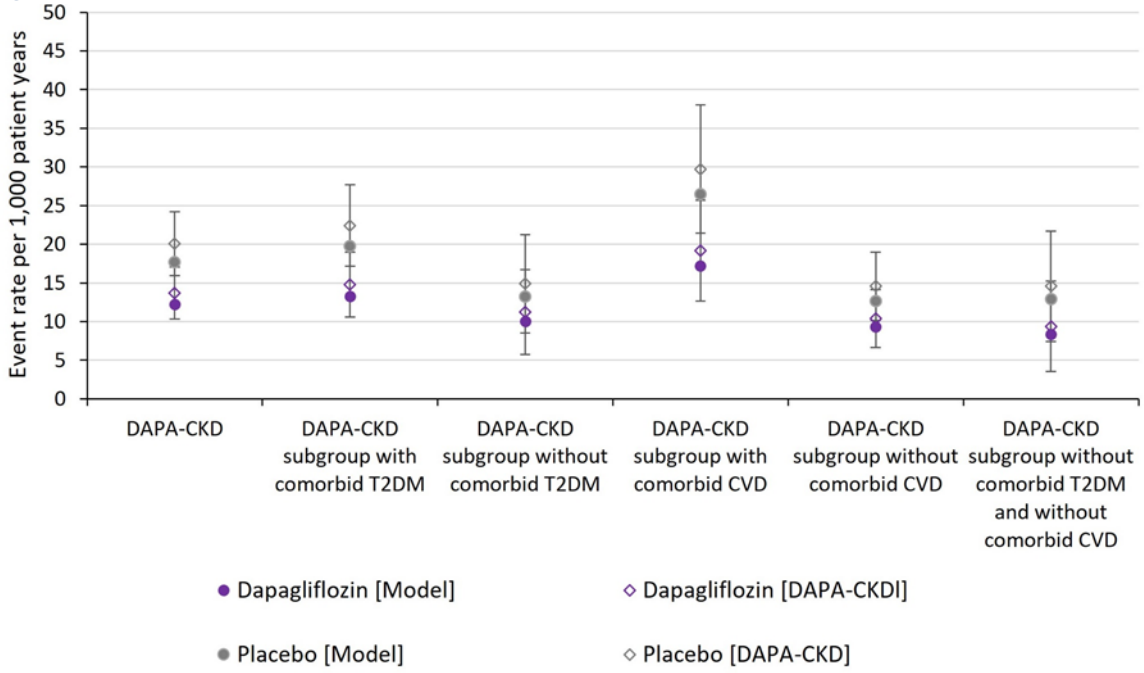
Key: purple – placebo arm; dark blue – dapagliflozin arm; solid line – observed; dotted line - predicted

Figure 29: Observed and predicted incidence of hospitalisation for HF



Footnotes: Observed event rates of hospitalisation for HF for the DAPA-CKD subgroup without comorbid T2DM and without comorbid CVD have not been plotted in this figure, as only one event was observed in the dapagliflozin arm of this subgroup, and no events were observed for the placebo arm of this subgroup. The model applied the modelled incidence event rates from the overall DAPA-CKD population for this subgroup.
Abbreviations: CKD: chronic kidney disease; CVD: cardiovascular disease; HF: heart failure; T2DM: type 2 diabetes mellitus.

Figure 30: Observed and predicted incidence of AKI



Abbreviations: AKI: acute kidney injury; CKD: chronic kidney disease; CVD: cardiovascular disease; T2DM: type 2 diabetes mellitus.

B.3.11 *Interpretation and conclusions of economic evidence*

The cost-effectiveness model of dapagliflozin as an add-on therapy to SOC for the treatment of CKD identified from the SLR and originally developed by AstraZeneca (see Section B.3.1) was adapted to address the current decision problem. The treatment effect of dapagliflozin and health state utility values were derived from the DAPA-CKD trial and supplemented with values from the literature where relevant. Costs were identified from UK sources, including NHS reference costs, the eMIT, the PSSRU, and the literature.

Model inputs for baseline characteristics were derived from a CPRD analysis to represent CKD patients in UK clinical practice that will [redacted]. The all-cause mortality survival equation, hospitalisation for HF risk equation and AKI risk equation were fully adjusted to account for the baseline characteristics from the CPRD analysis, to generate event rates adjusted to the characteristics of CKD patients in UK clinical practice. The results demonstrated that dapagliflozin is highly cost-effective versus placebo as an add-on therapy to SOC for the treatment of CKD, with an ICER of £6,655/QALY gained.

Extensive scenario analyses demonstrated the base case cost-effectiveness results to be robust to variation in model inputs and assumptions. Additionally, scenario analyses in patient subgroups with comorbid T2DM, with comorbid CVD, and without comorbid T2DM and without comorbid CVD, and patient subgroups by uACR levels showed the cost-effectiveness of dapagliflozin to be consistent across all subgroups, with the ICERs in all subgroups remaining below £7,000/QALY gained.

In summary, the cost-effectiveness analysis showed dapagliflozin to represent a highly cost-effective use of NHS resources, as an add-on therapy to SOC for the treatment of adults with CKD.

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Appendices

The following sections will be provided to support the submission as separate appendices.

- Appendix C: Summary of product characteristics (SmPC) and European public assessment report (EPAR)
- Appendix D: Identification, selection and synthesis of clinical evidence
- Appendix E: Subgroup analysis
- Appendix F: Adverse reactions
- Appendix G: Published cost-effectiveness studies
- Appendix H: Health-related quality-of-life studies
- Appendix I: Cost and healthcare resource identification, measurement and valuation
- Appendix J: Clinical outcomes and disaggregated results from the model
- Appendix K: Checklist of confidential information
- Appendix L: Additional clinical data
- Appendix M: Inflation factors

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Dapagliflozin for treating chronic kidney disease [ID3866]

Clarification questions

June 2021

File name	Version	Contains confidential information	Date
ID3866 dapagliflozin clarification letter to PM_[REDACTED]	v1.0	Yes	04.06.2021

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.

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Section A: Clarification on effectiveness data

Literature searching

A1. Company's submission (CS) Appendix D, Section D.1.1, page 5. Appendix D reports three phases of searching (in March, August and November 2020) with the searches from August onwards amended based on consultation. Please provide more detail of this consultation process and at what point in the screening process this took place.

The consultation was initiated after the searches were initially conducted (in March 2020) and the abstract review was ongoing. The consultation was performed by an independent systematic review team critically appraised the search strategy for the systematic literature review (SLR) using the following pre-defined criteria:

1. Critical review of the eligibility criteria to ensure that the SLR was designed to allow identification of all studies that might be relevant to the anticipated decision problem, particularly in relation to the potential comparators
2. Critical review of the search terms to confirm that they were suitably sensitive and specific
3. Literature searching in PubMed, Google and Google Scholar to ensure that the SLR search strategy and record review process did not miss any relevant articles

The searches conducted in August 2020 and November 2020 implemented the suggested amendments to the search strategy (highlighted in the response to A5). The eligibility criteria remained unchanged.

A2. CS Appendix D, Section D.1.1, Tables 1 to 3, pages 6 to 8. The ERG notes that on each occasion, MEDLINE and Embase were searched simultaneously with a single strategy. What attempts were made to identify and include appropriate subject headings for optimal retrieval in each database? For example, "chronic kidney

failure” in Embase can be mapped to either "Kidney Failure, Chronic" or "Renal Insufficiency, Chronic" in MEDLINE.

No additional work was done to identify and include appropriate subject headings for optimal retrieval in each database, as standard mapping of MeSH to Elsevier indexing should retrieve all relevant results, as per the Embase.com indexing guide (copied below).[1] Free-text terms were also generated from both MeSH and Emtree terms to ensure a comprehensive search.

From the Embase indexing guide:[1]

“More than 3,300 of the 5,200 journal titles currently indexed for MEDLINE are independently indexed for Embase by Elsevier, using the guidelines described in this Indexing Guide.

For articles from another 1,800 MEDLINE titles (with a focus on basic biomedicine, Allied Health and other topics that are peripheral to the core topics of Embase), MeSH index terms are mapped to Emtree to provide an index that is compatible with the Elsevier indexing.

- *MeSH terms and check tags (all MeSH terms are included in Emtree)*
- *MeSH subheadings (many are also found in Emtree; where this is not the case, or when the definition is slightly different, an appropriate translation is made)*
- *Publication types*
- *Numerical codes (molecular sequence numbers, clinical trial numbers): these are used to generate the corresponding Embase code*

Records licensed from MEDLINE are not indexed with Embase-specific indexing such as trade names and manufacturer names, or with Embase classifications.”

A3. CS Appendix D, Section D.1.1, Tables 1 to 3, pages 6 to 8. Why were subject headings searched as “mj” (major heading) only? This strategy is typically used for high specificity searches and seems inconsistent when also searching for the same terms in titles/abstracts. Would the presence of a term as a subject heading, even a minor one, not be more indicative of relevance than its occurrence in an abstract?

The SLR was designed to identify phase 3 or phase 4 randomised controlled trials in CKD, therefore it was considered highly unlikely that such a trial would not be indexed as a major heading. However, as noted, the approach to searching free-text terms was broader, this was by design to capture any studies where the major heading had not been used.

A4. CS Appendix D, Section D.1.1, page 6. When searching trials registers, the searches (in 2020) were limited to studies updated since 2018, *"assuming studies that have not been updated since 2018 would have published data and therefore would be identified in the search of peer-reviewed publications or conference proceedings".* Was any attempt made to identify trials completed by 2018 but never published or reported at conferences?

The Cochrane Handbook for Systematic Reviews of Interventions does not require individuals to seek unpublished data, for example by contacting organisations, and so no attempt was made.[2]

A5. Appendix D, Section D.1.1.1, page 5. The CS Appendix states that *"Initial database searches were conducted on the 25th March 2020 before being amended, updated and re-run on the 7th August 2020 following further consultation."* Please state what was amended and why?

Table 1 below shows the searches run from August 2020 onwards, based on the critical appraisal described in A1. To increase the sensitivity of the search, the terms highlighted below were added. To further increase sensitivity, a line item to focus only on studies in adults (using the prespecified limits in Embase.com *([young adult]/lim OR [adult]/lim OR [middle aged]/lim OR [aged]/lim OR [very elderly]/lim OR adult:ti,ab OR 'middle age':ti,ab OR 'aged':ti,ab OR 'very elderly':ti,ab)*), which was implemented in the March 2020 search, was also removed from the searches run from August 2020 onwards.

Table 1: Search strategy for MEDLINE and Embase (August 2020 onwards)

No.	Query
#1	'chronic kidney failure'/exp/mj OR 'mild renal impairment'/exp/mj OR 'moderate renal impairment'/exp/mj OR 'severe renal impairment'/exp/mj
#2	'kidney disease'/exp/mj
#3	chronic:ti,ab
#4	#1 OR (#2 AND #3)
#5	((chronic OR progressive) NEAR/2 (renal OR kidney) NEAR/2 (insufficien* OR disease* OR fail* OR impair* OR disorder*)):ti,ab
#6	ckd:ti,ab OR ckf:ti,ab OR crf:ti,ab OR crd:ti,ab
#7	'diabetic nephropathy'/exp/mj
#8	(diabetic NEXT/1 (kidney OR renal) NEXT/1 (insufficien* OR disease* OR fail* OR impair* OR disorder*)):ti,ab
#9	nephropath*:ti,ab
#10	#4 OR #5 OR #6 OR #7 OR #8 OR #9
#11	'clinical trial'/de OR 'randomized controlled trial'/de OR 'randomization'/de OR 'single blind procedure'/de OR 'double blind procedure'/de OR 'crossover procedure'/de OR 'placebo'/de OR 'prospective study'/de OR ('randomi?ed controlled' NEXT/1 trial*) OR rct OR 'randomly allocated' OR 'allocated randomly' OR 'random allocation' OR (allocated NEAR/2 random) OR (single NEXT/1 blind*) OR (double NEXT/1 blind*) OR ((treble OR triple) NEAR/1 blind*) OR placebo*
#12	#10 AND #11
#13	'chapter'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it
#14	'case report' OR 'case report*':ti,ab OR 'case study' OR 'case stud*':ti,ab
#15	#13 OR #14
#16	#12 NOT #15
#17	#16 NOT ('conference abstract'/it OR 'conference paper'/it OR 'conference review'/it)
#18	#17 NOT ('animal'/de NOT 'human'/de)
#19	#18 AND [1990-2020]/py
#20	#19 AND [english]/lim
#21	#20 AND ([medline]/lim OR [pubmed-not-medline]/lim)
#22	#20 AND [embase]/lim

Clinical effectiveness data

A6. Please provide the draft Summary of Product Characteristics (SmPC) for dapagliflozin including the chronic kidney disease (CKD) indication.

A copy of the draft SmPC has been provided separately.

A7. CS, Section B.2.3.8, Table 11, page 42 and Section B.3.3.1.1, Table 22, page 81 to 82. The proportion of patients who were female in DAPA-CKD is approximately 32.9%, whereas in the Clinical Practice Research Datalink (CPRD) dataset, the proportion of patients who were female is [redacted]. Please comment on this difference and whether sex is prognostic of outcome.

The patient population enrolled in the DAPA-CKD trial is considered broadly similar to the CKD patient population seen in UK clinical practice, and UK GPs and nephrologists did not comment on sex when discussing the generalisability of the trial to UK clinical practice.[3] In addition, subgroup analyses from DAPA-CKD (Table 2), DECLARE (Table 3) and DAPA-HF (Table 4) suggest that the beneficial treatment effect of dapagliflozin was consistent across male and female patients; sex was not a treatment effect modifier in these trials.

Table 2: Subgroup analysis of DAPA-CKD primary endpoint

	Dapagliflozin, n/N	Placebo, n/N	HR (95% CI)	p-value interaction
Primary endpoint (sustained decline in eGFR ≥50%, ESKD or death from renal or CV causes)				
Male	126/1,443	209/1,436	0.57 (0.46, 0.72)	[redacted]
Female	71/709	103/716	0.65 (0.48, 0.88)	

Abbreviations: CI: confidence interval; CV: cardiovascular; eGFR: estimated glomerular filtration rate; ESKD: end-stage kidney disease; HF: heart failure.
Sources: Heerspink et al. 2020[4] and AstraZeneca Data on File 2020: DAPA-CKD Clinical Study Report Figure 5.[5]

Table 3: Subgroup analysis of DECLARE-TIMI 58 co-primary endpoint

	Dapagliflozin, n/N	Placebo, n/N	HR (95% CI)	p-value interaction
Co-Primary Endpoint (hospitalisation for HF or CV death)				
Male	293/5,411	344/5,327	[redacted]	0.90
Female	124/3,171	152/3,251	[redacted]	

Abbreviations: CI: confidence interval; CV: cardiovascular; eGFR: estimated glomerular filtration rate; ESKD: end-stage kidney disease; HF: heart failure.
Sources: Wiviott et al. 2018[6] and AstraZeneca Data on File 2020: DECLARE Clinical Study Report Figures 12.[7]

Table 4: Subgroup analysis of DAPA-HF primary endpoint

	Dapagliflozin, n/N	Placebo, n/N	HR (95% CI)	p-value interaction
DAPA-HF Primary Endpoint (worsening heart failure or death from CV causes)				
Male	307/1,809	406/1,826	0.73 (0.63, 0.85)	[redacted]

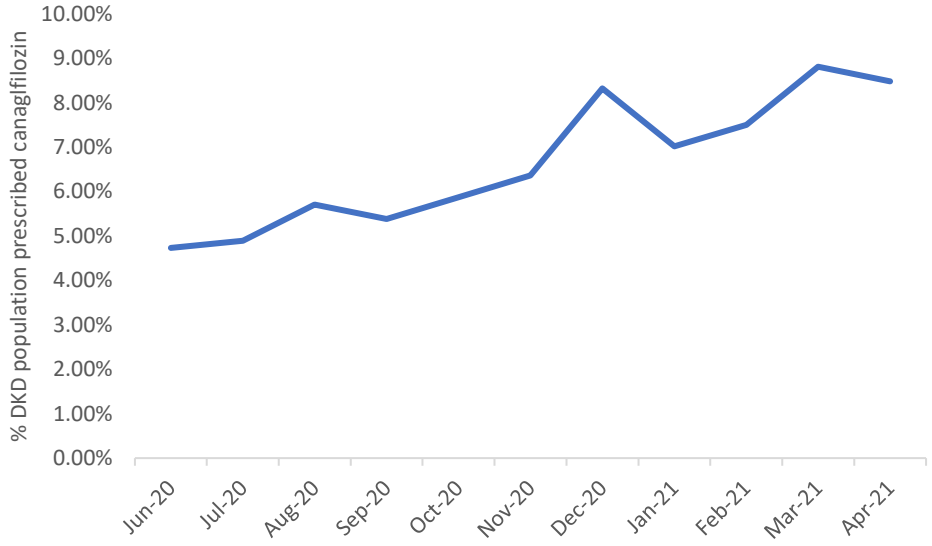
	Dapagliflozin, n/N	Placebo, n/N	HR (95% CI)	p-value interaction
Female	79/564	96/545	0.79 (0.59, 1.06)	

Abbreviations: CI: confidence interval; CV: cardiovascular.
Source: McMurray et al. 2019[8] and AstraZeneca Data on File 2019: DAPA-HF Clinical Study Report.[9]

A8. CS, Section B.1.3.3, page 25. The CS states *"...uptake of the only SGLT2 inhibitor to include renal outcomes trial data within its label in the UK (canagliflozin) has so far been limited in clinical practice."* Please suggest reasons why uptake is believed to be low.

As stated in the CS, according to monthly prescription data, the uptake of canagliflozin in patients with T2DM and concomitant CKD has been limited since the EMA licence for canagliflozin was amended in July 2020 allowing initiation in these patients.[10] The proportion of UK patients with T2DM and CKD stages 3a or 3b (eGFR 30 – 59 mL/min/1.73 m^2) who were prescribed canagliflozin increased slightly from 4.7% in June 2020 before the licence change to 8.5% in April 2021, representing a modest increase in uptake for the newly licenced population (Figure 1).[10]

Figure 1: Uptake of canagliflozin amongst all UK patients with DKD stage 3a and b (eGFR 30 – 59 mL/min/1.73 m^2)



Source: AstraZeneca Data on File: IQVIA Ltd, incorporating data derived from THIN, A Cegedim Database, Monthly, April 2021.[10]

The canagliflozin renal outcomes trial, CREDENCE, only included patients with CKD and concomitant T2DM.[11] Consequently, the EMA did not grant a new therapeutic indication for canagliflozin in CKD, since canagliflozin already had an existing licence for the treatment of insufficiently controlled T2DM.[12] Instead, in July 2020 the SmPC was updated allowing initiation of canagliflozin in patients with T2DM and an eGFR of <45 – ≥30 mL/min/1.73 m^2 and a UACR of >300 mg/g, and continuation of treatment in those with an eGFR <30 mL/min/1.73 m^2. Consequently, NICE determined that the label update for canagliflozin did not represent a significant new therapeutic indication and therefore a standard technology appraisal process

wasn't appropriate and the evidence from the CREDENCE trial would instead be assessed as part of the NICE CKD guidelines update process.

The absence of a new therapeutic indication and a NICE recommendation may have resulted in a lack of awareness about the broader population now licenced for treatment with canagliflozin. This is especially true amongst primary care physicians who typically consider SGLT2 inhibitors as T2DM drugs and may be less familiar than specialists with their cardiorenal benefits in patients with an eGFR <45 mL/min/1.73 m^2. Given that the majority of patients with DKD are treated in primary care, this lack of awareness and incomplete understanding of the appropriate use of canagliflozin is expected to have contributed to its limited uptake in the UK so far.

A9. CS, Section B.2.3.8, page 41. Is a later data-cut of DAPA-CKD expected? If so, please provide details of the date at which further analyses will be undertaken?

There will be no further data-cuts from DAPA-CKD. The DAPA-CKD trial was stopped early after recommendation by the Independent Data Monitoring Committee due to overwhelming efficacy associated with dapagliflozin.

A10. CS, Section B.2.3.2, page 37. The DAPA-CKD trial excluded patients with type 1 diabetes mellitus (T1DM). Please explain why this exclusion criterion was applied.

[redacted]

[redacted]

[redacted]

A11. CS, Section B.2.1, page 32. The CS indicates that studies were eligible for inclusion in the review if they were randomised controlled trials (RCTs) and if at least 50 patients were included in each trial arm:

(a) What was the basis for selecting a threshold of 50 patients? Were any otherwise eligible studies rejected because of this criterion?

(b) Given that the comparison of dapagliflozin versus canagliflozin in the scenario analyses is based on a matching adjusted indirect comparison (MAIC), why were includable studies required to be RCTs?

a) The eligibility criteria specified that only phase 3 or phase 4 studies would be included. However, as the reporting of study phase, particularly in older studies, was inconsistent, the limit of >50 patients per study arm was concurrently implemented to remove smaller studies which were unlikely to be a phase 3 or 4 study. We assessed the possibility of excluding relevant phase 3 or 4 studies because of the patient threshold is very low.

b) The MAIC of dapagliflozin versus canagliflozin was an anchored MAIC, which requires common comparator arms in the intervention trial and the comparator trial. The focus of the clinical SLR on RCTs is consistent with the "anchored" MAIC approach which required comparator trials to have a control arm that could be used to anchor the MAIC. The anchored approach is preferred when possible, as this methodology does not rely on the assumption that all prognostic factors, in addition to treatment effect modifiers, are accounted for in the matching-adjustment process. This is in line with TSD14 which recommends that only "anchored" forms of population adjustment should be used when a common comparator is available.[14]

A12. CS, Section 2.3.1, page 36. The CS states that in DAPA-CKD *"randomisation was capped so that no more than 10% of patients started the trial with an eGFR range corresponding to stage 2 CKD."* Please clarify why this cap was applied and why it was set equal to 10%.

The prevalence of CKD is greater at the less advanced stages, however individuals with CKD stage 2 (eGFR 60–75 mL/min/1.73 m^2) were at a very low risk of entering end stage kidney disease (ESKD) (dialysis or transplantation) during the study period. Given the importance of these 'hard' renal endpoints for both decision makers and patients, capping was required to ensure that the trial population included a range of risk profiles which could adequately demonstrate the impact of dapagliflozin on these outcomes.

A13. CS, Section B.2.3.3, page 37. Please clarify how many UK sites and how many UK patients were included in DAPA-CKD.

The DAPA-CKD trial recruited a total of [redacted] patients from nine UK sites.[5, 15] Of these [redacted] patients, [redacted] were randomised to the dapagliflozin arm and [redacted] were randomised to the placebo arm.[5]

A14. CS, Section B.2.4.1, Table 13, page 44. With respect to the primary endpoint and its component parts, the CS states that *"The contribution of each component of*

the primary composite endpoint to the overall treatment effect were also examined and no multiplicity adjustment was made to confidence intervals or p values." Please comment on why no adjustment was made to these analyses and whether such an adjustment would likely change the conclusions drawn from the results presented in CS Table 15, page 50.

As pre-specified in the statistical analysis plan, no multiplicity adjustment was made to confidence intervals as they should be interpreted descriptively and used as a measure of precision. No p-values were adjusted, and p-values for variables not included in the confirmatory testing sequence or following a non-significant test in the sequence are regarded as nominal.

Adjustment does not change the 95% confidence internals but alters the interpretation of the p-values, i.e. whether a given p-value can be deemed statistically significant or not. However, the individual components of the primary endpoint are exploratory analysis and not part of the hierarchy testing, and are hence presented descriptively in Table 15 of the CS.

A15. CS, Section B.2.6.3.4, page 55. The CS presents only a brief summary of health-related quality of life (HRQoL) outcomes in DAPA-CKD, stating that a clinically significant difference in KDQOL-36 and EQ-5D [redacted] observed. Please briefly provide the results of the statistical analyses from which this conclusion was drawn.

Change from baseline in KDQOL-36 and EQ-5D-5L was analysed in the DAPA-CKD trial using a repeated measures model including terms for randomised treatment group, visit, visit*treatment group and baseline score.[5] The model was used to derive a least squares estimate of the treatment difference with a 95% CI and corresponding two-sided p-value at given time points. Missing data was not imputed.

KDQOL-36 results

[redacted]

5 [redacted]

Table 5: Analysis of KDQOL-36 scores by subscale

Subscale/ treatment group	Absolute values		Repeated measures analysis						
			Change from baseline				Difference between dapagliflozin and placebo		
	Dapagliflozin (N=2,013), Mean (SD)	Placebo (N=2,019), Mean (SD)	Dapagliflozin		Placebo		LS Mean Difference (SE)	95% CI	p-value
			LS Mean (SE)	95% CI	LS Mean (SE)	95% CI			
Symptom/problem									
Baseline	[redacted]	[redacted]	-	-	-	-	-	-	-
12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Effects of kidney disease									
Baseline	[redacted]	[redacted]	-	-	-	-	-	-	-
12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Subscale/ treatment group	Absolute values		Repeated measures analysis						
			Change from baseline				Difference between dapagliflozin and placebo		
	Dapagliflozin (N=2,013), Mean (SD)	Placebo (N=2,019), Mean (SD)	Dapagliflozin		Placebo		LS Mean Difference (SE)	95% CI	p-value
			LS Mean (SE)	95% CI	LS Mean (SE)	95% CI			
Burden of kidney disease									
Baseline	[redacted]	[redacted]	-	-	-	-	-	-	-
12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SF-12 Physical health composite									
Baseline	[redacted]	[redacted]	-	-	-	-	-	-	-
12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Subscale/ treatment group	Absolute values		Repeated measures analysis						
			Change from baseline				Difference between dapagliflozin and placebo		
	Dapagliflozin (N=2,013), Mean (SD)	Placebo (N=2,019), Mean (SD)	Dapagliflozin		Placebo		LS Mean Difference (SE)	95% CI	p-value
			LS Mean (SE)	95% CI	LS Mean (SE)	95% CI			
SF-12 Mental health composite									
Baseline	[redacted]	[redacted]	-	-	-	-	-	-	-
12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: The repeated measures model includes terms for randomised treatment group, baseline scores, visit and visit by treatment group interaction.
Abbreviations: CI: confidence interval; LS: least squares; SD: standard deviation; SE: standard error; SF-12:12-Item Short Form Survey.
Source: AstraZeneca Data on File 2020: DAPA-CKD Clinical Study Report Table 14.2.7.14.[5]

EQ-5D results

The mean baseline EQ-5D-5L utility score was [redacted] in both the dapagliflozin and placebo arms. The difference in mean change from baseline in EQ-5D-5L utility scores between dapagliflozin and placebo at 4, 8, 12, 24 and 36 months is presented in Table 6.

Table 6: Difference in change from baseline EQ-5D-5L utility scores between dapagliflozin and placebo treatment arms

Characteristic and timepoint	Difference in LS mean change from baseline between dapagliflozin 10 mg and placebo		
	LS Mean difference (SE)	95% CI	p-value
4 months	[redacted]	[redacted]	[redacted]
8 months	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]
36 months	[redacted]	[redacted]	[redacted]

Footnotes: The EQ-5D-5L health states were converted to utility scores using the UK-specific value set. Utility scores range in the interval [-0.594,1] where 1 corresponds to the full health (the health state 11111) and -0.594 corresponds to the worst health (the health state 55555).
Abbreviations: CI: confidence interval; LS: least squares; SE: standard error.
Source: AstraZeneca Data on File 2020: DAPA-CKD Clinical Study Report Table 14.2.7.16.[5]

A16. CS, Section B.2.3.5, Table 9, pages 39 to 40. Options for dialysis may include haemodialysis, peritoneal dialysis and continuous ambulatory dialysis. Please clarify what the outcome of "chronic dialysis" in DAPA-CKD refers to.

Chronic dialysis included haemodialysis, peritoneal dialysis and continuous ambulatory dialysis and was met if either of the following was true:[5]

- the treatment had been ongoing for at least 28 days
- the dialysis treatment was stopped before Day 28 due to death, futility or patient electing to stop dialysis and the renal deterioration was deemed irreversible

Section B: Clarification on cost-effectiveness data

The original company base case and the revised company base case are summarised in Table 7. The revised company base case is based on the amendments described in response to B7, B17, B24, B25, B27 and B29. Results of other scenario analyses conducted in response to questions in Section B have been presented as amendments to both the original company base case and the revised company base case in the responses provided in this section. Explanations for how to set the model to generate each scenario can be found in the 'ERG Scenarios' sheet of the revised model.

Table 7: Original company base case and revised company base case

	Dapagliflozin + SOC (intervention)	Placebo + SOC (comparator)	Incremental	ICER (£/QALY)
Original company base case				
Life years	9.260	8.254	1.007	£6,655
QALYs	6.800	6.031	0.769	
Costs (£)	£56,526	£51,408	£5,118	
Revised company base case, based on amendments described in B7, B17, B24, B25, B27 and B29				
Life years	8.785	8.096	0.689	£6,158
QALYs	6.209	5.706	0.503	
Costs (£)	£53,366	£50,271	£3,095	

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years; SOC: standard of care.

Baseline models and relative treatment effectiveness

B1. Priority question. CS, Section B.3.5.1, Table 32, page 98. The economic model assumes that [redacted] of patients are not on ACE inhibitors or ARBs. The inclusion criteria in DAPA-CKD required patients to be on a maximum tolerated labelled dose of an ACE inhibitor or ARB, unless contraindicated. Please comment on the apparent disconnect between the population included in the trial and the target population represented by the model.

According to CPRD analysis from 2019/20, [redacted] of the CKD population (CKD stages 1 – 4) in clinical practice in England are on an ACE inhibitor ([redacted]) or an ARB ([redacted]).[18] This relatively low uptake is likely to be due to a number of factors. Some of the patients included in this analysis with earlier stages of CKD may not meet the threshold for ACE inhibitor/ARB therapy initiation recommended in the NICE CKD guidelines.[19] ACE inhibitors and ARBs are also associated with adverse events such as hyperkalaemia and hypotension which may necessitate their discontinuation and treatment may not always be reinitiated.

The DAPA-CKD trial population is part of the target population represented by the model. The patients enrolled had relatively advanced stage CKD (eGFR ≤75 – ≥25 mL/min/1.73m^2 and uACR ≥200 – ≤5000 mg/g) and 97% were receiving an optimised dose of an ACE inhibitor or ARB unless contraindicated.[20] In clinical practice, patients with more severe stages of CKD are more likely to be on an ACE inhibitor or ARB, however the proportion is still expected to be considerably lower than in the DAPA-CKD trial.[3, 21] Consequently, renal and CV outcomes of these patients in current clinical practice are likely to be worse than those observed in the DAPA-CKD trial and therefore the outcomes observed in the DAPA-CKD trial are likely to be conservative.

In clinical practice, dapagliflozin is expected to be used in addition to optimised SOC, which may or may not include an ACE inhibitor or ARB, as these medications are not recommended in all patients with CKD and may not be tolerated by some patients.[3] As discussed in Section B.1 of the CS, the haemodynamic mechanisms by which SGLT2 inhibitors act are thought to be both

distinct and complementary to ACE inhibitors or ARBs (i.e. RAAS inhibition), therefore the relative treatment effect of dapagliflozin as add-on therapy to standard care is likely to be similar irrespective of background therapy with ACE inhibitors or ARBs.[22] The significant treatment benefit observed in the DAPA-CKD trial is therefore expected to extend to patients who are not receiving ACE inhibitor or ARB therapy, and this is supported by subgroup analyses of the DECLARE-TIMI 58 and DAPA-HF trials and presented in Section B.2.13.2 (pages 73 and 74) of the CS, as well as by clinical experts consulted by the company.[3]

In summary, whilst a greater proportion of the DAPA-CKD cohort were treated with an ACE inhibitor or ARB compared with the treatment rates observed in clinical practice for the modelled population, the treatment effect with dapagliflozin is expected to be consistent regardless of background therapy.

B2. Priority question. CS, Section B.3.3.1.2, pages 82 to 85. Last observation carried forward (LOCF) imputation has been applied to generate the transition matrices from patient-level count data in DAPA-CKD.

(a) Please clarify if any cell corrections or priors have been applied to account for blank cells (missing transitions) in the matrices.

(b) Please provide more information on the process used to convert the imputed data to monthly transition matrices.

(c) Please provide an alternative “complete case” analysis in which the CKD stage count data are generated using consecutive pairs of CKD observations (missing data excluded).

(d) Please consider generating the matrices using alternative imputation rules e.g., using multiple imputation by chained equations (MICE).

a) Data informing the transition matrices was obtained by dividing eGFR observations into windows of length 365.25/12 days (corresponding to one month, and one model cycle), with the last observation before or at the window opening informing the “from” state, and the last observation before or at the window close informing the “to” state. These windows corresponded to the highest frequency of eGFR measurement available during the DAPA-CKD trial, but not all patients had measurements within each window. During the main phase of the trial, the majority of patients would be expected to have no updated eGFR measurements in the majority of windows as regular central laboratory assessment was only scheduled every 4 months as per the study protocol, with crossing of critical outcome thresholds triggering a confirmatory measurement after 4 weeks. As such, the data were neither fully regular nor of a sufficiently high frequency that direct observations at the window boundaries could be relied upon to inform unbiased transition rates over the whole population. However, by using the last available measurement to inform the status of patients unmeasured at the start and/or end of the interval, state transitions were generated which corresponded to the information available by which clinical decisions were made and the information by which the utility values of health states in the economic model were valued. Patients ceased informing further transition counts after their death, or after discontinuation from trial. Counts of these completely informed transitions were then used to derived the transition matrices.

Two sets of transition matrices were generated: one to govern the period from 0–4 months and a second set for the period 5 months and onwards. This split was applied due to the observation in Heerspink et al. 2020[4] that eGFR function showed a different trend for the dapagliflozin arm compared to the placebo arm (initial eGFR decline) but that after 4 months, the trend was stable. Entries for the observed transitions represent the total number of patients experiencing a given transition over one of the two intervals (0–4 months or 5+ months).

The patient counts for each state transition followed a multinomial probability since there is a total of 8 possible states (CKD 1, 2, 3a, 3b, 4, 5 [pre-renal replacement], dialysis and transplant). For prior probabilities, a flat Dirichlet probability distribution was applied, where each transition had a value of "1" (as the lowest whole number, non-zero count for each from/to state combination). Transition probabilities were calculated using the Bayesian inference Using Gibbs Sampling (BUGS) framework with the WinBUGS v1.4.3 software from the Medical Research Council Biostatistics Unit of the University of Cambridge. The model code is shown below:

```
model{
      for (i in 1:8){
            r[i,1:8] ~ dmulti(pi[i,1:8],n[i])
            pi[i,1:8] ~ ddirch(prior[i,1:8])
      }
      for (i in 1:8){
            for (j in 1:8){
                  rhat[i,j]<-pi[i,j]*n[i]
                  dev[i,j]<-2*r[i,j]*log(r[i,j]/rhat[i,j])
            }
            resdev[i]<-sum(dev[i,1:8])
      }
      resdevtot<-sum(resdev[1:8])
}
```

A sample of the data structure (DAPA-CKD data for the first interval from 0–4 months) is shown here:

```
list(r =
structure(.Data=c(23,8,1,1,0,0,0,0,13,549,190,14,1,1,0,0,1,164,1562,
337,15,0,0,0,1,19,291,3002,375,1,0,0,1,4,10,284,1678,6,1,0,0,1,0,1,5
,1,0,0,0,0,0,0,0,1,0,0,0,0,0,0,0,0,0,0), .Dim = c(8,8)), n =
c(33,768,2079,3689,1984,8,1,0),prior =
structure(.Data=c(1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,
1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,
1,1,1,1,1), .Dim = c(8,8)))
```

The model was run with 3 chains and 10,000 updates with the result checked for convergence. The resulting matrices were therefore adjusted during this process, but some cells may retain a 0 probability as can be seen in the first interval dapagliflozin transition matrix.

b) The matrices generated according to section a) above were applied according to time point in the model, such that one set of matrices (dapagliflozin, placebo) were used for cycles up to month 4 and a separate pair of matrices was used after that point. Within a time period (i.e. 0–4 months, 5+ months) the matrices do not change month to month.

To clarify, the Last Observation Carried Forward (LOCF) approach does not refer to an imputation of missing data. It represents the maintenance of the last clinical assessment of a

patient in the absence of updated evidence of patient state. From the source trial data, no observations were missing; every patient had an observation of eGFR that could be assigned to one of the two transition matrix intervals of 0–4 months or 5+ months and thus no imputation was required. The first interval set of matrices (separate for dapagliflozin and placebo) was applied for each of the months up to month 4, after which a different pair of matrices was used for all subsequent months.

c) A “complete case” analysis is not appropriate when using the DAPA-CKD trial data, as the eGFR assessments become desynchronised with the timestep of the economic model, and assessment frequency increased per study protocol as patients crossed critical thresholds, thereby biasing observed transition data in favour of changing state as opposed to remaining in state. The appropriate transition data is based upon the extant clinical status of the patients by which health state utility was associated and clinical decisions were made, which is known at the boundaries of each interval in the absence of evidence to the contrary.

d) Imputing missing data in the trial would be useful only in determining the unmeasured status of patients. No relevant measures for the economic model are dependent upon these unmeasured statuses. Health state utility values are dependent upon observed state (per last observation); clinical decisions were made dependent upon observed clinical status; event rates and survival equations are dependent upon the observed states. In addition, the company considers post-hoc specification of an imputation model for these data to be potentially specious. The company therefore believes that an analysis using MICE would not support the economic evaluation of dapagliflozin for CKD in clinical practice, as the frequency of patient assessment within the DAPA-CKD trial is a good representation of the varying frequency at which clinical assessments and decisions would be made in clinical practice.

B3. Priority question. CS, Section B.3.3.1.2, Tables 23 and 24, pages 84 and 85. The generated transition probabilities suggest some findings which might be considered unexpected: (a) patients with CKD1 have a higher probability of undergoing dialysis or kidney transplant compared with patients with CKD2-4; (b) patients can transition from CKD5 to CKD1 in a single 1-month cycle. Please comment on these two findings.

The cause of the transitions identified above being slightly higher than expected was due to the use of uninformative priors of 1 for all transitions. The use of this prior has the effect of slightly increasing the estimates where there are few or no transitions e.g. from CKD 5 to CKD 1 and from CKD 1 to dialysis where there were zero observed transitions for either dapagliflozin or SoC at 0–4 or 5+ months). Alternative priors were attempted to resolve this issue, however, using priors less than 1 had an adverse effect on the estimates for the other categories, hence the decision to retain the prior of 1. To test how sensitive the model is to these transition probabilities, we have created an alternative model version with all of the unexpected transitions specified in this question set to zero. The results show that with the updated transition probabilities there would be a small reduction in incremental QALYs alongside a small reduction in incremental costs, leading to a broadly similar ICER (Table 8). The analysis illustrates that although these transitions may be unexpected, their inclusion did not have a meaningful impact on the ICER due to the low probabilities of these transitions.

Table 8: Scenario analysis B3 – updated transition probabilities without unexpected transitions

	Dapagliflozin + SOC (intervention)	Placebo + SOC (comparator)	Incremental	ICER (£/QALY)
Scenario when implemented to original company base case				
Life years	9.265	8.256	1.009	£6,538
QALYs	6.807	6.035	0.772	
Costs (£)	£56,169	£51,125	£5,044	
Scenario when implemented to revised company base case†				
Life years	8.791	8.100	0.691	£5,974
QALYs	6.217	5.712	0.505	
Costs (£)	£53,003	£49,988	£3,015	

Footnote: † The revised company base case includes amendments described in response to B7, B17, B24, B25, B27 and B29 have been applied.
Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years; SOC: standard of care.

B4. Priority question. CS, Section B.3.3.1.3, pages 86 to 88. Please clarify why only standard parametric survival models were fitted to the survival data from DAPA-CKD.

(a) Were more flexible parametric models considered?

(b) Did model selection include consideration of the assumptions regarding the underlying hazard function for each model and whether this was consistent with the observed survival data?

(c) The CS states that the Gompertz model produced the most plausible estimates of long-term survival and refers to external registry data and clinical input. Please provide more detail about what you asked the clinical experts.

(d) Please provide further information to support the assumption of a constant treatment effect (a hazard ratio (HR) applied to proportional hazards (PH) models, or a constant acceleration factor applied to accelerated failure time models) between CKD stages and between treatment groups.

a) To determine appropriate survival models in a robust and transparent manner, the recommendations of the NICE Decision Support Unit in Technical Support Document 14 were followed.[23] In this guidance, an algorithm is specified which requires the rejection of the standard models prior to investigation of alternative modelling techniques:[23]

"*Exponential, Weibull, Gompertz, Log-logistic, log normal and Generalised Gamma models should be considered and if these appear unsuitable due to poor fit or implausible extrapolation, the use of piecewise modelling and other novel survival modelling methods such as those demonstrated by Royston and Parmar and Jackson et al should be considered*".

As the Gompertz model was selected as a credible model based upon these criteria, it was inconsistent with the provided guidance to continue investigating more flexible methods; scenario analysis considering other models of all-cause mortality was provided in the company submission to evaluate the sensitivity of the decision problem to this modelling decision. Therefore, there was no reason to further explore additional modelling approaches.

b) Model selection was undertaken using the guidance provided by TSD 14, including consideration of both internal goodness of fit (visually and per information criteria) and clinical plausibility. Given the hazard of mortality observed in the DAPA-CKD trial, models that predicted marginally constant or long-term monotonically decreasing hazard would result in survival rates in excess of the matched general population in extrapolation, and so these models (e.g. exponential, log-logistic, lognormal) were considered to have poor clinical face validity. The Gompertz model was considered to have good marginal properties as a monotonically increasing hazard function eponymously proposed as a model of human mortality which, possessing the proportional hazards property, had statistical face validity in a model incorporating time-varying covariates (in opposition to accelerated failure models, whose accelerative property is not intuitively linked to the time-varying hazards experienced by an individual or sub-cohort).[24] The clinical expert elicitation exercise to obtain long-term survival estimated for CKD patients provided confirmation about the clinical validity of the Gompertz model (see response to question B4 c below).

c) A remote clinical expert elicitation survey was conducted to obtain long-term survival estimates for placebo in a patient population similar to the DAPA-CKD trial.

Six clinical experts were first provided with a data book that summarised 13 publications reporting all-cause mortality or Kaplan–Meier survival curves for non-dialysis-dependent patients aged ≥18 years with CKD and elevated albuminuria identified as part of a systematic literature review. Randomised control trials, observational studies and national CKD registry reports were included in the data book.[25]

As part of the Excel-based formal expert elicitation survey, experts were trained on the impact of common cognitive biases and heuristics on decision making. Experts were then asked 10 calibration questions with known answers and 3 survey questions about long-term survival of patients enrolled in the DAPA-CKD trial (Table 9), which they answered using their expertise and knowledge of the field with support from the data book. Answers to the calibration questions were used to assess the quality of each participant's response to the survey questions.[25]

Table 9: Calibration and survey questions used in the expert elicitation survey

Calibration questions	
1	[redacted]
2	[redacted]
3	[redacted]
4	[redacted]
5	[redacted]
6	[redacted]

Calibration questions	
7	[redacted]
8	[redacted]
9	[redacted]
10	[redacted]
Survey questions	
1	[redacted]
2	[redacted]
3	[redacted]

Abbreviations: CKD: chronic kidney disease; ESKD: end-stage kidney disease; RRT: renal replacement therapy; UK: United Kingdom; US: United States of America.
Source: Willigers et al. 2021.[25]

For each survey question, experts provided low, high and median estimates for survival (%).

- Low: P10, expert is 90% confident that the true value is higher
- High: P90, expert is 90% confident that the true value is lower
- Median: P50, expert believes the true value is equally likely to be higher/lower that this number

Responses to the survey questions were weighted using the calibration question responses and then averaged to generate group estimates for % survival of patients at 10 and 20 years. Overall survival predictions for the patient population enrolled in the DAPA-CKD trial at 10 and 20 years were [redacted]% ([redacted]%) and [redacted]% ([redacted]%), respectively (presented as P50 [P10–P90]). These values were in line with survival curves generated from the literature using standard mortality ratios with mortality data from an age- and sex-adjusted general population. The expert elicited values fell within the survival range defined by the highest and lowest literature survival data.[25]

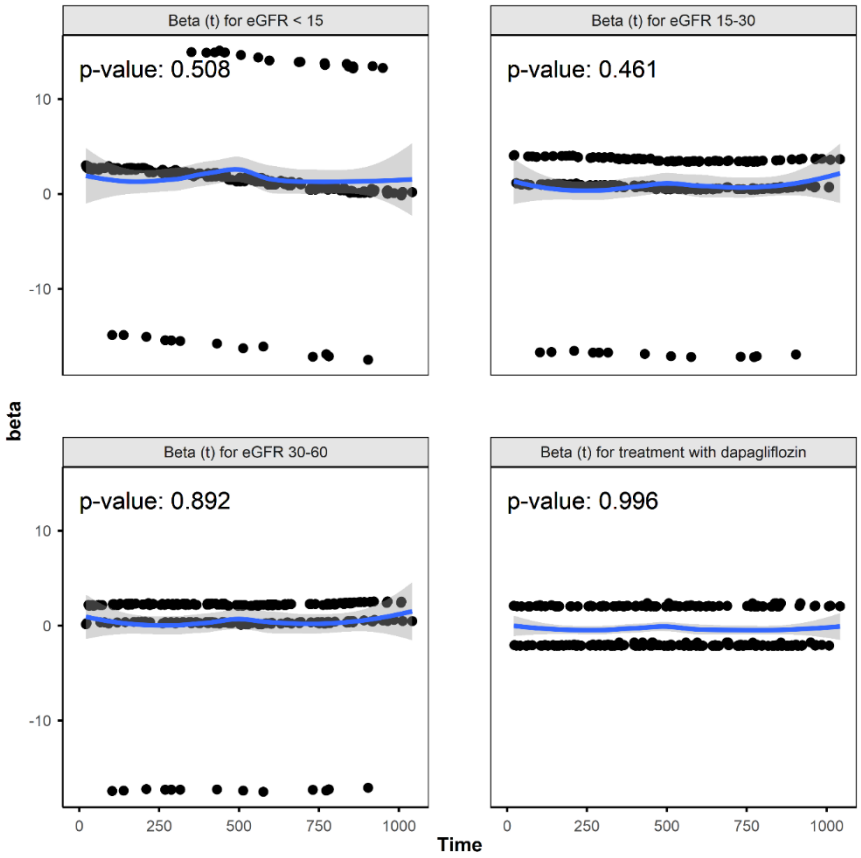
Risk equation-based survival modelling of data from DAPA-CKD was then conducted using the following seven distributions: exponential, gamma, generalised gamma, Gompertz, loglogistic, lognormal or Weibull. An overview of the survival extrapolations produced by each distribution is presented in Figure 1, alongside the clinical expert elicited survival estimates at 10 and 20 years. Based on the results of the clinical expert elicitation survey, the Gompertz model produced the best match to the experts P50 survival estimates (Figure 2).[25]

Figure 2*:* Risk equation-based overall survival predictions for patients in the placebo arm of the DAPA-CKD trial

Source: Willigers et al. 2021.[25]

d) A simple cox proportional hazards model was fitted to the DAPA-CKD data, conditional upon treatment with dapagliflozin and eGFR strata (<15; 15-30; 30-60, reference ≥60). The scaled Schoenfeld residuals for each term of this model are shown in Figure 3. A test for proportionality of hazards per Grambsch and Thernau was performed.[26] No terms rejected the assumption of constant proportionality at the 5% level.

Figure 3: Schoenfeld residuals of simple models of OS conditional upon treatment and eGFR category



Footnotes: Blue lines and shaded confidence intervals are LOESS smoothers of the residuals. Time dependence of the value of the smoothed line (e.g. positive/negative gradient) would be indicative of time-dependent hazard ratios.
Abbreviations: eGFR: estimated glomerular filtration rate; OS: overall survival

B5. Priority question. Model, Visual Basic for Applications (VBA), Module "modRiskEq", user-defined function "fncProbDeath". Survival in the dialysis and transplant states is assumed to follow an exponential distribution (constant hazard), based on Sugrue *et al*. Please explain how this study was identified, why it was selected to inform these parameters, and whether other potentially relevant

alternative sources exist. Please also justify the assumption that the hazard of death is constant in each of these health states.

The modelling team for the DAPA-CKD cost-effectiveness model conducted a systematic literature review of modelling approaches in CKD as part of the model conceptualisation and development process (published as Sugrue et al. 2019). Survival in dialysis and transplant states was modelled using a fixed probability (exponential distribution) based on the findings of this systematic literature review. This review included 101 studies, and the values applied in the model represent the mean transition probabilities from 56 and 12 observations of the probability of transitions from dialysis and transplant to death, respectively. We have subsequently also searched for other systematic reviews published in this area, however, most of these studies focus on the estimation of state specific utilities.[27-29] Only one study looked at cost-effectiveness studies more generally, and this focussed on phosphate binders, only included 27 studies and did not report modelled transition probabilities between states.[30]

B6. Priority question. Model, VBA, Module "modRiskEq", user-defined function "fncProbDeath". The economic model applies the treatment effect covariate from the survival analysis of DAPA-CKD to the survival model for patients in dialysis based on Sugrue *et al*. Please justify this approach.

The model assumes that treatment effect continues into the dialysis phase in line with previous modelling approaches found through a systematic literature review of cost-effectiveness models in CKD.[31] However, a scenario analysis has been provided in which the treatment effect covariate from the survival analysis of DAPA-CKD is not applied to the survival model for patients in dialysis (i.e. there is assumed to be no different in survival between treatment and control). The ICER of this scenario analysis was £2,571/QALY gained when applied to the original submission base case and £696/QALY gained when applied to the revised submission, which is lower than the company original base case (Table 10). This can be explained by the high cost and low HRQoL associated with the dialysis and transplant health states, which meant that the removal of the dapagliflozin survival benefits in these health states led to a reduction in the incremental costs which more than offset the reduction in incremental QALYs in this scenario compared with the company original base case.

Table 10: Scenario analysis B6 – no coefficient for dapagliflozin in the survival equations for the dialysis and transplant states

	Dapagliflozin + SOC (intervention)	Placebo + SOC (comparator)	Incremental	ICER (£/QALY)
Scenario when implemented to original company base case				
Life years	9.142	8.254	0.889	£2,571
QALYs	6.739	6.031	0.708	
Costs (£)	£53,230	£51,408	£1,821	
Scenario when implemented to revised company base case†				
Life years	8.690	8.096	0.594	£645
QALYs	6.164	5.706	0.458	
Costs (£)	£50,566	£50,271	£295	

Footnote: † The revised company base case includes amendments described in response to B7, B17, B24, B25, B27 and B29 have been applied.
Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years; SOC: standard.

B7. Priority question. Model, worksheets "Treatment Trace" and "Control Trace". The model predicts cumulative survival probabilities which are better than those in the general population at later ages. Please amend the model to assume that per cycle mortality risk is at least as high as that for the age- and sex-matched general population in England. For the base case model, this should be done using a weighted survival model for the general population derived from life tables for a population with initial age [redacted] years and in whom [redacted] of patients are female at baseline.

As requested, the model has been amended to ensure that the per cycle mortality risk is at least as high as that for the age- and sex-matched general population in England. The weighted survival model can be found in the worksheets entitled: 'Life Tables' and 'ACM Calculation'. The per cycle risk of general population mortality is compared to the risk of mortality generated using the survival equation derived from DAPA-CKD and the greatest of the two transition probabilities is used in the model.

When this modelling approach was implemented to the company original base case, the general population all-cause mortality cap only affected the all-cause mortality risks in the transplant and dialysis states, as the all-cause mortality risk estimated from the survival equations based on DAPA-CKD were higher than the general population mortality in all other health states.

The ICER associated with this scenario analysis was £5,645, which is lower than the ICER of the original company base case (Table 11). Similarly to scenario analysis B6, the alternative modelling approach used in scenario analysis B7 meant that patients in the dapagliflozin arm spent fewer life years in the dialysis and transplant health states, which led to a reduction in the incremental costs which more than offset the reduction in incremental QALYs in this scenario compared with the original company base case.

The change made to the model in this scenario analysis has also been implemented in the updated company base case.

Table 11: Scenario analysis B7 – all-cause mortality in model assumed to be at least as great as the general population morality risk

	Dapagliflozin + SOC (intervention)	Placebo + SOC (comparator)	Incremental	ICER (£/QALY)
Scenario when implemented to original company base case				
Life years	8.798	8.108	0.690	£5,645
QALYs	6.472	5.934	0.538	
Costs (£)	£52,875	£49,838	£3,037	

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

B8. Priority question. CS, Section B.3.3.1.3, pages 86 to 88. Please justify the assumption that treatment effects on mortality risk are maintained indefinitely whilst patients remain on treatment. Please provide the results of a scenario analysis in which this is not assumed.

There is no evidence to suggest that the treatment effect of dapagliflozin is associated with any treatment waning. The treatment effect of dapagliflozin was stable over the duration of the DAPA-CKD trial (median follow-up 2.4 years), as well as over the duration of previous trials in patients with T2DM, including the DECLARE-TIMI 58 trial (median follow-up 4.2 years). [redacted]. Furthermore, the Committee-preferred assumptions in prior NICE appraisals of dapagliflozin in type 2 diabetes (T2DM [TA390, TA418 and TA288]) and heart failure with reduced ejection fraction (HFrEF [TA679]) did not include treatment waning.[32-35]

In the DECLARE-TIMI 58 trial, a sustained reduction in uACR (Figure 4) and a sustained reduction in the decline of eGFR (Figure 5) was observed over a median follow-up of 4.2 years.[6] By slowing the progression of CKD (i.e. progression to higher uACR and lower eGFR levels), dapagliflozin reduces the risk of mortality due to the association between higher eGFR and lower uACR with reduced risk of all-cause mortality.[36] It is also likely that dapagliflozin contributes to reduced risk of mortality through a mechanism independent of its effect on CKD progression, as the treatment effect of dapagliflozin extends to other endpoints such as hospitalisation for heart failure (hHF), which is also associated with an increased mortality risk.[37, 38] Therefore, the benefits of dapagliflozin on reducing risk of mortality are expected to persist over a patient's lifetime.

Figure 4: Mean percentage change from baseline in uACR over time in the DECLARE-TIMI 58 trial

Abbreviations: uACR: urine albumin-to-creatinine ratio.
Sources: AstraZeneca Data on File 2020: DECLARE Clinical Study Report Figure 16.[7]

Figure 5: Mean percentage change from baseline in eGFR over time in the DECLARE-TIMI 58 trial

Abbreviations: eGFR: estimated glomerular filtration rate.
Sources: AstraZeneca Data on File 2020: DECLARE Clinical Study Report Figure 19.[7]

To investigate the impact of treatment waning on the ICER, a conservative scenario analysis has been provided in which the treatment effects on mortality risk are removed after 29 cycles (based

on the median follow-up of 2.4 years in the DAPA-CKD trial). The functionality to modify this time point has been provided in the updated model (see 'ERG Scenarios' sheet of the revised model).

The results of this scenario analysis can be found in Table 12 for both the scenario applied to the original company base case and the revised company base case. As expected, the total number of life years accrued in the dapagliflozin arm was reduced in these scenarios compared to the base case, however, the additional mortality resulted in lower costs from fewer life years spent in the more expensive later stage health states. Consequently, dapagliflozin was associated with cost-savings and QALY gains in this scenario analysis.

Table 12: Scenario analysis B8 – mortality benefits of dapagliflozin assumed to stop after 2.4 years

	Dapagliflozin + SOC (intervention)	Placebo + SOC (comparator)	Incremental	ICER (£/QALY)
Scenario when implemented to original company base case				
Life years	8.604	8.254	0.350	Dominant
QALYs	6.346	6.031	0.315	
Costs (£)	£49,615	£51,408	-£1,794	
Scenario when implemented to revised company base case†				
Life years	8.398	8.096	0.302	Dominant
QALYs	5.968	5.706	0.262	
Costs (£)	£48,325	£50,271	-£1,945	

Footnote: † The revised company base case includes amendments described in response to B7, B17, B24, B25, B27 and B29 have been applied.
Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years; SOC: standard

B9. CS, Section B.3.3.1, pages 81 to 82. Survival, hospitalisation for heart failure (hHF) risks and acute kidney injury (AKI) risks have been adjusted to reflect the CPRD population. However, the CKD transition probabilities are unadjusted and reflect the DAPA-CKD trial population. Please justify not adjusting the transition probabilities.

To the company's knowledge, there are no methods for the derivation of adjusted transition probabilities that are equivalent to those used to generate the adjusted survival equations and risk equations used in the dapagliflozin cost-effectiveness model. The only alternative approach would be to subset the health state transition data by subgroups of interest. This approach is severely limited due to the loss of power and is not considered necessary to use subgroup-specific transition probabilities, given the generalisability of the DAPA-CKD trial, as discussed in our response to B32.

As discussed in the CS, UK nephrologists and GPs from 1:1 interviews and a clinical advisory board considered the DAPA-CKD trial to be generally representative of UK clinical practice.[3, 39]

To further ensure the generalisability of the cost-effectiveness estimates to UK clinical practice, the baseline characteristics of the base case cost-effectiveness analysis were derived from patients with stage 1–4 CKD from the CPRD. A higher proportion of patients had CKD stage 1-3a in this CPRD population compared with the trial population. Current CKD status is used as a

predictor of future CKD status by applying the baseline CKD characteristics of this CPRD population. The change in CKD stage distribution over time in the modelled population, through the application of transition probabilities, impacts the survival, hHF and AKI risk profiles of the population. These outcomes are modelled through adjusted survival and risk equations which include time-varying CKD stage distribution as one of the covariables. The CKD transitions, being dependent upon current CKD stage are intrinsically appropriate to the modelled population, and therefore the transition probabilities derived from DAPA-CKD are expected to be generalisable to CKD patients in UK clinical practice.

B10. CS, Section B.3.3.1.2, pages 83. The CS states "The transition probabilities between dialysis and kidney transplant were sourced from Sugrue et al. 2019 as there were not enough observed events in the DAPA-CKD trial to reliably derive these transition probabilities de novo." How many of these events were observed in DAPA-CKD? How many events would be considered to be "enough"?

Across both treatment arms and the full duration of the trial, 121,734 patient transitions were observed. Of these, 6 involved patients moving from dialysis to transplant (2 in the dapagliflozin arm and 4 in the placebo arm) representing 0.005% of the recorded patient transitions. This count was deemed insufficiently informative for modelling purposes.

B11. CS, Sections B.3.3.1.2 and B.3.3.1.3, pages 82 to 88. Treatment effects are applied as covariates in the parametric survival model and separate matrices are applied to transition probabilities in each treatment group. Please justify this approach and comment on whether assuming treatment effects on both mortality risk conditional on CKD state and on CKD transitions might be double-counting the benefits of dapagliflozin. Please present a scenario in which treatment effects are applied to transitions but not survival.

The DAPA-CKD trial demonstrated that dapagliflozin is associated with a reduction in the risk of disease progression (HR for sustained ≥50% decline in eGFR: 0.53, 95% CI: 0.42, 0.67, p-value<0.0001, see Table 15 of company submission) as well as a reduction in all-cause mortality even after controlling for dapagliflozin's effect on reducing the population rate of disease progression (HR 0.69; 95% CI: 0.53, 0.88; p=0.004, see Section B.2.6.2.3 of company submission). As such, the application of treatment-specific transition probabilities and a dapagliflozin coefficient in the parametric survival equations can be justified.

Importantly, the multivariable survival equation was derived in the context of the observed delay in CKD progression associated with dapagliflozin over time, where CKD stages were covariables in the survival equation. As such, a proportion of the treatment effect of dapagliflozin on all-cause mortality is mediated through the delay in CKD progression and a proportion of the benefits is mediated directly through the dapagliflozin coefficient of the all-cause mortality survival equation. The AIC and BIC of the parametric survival equations evaluated were calculated based on comparison of the fitted survival equation, when taking treatment-specific CKD state observations into account, and the all-cause mortality observed in the DAPA-CKD trial.

Therefore, the removal of either the dapagliflozin coefficient from the all-cause mortality survival equation, or the use of treatment-independent transition probabilities would systematically underestimate the treatment effect associated with dapagliflozin.

B12. CS, Section B.3.3.1.3, pages 86 to 88. The CS states that *"Multivariable analysis was then carried out using all covariables to assess which covariables were still influential after multivariable adjustment, the effect size of each covariable, and the clinical face validity of the directionality of the effects."* Please clarify who made these decisions about clinical face validity?

The cost-effectiveness model was developed in close collaboration with [redacted], who provided clinical expert input and validation of the survival equation for all-cause mortality and risk equations for hHF and AKI derived from DAPA-CKD. Additionally, a clinical expert elicitation exercise was carried out in collaboration with 6 clinical experts (see response to B4c). This elicitation study confirmed that the Gompertz survival equation for all-cause mortality selected for the cost-effectiveness model has clinical validity.[25]

B13. CS, Section B.3.3.1.4 and B.3.3.1.5, pages 88 to 89. hHF and AKI are modelled using generalised estimating equations (GEE). Please provide more detail regarding the data used to inform the analysis and the model selection process for each of these two models.

hHF is defined as a recurrent event, with one event per patient per hospital visit at date of entry to hospital. This event is classified and adjudicated as per the definition within the DAPA-CKD study analysis plan. A longitudinal dataset was created with 30 day slices for time updated covariates. In each slice for each patient, an hHF event flag is set to 1 when at least one event was observed to occur and 0 otherwise. Poisson family GEE models with a log link conditional upon baseline and time-updated covariates were fitted to these data, using patient ID as a cluster term and using an "independence" correlation structure. The selected model was determined by stepwise selection from a set of potential covariates. The superset of covariates to select from was:

Age, Sex, Type 2 Diabetes Mellitus at baseline, Race (Asian, Black or African American, Other, White), Smoking Status (Current, former), Prior HF, prior MI, Prior Stroke, Glomerulonephritis, UACR, baseline Haemoglobin, BMI, Potassium, eGFR, systolic BP.

The model structure described for hHF was repeated for AKI. AKI was a recurrent event, measured as a doubling in serum creatinine, between subsequent measurements.

B14. CS Appendix D.3, pages 49 to 67. To inform sensitivity analysis 7, an anchored MAIC was conducted between DAPA-CKD and CREDENCE.

(a) CS Appendix D.3.2.2 lists 21 variables that were available in CREDENCE and considered to be either treatment effect modifiers of prognostic variables. Please clarify which of these were considered by the clinical experts to be potential treatment effect modifiers (rather than prognostic variables).

(b) Please clarify whether there were any potential treatment effect modifiers that were not available in CREDENCE.

(c) CS Appendix D.3.2.5 details the selection of covariates. Six adjustment sets were determined. Please clarify which of the variables were included in each of these.

(d) CS Appendix D.3.4 states [redacted]. Please provide details of the PH testing. Given that there is evidence to suggest non-proportional hazards for at least some outcomes, comment on the applicability of the Cox PH model. Were other methods (not assuming PH) considered?

a) The variables that made up the "Clinical unranked" matching set were the complete set of all covariates indicated at any time by the two clinical experts involved to be a potential treatment effect modifier on either a relative or absolute scale. These were:

- Race (Black or African American)
- History of heart failure
- Duration of diabetes
- Baseline BMI
- Baseline SBP
- Baseline eGFR
- Baseline UACR
- Insulin treatment
- RAASi treatment

b) During the feasibility assessment of the MAIC and development of the indirect treatment comparison protocol, clinical experts were consulted. As part of this process, as well as nominating which of the reported covariates they considered to be potential treatment effect modifiers, they were asked if there were any other potential treatment effect modifiers that may have been unreported by either trial. No additional treatment effect modifiers were identified.

c) Please see Table 13 below. Where a variable is represented as both a continuous and a categorised measure (e.g. eGFR), the representation used in the reduced sets was used in the "All" matching set.

Table 13: Variables included in adjustment sets

		Matching Set											
Variable	Aggregate Data	Primary	Clinical " A"	Clinical " A/B"	Clinical unranked	CREDENCE primary	CV death*	ACM*	ESRD	HHF	Doubling of serum creatinine	CREDENCE renal composite	CREDENCE exploratory renal
Age	Mean, SD												
Sex	Proportion												
Race (white)	Proportion												
Race (black)	Proportion			✓	✓								
Race (Asian)	Proportion												
Smoking status (current)	Proportion	✓								✓			
Hx HTN	Proportion	✓									✓		
Hx HF	Proportion	✓		✓	✓					✓			
Hx MI	Proportion	✓											✓
Hx Stroke	Proportion												
Hx Amputation	Proportion												
Duration of diabetes	Mean, SD	✓			✓	✓	✓	✓	✓		✓	✓	
BMI	Mean, SD				✓								
SBP	Mean, SD	✓	✓	✓	✓								✓
DBP	Mean, SD												
HbA1c	Mean, SD												
EGFR	Mean, SD												
EGFR < 45	Proportion	✓	✓	✓	✓								✓
60 <= EGFR	Proportion	✓	✓	✓	✓								✓
UACR <= 1000	Proportion		✓	✓	✓								

		Matching Set											
Variable	Aggregate Data	Primary	Clinical " A"	Clinical " A/B"	Clinical unranked	CREDENCE primary	CV death*	ACM*	ESRD	HHF	Doubling of serum creatinine	CREDENCE renal composite	CREDENCE exploratory renal ..
BLCM – Insulin	Proportion				✓								
BLCM - Sulfonylurea	Proportion												
BLCM – Biguanides	Proportion												
BLCM – GLP1RA	Proportion												
BLCM – DPP4i	Proportion												
BLCM – Statin	Proportion												
BLCM – Antithrombotic	Proportion												
BLCM – RAASI	Proportion	✓	✓	✓	✓					✓			✓
BLCM – Beta-blocker	Proportion												
BCLM – Diuretic	Proportion												

Footnotes: * No treatment effect modifying covariates identified – duration of diabetes used as a placeholder.
Abbreviations: ACM: all-cause mortality; BLCM: Baseline concomitant medication; BMI: body mass index; CV Death: cardiovascular death; DBP: diastolic blood pressure; DPP4i: dipeptidyl peptidase-4 inhibitor; EGFR: estimated glomerular filtration rate; ESRD: end-stage renal disease; GLP1RA: glucagon-like peptide-1 receptor agonists; HbA1c: glycated haemoglobin; HF: heart failure; HHF: hospitalisation for heart failure; HTN: hypertension; Hx: history of; MI: myocardial infarction; RAASI: renin-angiotensin-aldosterone system inhibitor; SBP: systolic blood pressure; SD: standard deviation; UACR: urine albumin to creatinine ratio.

d) The only available data for the treatment effect of canagliflozin plus SoC versus SoC was expressed in terms of constant hazard ratio, and thus this was the measure used to accomplish an anchored MAIC. The constancy of the hazard ratio in the weighted and unweighted DAPA-CKD data for some outcomes was considered to be in potential violation of proportional hazards when inspecting divergent-convergent empirical cumulative hazard functions. However, these data were still preferred as providing representative information, whereas alternative methods of establishing a treatment effect given the available aggregate data would be subject to a greater risk of residual bias.

In the absence of a well-established treatment effect measure, determination of treatment effect modifiers would be challenging, and the fallback would be to undertake adjustment upon all prognostic variables in order to predict absolute outcomes in the matched population (at which point an unanchored comparison would be unbiased) and form some more complex measure of treatment effect, e.g. using fractional polynomial models or independent models of the outcomes. Formation of these models would require digitisation and reconstruction of pseudo-individual-patient-data from the comparator trial, further increasing uncertainty. It is unclear whether, given the data reported, complete adjustment for all differences in prognostic variables is possible. In addition, the assumption of continuity in the case of extrapolation of a fractional polynomial based treatment effect is not well justified, and may be as inaccurate as the assumption of the extrapolation of the approximate mean hazard ratio over log time, as determined by Cox modelling.

Despite its limitations, the constant hazard ratio has the advantage of being available, understood, and easily measured. It is representative of an average measure over trial follow-up, and so can be compared between trials of similar follow-up even if the true hazard ratio varies with time.

Discontinuation

B15. CS, Section B.3.3.1.7, pages 90 to 91. Please justify the assumption that the probability of discontinuing dapagliflozin is constant in every cycle over the model time horizon. Please also comment on the plausibility of assuming an ongoing risk of discontinuation given the lack of effective alternative treatments which can slow progression of CKD. Please explore scenarios in which the risk of discontinuation plateaus over time.

Clinical trials are not generally designed to estimate long term outcomes such as discontinuation, so even with the DAPA-CKD trial which observes patients for a median duration of 2.4 years, there is a lack of evidence on which to base assumptions of long-term treatment discontinuation. However, the treatment discontinuation probability was derived from the trial and assumed to be constant in the long term. This value can be altered in the model for scenario analysis to determine the impact and was tested within the DSA with lower and upper bounds of 0% and 10%, leading to ICER shifts of approximately £1,000.

An additional scenario analysis has been undertaken in response to this question, in which the dapagliflozin discontinuation rate linearly tapers to 0% over a four-year period from the start of the model. The functionality to specify different annual discontinuation rates for the first four years and all subsequent years of the modelled horizon has been provided in the updated model.

The results of this scenario analysis can be found in Table 14 for the scenario applied to the original company base case and to the revised company base case and show this scenario has a modest effect on the ICER..

Table 14: Scenario analysis B15 – dapagliflozin discontinuation assumed to linearly taper over the first 4 years of model

	Dapagliflozin + SOC (intervention)	Placebo + SOC (comparator)	Incremental	ICER (£/QALY)
Scenario when implemented to original company base case				
Life years	9.611	8.254	1.357	£7,486
QALYs	7.058	6.031	1.027	
Costs (£)	£59,099	£51,408	£7,691	
Scenario when implemented to revised company base case†				
Life years	8.950	8.096	0.854	£6,841
QALYs	6.323	5.706	0.616	
Costs (£)	£54,488	£50,271	£4,217	

Footnote: † The revised company base case includes amendments described in response to B7, B17, B24, B25, B27 and B29 have been applied.
Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years; SOC: standard

B16. CS, Section B.3.3.1.7, pages 90 to 91. Please present a survival analysis of time to treatment discontinuation in DAPA-CKD. Please describe which parametric survival models have been fitted and report goodness-of-fit statistics (Akaike Information Criterion and Bayesian Information Criterion) for each fitted model. Please include functionality to include any of these distributions in the economic model. Please also present the empirical hazard function and the Kaplan-Meier survival function for time to discontinuation in DAPA-CKD.

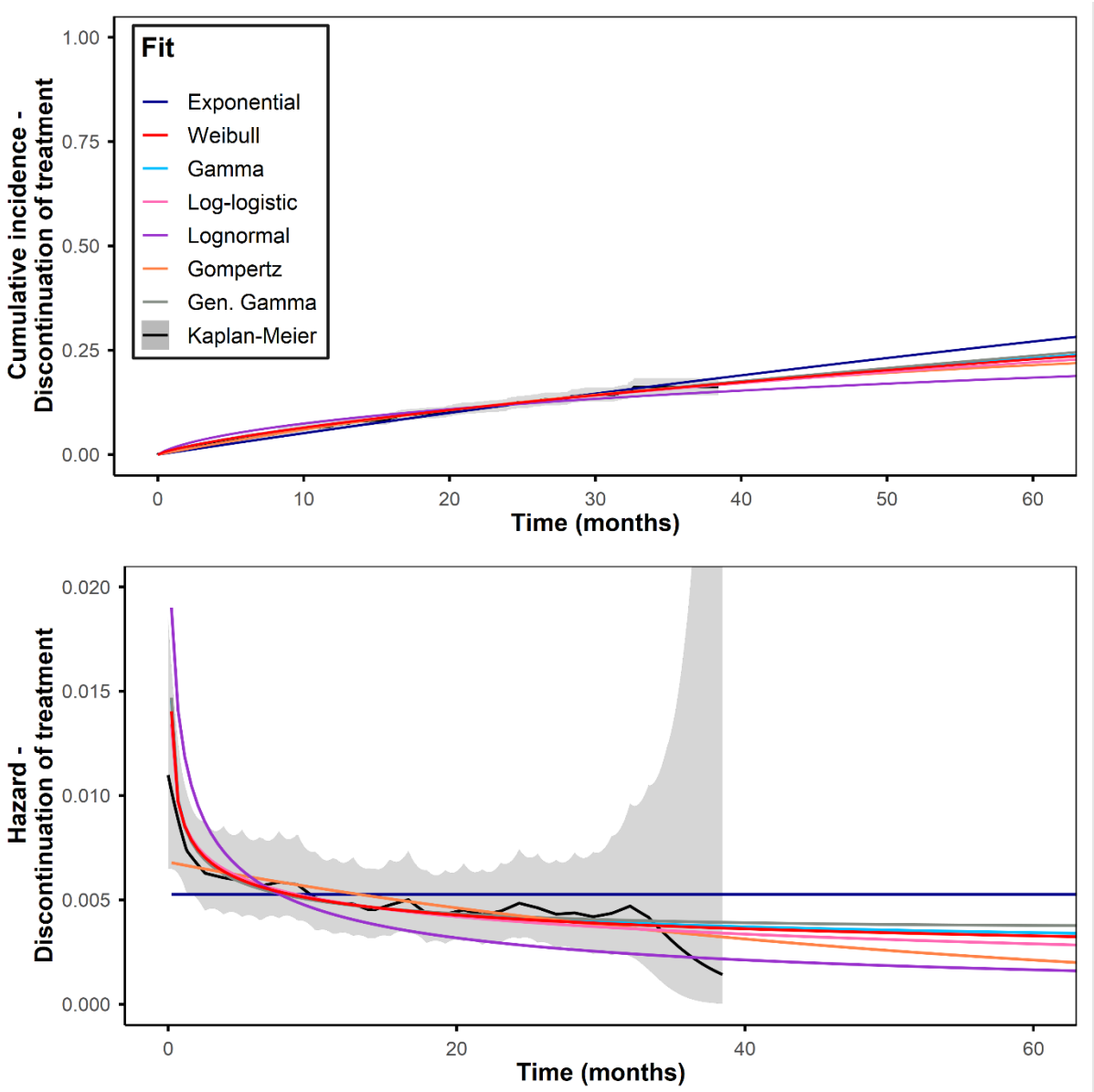
The seven standard unimodal survival distributions investigated for modelling of all-cause mortality were investigated for use in modelling discontinuation of treatment in DAPA-CKD. The results of the model fit are shown in Table 15. The Gamma, Weibull and log-logistic models had similar goodness of fit, and displayed an initially sharply decreasing hazard profile, followed by a more gradual decrease in the long term (Figure 6). These models were made available to use in the economic model and a scenario was run using the gamma model as the model with best statistical fit and consistent following of the empirical hazard profile over the whole trial. The results of this scenario analysis can be found in Table 16 for the scenario applied to the original company base case and to the revised company base case and show that although the impact of this change to discontinuation does increase the ICER, the overall result it still highly cost-effective for dapagliflozin. The changes are comparable to those seen in the scenario of question B15.

Table 15. Parameters and goodness of fit of models of discontinuation to DAPA-CKD data

Model	Parameter			AIC	BIC
	1	2	3		
Weibull	7.582E-01	3.555E+02	N/A	3439.14	3450.49
Log-logistic	7.855E-01	2.979E+02	N/A	3441.24	3452.59
Lognormal	7.054E+00	3.293E+00	N/A	3510.08	3521.43
Gompertz	-1.945E-02	6.813E-03	N/A	3456.81	3468.16
Exponential	5.266E-03	N/A	N/A	3462.59	3468.27
Gamma	7.393E-01	2.205E-03	N/A	3438.06	3449.41
Generalised Gamma	5.730E+00	6.537E-01	2.093E+00	3439.35	3456.37

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; N/A, not applicable.

Figure 6. Cumulative incidence and hazard function of models of discontinuation to DAPA-CKD data



Footnotes: The black line on the grey area on the hazard plot is a B-spline based estimator of hazard of discontinuation and associated 95% confidence interval. The domain of this estimator is limited by the first and last events of the dataset.

Table 16: Scenario analysis B16 – dapagliflozin discontinuation assumed to have Gamma hazard function

	Dapagliflozin + SOC (intervention)	Placebo + SOC (comparator)	Incremental	ICER (£/QALY)
Scenario when implemented to original company base case				
Life years	9.365	8.254	1.111	£6,970
QALYs	6.877	6.031	0.846	
Costs (£)	£57,306	£51,408	£5,898	
Scenario when implemented to revised company base case†				
Life years	8.834	8.096	0.738	£6,414
QALYs	6.242	5.706	0.536	
Costs (£)	£53,710	£50,271	£3,439	

Footnote: † The revised company base case includes amendments described in response to B7, B17, B24, B25, B27 and B29 have been applied.

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

Health utilities

B17. Priority question. Model, VBA, module "ModMarkov", sub-routine "RunTrace". Please amend the model to include the adjustment of utilities for increasing age, using the linear model of EQ-5D-3L by age reported by Ara and Brazier (Value in Health, 2010;13(5)), assuming adjustment weights are applied multiplicatively.

As requested, the model has been amended to include the impact of age on utility. With this approach, we first defined the baseline age-dependent utility of patients initiated in the model using the general population utility model described in Ara and Brazier and the baseline patient age.[40] We then estimated the general population utility for each cycle thereafter in a similar way and divided through by the baseline utility to derive an age-dependent multiplication factor. This factor was then applied to all utility estimates in the model in the given cycle. The age-dependent utility adjustment factors may be found in the 'Age-dependent Utility' worksheet and the ability to turn off the adjustment is provided on the 'Model Interface' worksheet in cell K10.

The impact of this change in isolation is described in **Error! Reference source not found.**. There is a small increase in the ICER associated with this scenario analysis compared to the original company base case, due to the slightly diminished QALY gains as patients age. Nevertheless, dapagliflozin remain highly cost-effective with an ICER well below the cost-effectiveness threshold. The change made to the model in this scenario analysis has also been implemented in the updated company base case.

Table 17: Scenario analysis B17 – age-adjusted utility values

	Dapagliflozin + SOC (intervention)	Placebo + SOC (comparator)	Incremental	ICER (£/QALY)
Scenario when implemented to original company base case				

	Dapagliflozin + SOC (intervention)	Placebo + SOC (comparator)	Incremental	ICER (£/QALY)
Life years	9.260	8.254	1.007	£7,151
QALYs	6.518	5.803	0.716	
Costs (£)	£56,526	£51,408	£5,118	

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

B18. CS, Section B.3.4.1, pages 91 to 92. Health state utility values have been derived from a linear mixed effects regression model fitted to EQ-5D data collected in DAPA-CKD. EQ-5D response data are known not to be normally distributed. Please comment on the appropriateness of this approach, and clarify why alternative models, such as Adjusted Limited Dependent Variable Mixture Models (ALDVMM), have not been used.

The Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life Endpoints Data (SISAQOL) Consortium reported in 2020 upon recommendations for the analysis of quality-of-life outcome endpoints in cancer randomised controlled trials, concluding that linear mixed models were recommended to describe response trajectories.[41] The derived HSUVs provide plausible estimates and the use of linear mixed models informed by a large cohort is consistent with NICE Decision Support Unit guidance in Technical Support Document 12, which states that "in the majority of cases, the uncertainty in the mean can be adequately described by sampling from a normal distribution."[42]

B19. CS, Section 3.4.5.3, page 96, Table 31. The utility values for all CKD health states, including people with CKD 5 pre-dialysis/transplant, appear to be [redacted] and are [redacted] to EQ-5D estimates for the age- and sex-matched general population. Please comment on the face validity of the predictions of the linear mixed effects model for EQ-5D.

The utility values predicted by the linear mixed effects model for EQ-5D are aligned with those observed in the literature for patients with CKD in the UK (Table 18).

Table 18: Utility values observed in studies conducted in the UK of patients with pre-dialysis CKD in the HRQoL SLR (Company Submission, Appendix H)

Study	Population	EQ-5D utility scores at baseline
Submission values		
DAPA-CKD[5]	DAPA-CKD trial	CKD 1: 0.770 CKD 2: 0.770 CKD 3: 0.770 CKD 4: 0.760 CKD 5 (pre-RTT): 0.730
UK studies		
BiCARB study group, 2020[43]	Advanced CKD (eGFR <30 mL/min/1.73 m^2)	0.73–0.74
Blakeman 2014[44]	Stage 3 CKD	0.67
Dharmarartnam 2019[45]	Pre-dialysis CKD with mean eGFR: 40.6 (SD: 26.6) ml/min/1.73m^2)	0.70
Fraser 2020[46]	Stage 3 CKD	Karnofsky score of 90[a]: 0.94 Karnofsky score of 60[a]: 0.45
Jesky 2016[47]	Pre-dialysis CKD	G1/G2: 0.85 (0.70, 1.00) G3a: 0.80 (0.69, 1.00) G3b: 0.80 (0.68, 1.00) G4: 0.74 (0.62, 0.85) G5: 0.73 (0.62, 1.00)
Munyombwe 2020[48]	Chronic renal failure, 12-months following hospitalisation for an acute coronary syndrome	0.60
Schlackow 2017[49]	Moderate-to-advanced CKD	0.86[b]

Footnotes: [a] The Karnofsky Performance Status scale defines functional impairment as a score of ≤70. [b] Intercept (60-year-old white female not on dialysis, non-smoker, A-levels or above, BMI >25 <30 kg/m^2, without previously failed transplant, diabetic nephropathy or history of vascular disease).

Furthermore, the utility values derived for CKD in a previous NICE appraisal (TA599) are presented in Table 19 below. The values proposed by the ERG were ultimately preferred by the Committee and these values are in line with those used in the present company submission.[50] Table 20 shows the results of a scenario analysis using the ERG-preferred values from TA599, with the additional assumption that the utility values for CKD stage 1 and 2 are the same as CKD stage 3a/3b (because stage 1 and 2 were not discussed in TA599). This scenario analysis was associated with a lower ICER compared to the original company base case for the current appraisal.

Table 19: Utility values for patients with CKD from the ERG review for TA599

Study	ERG estimates (SE)
Sodium zirconium cyclosilicate NICE appraisal (TA599)	
3a / 3b	0.80 (0.02)
4	0.74 (0.02)
5 (pre RRT)	0.71 (0.02)

Abbreviations: ERG: evidence review group; RRT: renal replacement therapy; SD: standard deviation; SE: standard error.
Source: NICE TA599: Committee papers.[50]

Table 20: Scenario analysis B19 – Committee preferred CKD health state utility values from TA599

	Dapagliflozin + SOC (intervention)	Placebo + SOC (comparator)	Incremental	ICER (£/QALY)
Scenario when implemented to original company base case				
Life years	9.260	8.254	1.007	£6,453
QALYs	6.916	6.123	0.793	
Costs (£)	£56,526	£51,408	£5,118	
Scenario when implemented to revised company base case†				
Life years	8.785	8.096	0.689	£5,941
QALYs	6.316	5.795	0.521	
Costs (£)	£53,366	£50,271	£3,095	

Footnote: † The revised company base case includes amendments described in response to B7, B17, B24, B25, B27 and B29 have been applied.
Abbreviations: ERG: evidence review group; ICER: incremental cost-effectiveness ratio; QALY: quality adjusted life year; SOC: standard of care.

Costs

B20. Priority question. CS, Section B.3.5.2, pages 98 to 99. The study reported by Kent *et al* which is used to inform CKD-specific health state costs does not include costs associated with (i) drugs, (ii) primary care, (iii) prescribing or (iv) outpatient attendances because these were not collected in the SHARP trial. Given that dapagliflozin is predicted to extend survival, excluding these costs may underestimate the ICER. Please amend the model to include plausible assumptions regarding these missing cost components, with explicit consideration of the costs of managing both CKD and comorbid conditions (Type 2 diabetes mellitus, hypertension [HTN] and cardiovascular disease [CVD]).

To address this question, alternative estimates of the costs for the management of CKD were generated using data from the CPRD cohort of the DISCOVER CKD study, an observational study in patients with CKD, aged ≥18 years, with ≥1 uACR measure and two eGFR measures of 0-75ml/min/1.73m^2 recorded at least 90 days apart between January 2008 and September 2018.

Annual costs for the management of CKD were estimated based on the healthcare resource use from the CPRD cohort of the DISCOVER CKD study, including GP visits, outpatient visits, clinical care visits and ambulance use, and costed using unit costs from PSSRU and NHS reference costs, and inflated where relevant to a 2019 cost year. Inpatient hospitalisation costs were not included in these analysis to avoid double-counting with the HF hospitalisation and AKI hospitalisation events in the model. The omission of cost of hospitalisation for other causes is likely to be conservative with respect to dapagliflozin, as it is expected that dapagliflozin would be associated with a reduction in the risk of hospitalisation also for other causes, especially those related to CKD. Drug costs were also excluded from the disease management costs to avoid

double-counting in the model, as drug costs are captured as part of background therapy costs (see B21).

The results from the analysis of the CPRD cohort of the DISCOVER CKD study are shown in Table 21. Because CKD stage 1 patients were not included in DISCOVER CKD, it was not possible to estimate the cost of managing CKD stage 1 based on these data.

Table 21: Annual health state costs and per-event costs

	CPRD cohort of DISCOVER CKD					CS base case (Kent et al. 2015[51])
	GP visit	Outpatient visit	Clinical care visit	Ambulance use	Total	
CKD 1	N/A	N/A	N/A	N/A	N/A	£1,211.41
CKD 2	£515.89	£1,012.60	£169.07	£264.24	£1,961.80	£1,211.41
CKD 3a	£525.34	£1,167.21	£163.46	£263.32	£2,119.33	£1,211.41
CKD 3b	£594.52	£1,133.46	£199.07	£314.75	£2,241.79	£1,211.41
CKD 4	£684.22	£1,864.10	£220.03	£348.94	£3,117.29	£4,241.65
CKD 5 (pre-RRT)	£796.04	£4,611.27	£222.66	£314.71	£5,944.68	£14,872.17

Footnote: The annual costs were converted to monthly costs in the model before being applied to the monthly model cycles. [a]Where SEs were not reported in the literature, SEs were assumed to be 10% of the mean value
Abbreviations: CKD: chronic kidney disease; CPRD, Clinical Practice Research Datalink; CS, company submission; N/A, not available
Source: Kent et al. 2015[51]

The results from a scenario analysis using these alternative health state costs for CKD stage 2, 3, 4 and 5 (pre-RRT) are shown in Table 22. Because the annual health state costs for CKD stage 1 could not be estimated from the CPRD cohort of DISCOVER CKD, this cost was assumed to be £1,211.41 based on Kent et al. 2015.[51] The ICER of this scenario analysis is somewhat higher than in the CS base case, but still well below the £20,000–£30,000/QALY gained ICER threshold.

Table 22: Scenario analysis B20 – alternative annual health state costs based on CPRD cohort of DISCOVER CKD study

	Dapagliflozin + SOC (intervention)	Placebo + SOC (comparator)	Incremental	ICER (£/QALY)
Scenario when implemented to original company base case				
Life years	9.260	8.254	1.007	£7,693
QALYs	6.800	6.031	0.769	
Costs (£)	£57,009	£51,093	£5,917	
Scenario when implemented to revised company base case†				
Life years	8.785	8.096	0.689	£7,621
QALYs	6.209	5.706	0.503	
Costs (£)	£53,736	£49,905	£3,830	

Footnote: † The revised company base case includes amendments described in response to B7, B17, B24, B25, B27 and B29 have been applied.
Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years; SOC: standard of care.

Explicit costs of managing comorbid conditions have not been included, as they should be considered as unrelated costs and therefore not part of the NICE reference case.[52] Some of these comorbidities may be associated with an increased risk of CKD-related events, such as hHF and faster CKD disease progression, which are intrinsically captured as part of the CKD management costs as patients in the CPRD cohort of the DISCOVER CKD study have a range of comorbidities which contribute to non-CKD related healthcare resource use and costs.

B21. Priority question. CS, Section B.3.5.2, Table 32, page 98. The standard care drug costs applied in the model do not include antidiabetic drugs or other drugs for the management of complications arising from CKD or comorbid conditions. Please amend the model to include these missing costs. Please also comment on whether DAPA-CKD suggests that dapagliflozin reduces the need for other standard care drugs. Please also comment on the assumption that the standard care drug costs are the same across all CKD stages.

Additional background therapy costs

The cost of background therapy applied in the original company base case captured standard care medications for CKD, including ACEis, ARBs, statins and antiplatelets. The cost of additional medications for the management of comorbid conditions should be considered as unrelated costs and should not be included, as per the NICE reference case (also see response to B20), and as such the cost of antidiabetic drugs were not included in the base case.[52] The cost of medications used to manage complications of CKD may be considered as related costs,

and these costs have therefore been included in a scenario analysis (scenario B21a). In this scenario analysis, an additional annual cost of £51.17 (uplifted from £50.06, 2018/19 cost year) was added to the background therapy cost, based on the CKD concomitant medication cost in NICE TA623 to cover the costs of vitamin D, EPOs/ESAs, and phosphate binders, used to treat complications of CKD.

As an additional scenario analysis (B21b), an annual cost of £335.02 (uplifted from £327.78, 2018/2019 cost year) was added to the proportion of patients with comorbid T2DM to account for the cost of diabetes management, even though this cost should be considered as unrelated and therefore excluded from the cost-effectiveness analysis. This annual cost was based on prescribing costs for diabetes, covering the cost of insulin, testing strips and medicines taken to control blood sugar levels.[53] The average total background therapy cost in this scenario was £159.92 (£15.28 [ACEi, ARB, statin, antiplatelet] + £51.17 [vitamin D, EPOs/ESAs, and phosphate binders] + £335.02 × 27.9% comorbid T2DM [antidiabetic drugs]).

These scenarios with additional drug costs do not substantially increase the ICER compared with the base case and dapagliflozin remains highly cost-effective (Table 23 and Table 24).

Table 23: Scenario analysis B21a – drug costs for the management of CKD complications added

	Dapagliflozin + SOC (intervention)	Placebo + SOC (comparator)	Incremental	ICER (£/QALY)
Scenario when implemented to original company base case				
Life years	9.260	8.254	1.007	£6,722
QALYs	6.800	6.031	0.769	
Costs (£)	£57,000	£51,831	£5,169	
Scenario when implemented to revised company base case†				
Life years	8.785	8.096	0.689	£6,229
QALYs	6.209	5.706	0.503	
Costs (£)	£53,815	£50,685	£3,131	

Footnote: † The revised company base case includes amendments described in response to B7, B17, B24, B25, B27 and B29 have been applied.
Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years; SOC: standard of care.

Table 24: Scenario analysis B21b - drug costs for the management of CKD complications and for the management of T2DM added

	Dapagliflozin + SOC (intervention)	Placebo + SOC (comparator)	Incremental	ICER (£/QALY)
Scenario when implemented to original company base case				
Life years	9.260	8.254	1.007	£6,844
QALYs	6.800	6.031	0.769	
Costs (£)	£57,866	£52,602	£5,264	
Scenario when implemented to revised company base case†				
Life years	8.785	8.096	0.689	£6,357
QALYs	6.209	5.706	0.503	
Costs (£)	£54,637	£51,442	£3,195	

Footnote: † The revised company base case includes amendments described in response to B7, B17, B24, B25, B27 and B29 have been applied.
Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years; SOC: standard of care.

Use of medication during study

Data on the use of CKD and CV medications were collected at baseline, 4 months, 8 months, 12 months and 24 months in the DAPA-CKD trial. There were no substantial differences in the use of CKD and CV medications during the study (Table 25).

Table 25: CKD and CV medication during DAPA-CKD

Treatments	Number (%) of subjects									
	Baseline (N=4,304)		4 months (N=4,254)		8 months (N=4,042)		12 months (N=4,005)		24 months (N=3,778)	
	Dapagliflozin (N=2,152)	Placebo (N=2,152)	Dapagliflozin (N=2,152)	Placebo (N=2,152)	Dapagliflozin (N=2,152)	Placebo (N=2,152)	Dapagliflozin (N=2,152)	Placebo (N=2,152)	Dapagliflozin (N=2,152)	Placebo (N=2,152)
ACE inhibitor	[redacted]									
ARB	[redacted]									
Beta Blocker	[redacted]									
Calcium channel blockers	[redacted]									
Antiplatelets	[redacted]									
Diuretics	[redacted]									
Loop diuretics	[redacted]									
Thiazide diuretics	[redacted]									
MRAs	[redacted]									
Other diuretics	[redacted]									
Statins	[redacted]									

Abbreviations: ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker; CKD: chronic kidney disease; CV: cardiovascular; MRA: mineralocorticoid receptor antagonists.
Source: AstraZeneca Data on File 2020: DAPA-CKD Clinical Study Report Figure 14.1.5.5.[5]

Data on the use of T2DM medications during the DAPA-CKD trial were not collected. No substantial differences in the use of T2DM medications between the dapagliflozin and placebo arms during the DAPA-CKD trial are expected.

The DAPA-CKD trial protocol suggested that patients treated with insulin or sulfonylurea could require lower doses to minimise risk of hypoglycaemic events, with a suggestion to consider a dose reduction of insulin by 10% to 20% (total daily dose) and sulfonylurea by 25% to 50% in patients with baseline HbA1c ≤7% at randomisation. Given the double-blind design of the DAPA-CKD trial, it is expected that similar dose reductions would have been applied in both treatment arms. In clinical practice, it is possible that CKD patients with comorbid T2DM treated may require lower doses of concomitant insulin and/or sulfonylurea when treated with dapagliflozin compared with patients not treated with dapagliflozin, and as such, it is possible that the overall background treatment costs could be lower when dapagliflozin is used. The assumption of equal therapy costs for the treatment of concomitant T2DM is therefore conservative with respect to dapagliflozin.

Drug costs associated with management of CKD stages

Drug costs associated with the management of CKD is likely to increase with later stages of CKD, as complications of CKD become increasingly prevalent. The annual background therapy cost applied in the cost-effectiveness model is an estimate of the average cost of CKD management across CKD stages, and therefore likely to be an overestimate of the cost for the management of earlier stages of CKD and an underestimate of the costs for later stages of CKD. In the cost-effectiveness model, the background therapy costs are therefore initial overestimated, when discounting has a smaller effect, and subsequently underestimated for later stage CKD, when the effect of discounting reduces the potential discrepancy in costs. As such, the approach to apply the average annual background therapy for all stages of CKD is conservative with respect to dapagliflozin.

The biggest change in costs for the management of CKD occurs when patients reach ESKD and require dialysis or transplantation. The cost of these therapies are explicitly captured within the cost-effectiveness model.

B22. CS, Section B.3.5.2, pages 98 to 99. The CS indicates that the costs of dialysis were intended to be modelled as an initial cost (£27,032.64 per transplant), with health state costs (£5,948.98 per year) applied in subsequent years. However, the model uses a monthly cycle length:

(a) Are health state costs applied in the cycle immediately after the transplant procedure occurs? In order to be consistent with the description in the CS, should these costs be delayed until after 12 model cycles have elapsed?

(b) How does the model apply these costs?

The dialysis costs are applied in the year of dialysis initiation and in all subsequent year. This is applied in the cost-effectiveness model as 1/12 of the annual dialysis cost (£32,360.41) in each of the relevant cycles.

The initial transplant costs (£27,032.64) are only applied in the cycle in which patients transition into the transplant health state. These initial transplant costs cover the cost of transplant surgery, the cost of pre- and post-surgery activities for recipient, and the cost of pre- and post-surgery activities for live donors in the proportion of transplant for which this is relevant. As such, there is no reason why these initial costs of transplant should be delayed for 12 model cycles. The transplant maintenance cost covers the cost associated with immune suppression treatments, a requirement for all kidney transplants. Immunosuppressive therapy is used to reduce the risk of rejection of the transplanted kidney and prolong its survival and is recommended for use immediately and for the lifetime of the transplanted organ.[54] In all model cycles subsequent to the cycle in which the patient transition into the transplant health state, 1/12 of the annual transplant maintenance cost is applied (£5,948.98) whilst the patient resides within the transplant health state.

During the NICE clarifications TC, the ERG asked for details of how the initial transplant costs applied in the cost-effectiveness model were calculated from the NICE Reference costs. The inputs and calculations used to derive the initial transplantation cost are outlined in Table 26.

Table 26: Inputs and calculations used to derive the initial transplantation costs

Step	Description	Currency codes / inputs	Calculation
1	Calculate weighted average cost for kidney transplant HRG calculated	LA01A, LA02A, LA03A	(722 × £12,605 + 1,196 × £12,989 + 713 × £12,292) / (772+1,196+713) = £12,693
2	Calculate weighted average pre-transplantation and post-transplantation of recipient costs, when distributed across the transplantation events that actually go ahead	LA12A, LA13A, LA01A, LA02A, LA03A	(10,380 × £408 + 110,124 × £275) / (772+1,196+713) = £12,888
3	Calculate weighted average pre-transplantation and post-transplantation of live donor costs, when distributed across the transplantation events that actually go ahead	LA11Z, LA14Z, LA01A, LA02A, LA03A	(3,780 × £388 + 3,489 × £245) / (772+1,196+713) = £867
4	Calculate the total weighted cost of transplantation, pre- and post-transplantation activities in recipient, and pre- and post-transplantation activities in live donor	Weighted averages from steps 1–3	£12,693 + £12,888 + £867 = £26,448
5	Uplift the total weighted cost to a 2019/2020 cost year	Inflation multiplier: 1.0221	£26,448 × 1.0221 = £27,033

Abbreviations: HRG, healthcare resource group.

Model implementation

B23. Priority question. The model has been written entirely in VBA with minimal annotation. Please improve the annotation of the VBA sub-routine "RunTrace"

An updated version of the model has been provided with additional annotation as requested.

B24. Priority question. The ERG found it difficult to understand the logic of the model based on the brief description contained in the CS and the limited annotation of the VBA code. The ERG has rebuilt the company's model using Excel spreadsheet formulae for transparency. There are two areas in which the models appear to be slightly discrepant, which may reflect a misunderstanding on the part of the ERG, or an error in one of the models:

(a) Model trace. The ERG's model trace for the standard care group is identical to the company's. However, there is a small difference in the dapagliflozin group trace which may relate to when the event of discontinuation is applied. Please look at the ERG's trace calculations in worksheet "Model_dapa" (columns E:BI) and explain what the company's model is doing differently.

(b) Transplant costs. The ERG's estimates of lifetime transplant costs are higher than the company's. The ERG has calculated this cost as the incident number of new patients undergoing transplant multiplied by the cost of the initial transplant procedure, plus the number of surviving patients who underwent transplant in previous cycles multiplied by the monthly health state cost. Please look at the ERG's formula in worksheet "Model_SC" cell BN6 and explain why the company's estimates are different.

a) ERG's model and compared traces - We considered that the difference in ordering of events between the two models may explain the small differences between the traces (company ordering: transient events, mortality, transition, discontinuation; ERG ordering: transient events, mortality, discontinuation, transition) – however, we have been unable to exactly replicate the traces between the models in order to validate this. Given that the differences between the traces are very small and the ICERs obtained between the models are very similar (£6,671 compared to £6,655) we are satisfied that the ERGs model closely replicates the company's submitted model.

b) Transplant costs - The difference is due to the assumption applied within the VBA code that initial transplant costs should deduct one year's maintenance transplant costs. However, given the input costs for transplant (initial and maintenance) do not include any double counting, we have provided an updated base case where both costs are applied additively in the first year. Table 27 shows the impact of including this change on the original submitted base case.

Table 27: Scenario analysis B24 – initial transplant costs and maintenance transplant costs both applied in year of transplant

	Dapagliflozin + SOC (intervention)	Placebo + SOC (comparator)	Incremental	ICER (£/QALY)
Scenario when implemented to original company base case				
Life years	9.260	8.254	1.007	£6,661
QALYs	6.800	6.031	0.769	
Costs (£)	£56,759	£51,636	£5,122	

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years; SOC: standard of care.

B25. Model, VBA, module "ModMarkov", sub-routine "RunTrace". The transition matrices for the second period (5 months plus) are applied in the fourth model cycle (at the end of month 3). This appears to be one cycle too early. Please confirm this is an error and amend the model accordingly.

We can confirm that this is an error and have amended accordingly. The following piece of VBA code was amended:

Original: If lngCycleIndex = 4 Then

Amended: If lngCycleIndex = 5 Then

The impact of this change on the ICER was minor (+£125/QALY gained compared with the base case, Table 28). The results show that with the updated transition probabilities there would be a small reduction in incremental QALYs alongside a small reduction in incremental costs, leading to a broadly similar ICER. The analysis illustrates that although these transitions may be unexpected, their inclusion did not have a meaningful impact on the ICER due to the low probabilities of these transitions. The change made to the model in this scenario analysis has also been implemented in the updated company base case.

Table 28: Scenario analysis B25 – 2nd set of transition probabilities implemented in cycle 5

	Dapagliflozin + SOC (intervention)	Placebo + SOC (comparator)	Incremental	ICER (£/QALY)
Scenario when implemented to original company base case				
Life years	9.251	8.246	1.005	£6,780
QALYs	6.790	6.023	0.767	
Costs (£)	£56,860	£51,659	£5,201	

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years; SOC: standard of care.

B26. Model, VBA, module "ModMarkov", sub-routine "RunTrace". The standard care group model determines health state occupancy as a function of CKD transitions and CKD stage-specific survival distributions. The dapagliflozin group also includes discontinuation in this function. Please clarify the order in which calculations relating

to transitions, mortality and discontinuation are applied in each cycle (see also question B25).

Calculations are undertaken in the following order:

1. Transient event incidence (HF hospitalisation, AKI, adverse events)
2. Mortality
3. CKD transitions
4. Discontinuation

It is not anticipated that changing the order of evaluation would significantly impact results and conclusions.

B27. Model, worksheet “Treatment Trace”. The model does not seem to apply any discontinuation in the first model cycle. This can be seen by setting the probability of discontinuation equal to 1.0 in worksheet “Model Interface”, cell range “rngDSA21” and then viewing column N in worksheet “Treatment Trace”. Please confirm that this is the case and explain why this approach has been taken. If appropriate, consider amending the model.

In light of the ERG comments, we have opted to amend the model functionality such that discontinuation is assumed to be applied from the end of each cycle. As such in the hypothetical scenario where a per-cycle discontinuation rate of 100% is applied, it is assumed that all patients are initiated on treatment at model initiation, and subsequently receive one cycle of treatment, with discontinuation conceptually applied at the end of the cycle. Consistent with this, we assume one cycle of treatment effect and one cycle of treatment cost.

To achieve this amendment the following pieces of VBA code have been added or moved:

Code added: *mtxOnTreatment.At(lngCycleIndex, 0) = mtxOnTreatment.At(lngCycleIndex, 0) - mtxHold.RowSum.ColSum.Value*

Code moved:

```
mtxCostsTreat.At(lngCycleIndex, 0) = mtxCostsTreat.At(lngCycleIndex, 0) + _
                                    mtxMarkovCKD_Current.RowSum.ColSum.Value *
dblCostTreatment / 12

If lngCycleIndex = 12 Then

mtxCostsTreat.At(lngCycleIndex, 0) = mtxCostsTreat.At(lngCycleIndex, 0) +
(mtxMarkovCKD_Current.RowSum.ColSum.Value * dblCostMonitorVisit)

End If
```

The impact of this change on the ICER was minor (-£23/QALY gained compared with the base case, see Table 29).

The changes made to the model in this scenario analysis have also been implemented in the updated company base case.

Table 29: Scenario analysis B27 – discontinuation applied from first model cycle

	Dapagliflozin + SOC (intervention)	Placebo + SOC (comparator)	Incremental	ICER (£/QALY)
Scenario when implemented to original company base case				
Life years	9.260	8.254	1.007	£6,632
QALYs	6.800	6.031	0.769	
Costs (£)	£56,509	£51,408	£5,100	

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years; SOC: standard of care.

B28. CS, Section B.3.2.2., page 79. The ERG has rebuilt the company's model using spreadsheet formulae. Whilst the CS states that a half-cycle correction has been applied, this does not appear to be the case. Please confirm whether half-cycle correction has been applied and explain where this features in the VBA code. Please also clarify whether the correction is applied to the Markov trace, or to costs and QALYs generated from the uncorrected trace.

It was incorrectly stated in the CS that there was a half cycle correction. A half cycle correction was not applied in the model, however, given the cycle length of one month, we do not consider that this is likely to change the results considerably.

B29. Model, worksheets "Treatment Trace" and "Control Trace". The "lifetime" horizon applied in the model runs for 304 monthly cycles. Given a mean starting age of [redacted], this means that patients are aged [redacted] years in the final cycle. Was this intentional? If not, please amend the model to use a lower final age (e.g. age=100 years).

As suggested, the VBA code has been amended so that the maximum modelled age is 100 years. The following piece of VBA code was amended:

Original: lngNumCycles = Application.Min((101 - dblAge) * 12, 50 * 12) + 1

Amended: lngNumCycles = Application.Min((100 - dblAge) * 12, 50 * 12) + 1

The impact of this change on the ICER was minor (+£18/QALY gained compared with the base case,

Table 30).

The change made to the model in this scenario analysis has also been implemented in the updated company base case.

Table 30: Scenario analysis B29 – lifetime time horizon restricted to 100 years of age

	Dapagliflozin + SOC (intervention)	Placebo + SOC (comparator)	Incremental	ICER (£/QALY)
Scenario when implemented to original company base case				
Life years	9.238	8.238	1.000	£6,572
QALYs	6.786	6.021	0.765	
Costs (£)	£56,180	£51,154	£5,025	

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years; SOC: standard of care.

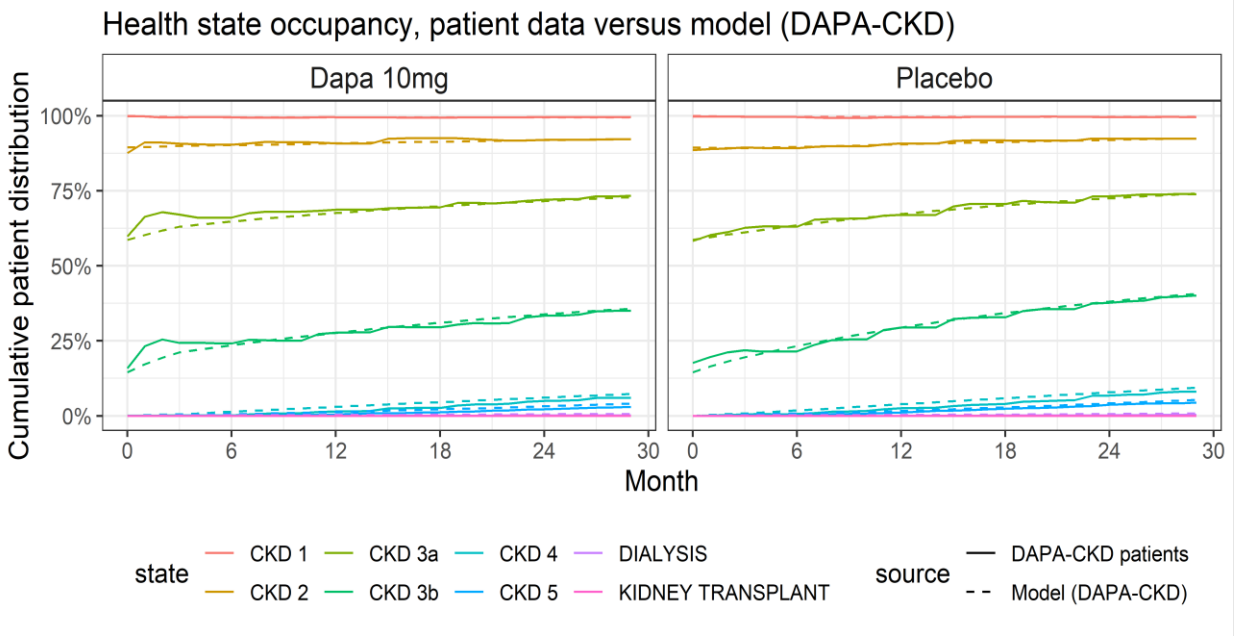
Model validation

B30. CS, Section B.3.10, pages 127 to 128. Please provide a plot of the distribution of observed CKD health state in DAPA-CKD versus modelled CKD health state occupancy over time, based on the unadjusted population.

The requested plots are shown as overlays in Figure 7, where the observed patient data are compared to the modelled results using the DAPA-CKD patient baseline characteristics. These observed health states were based upon the allowable transitions in the cost effectiveness model; i.e. once a patient was observed to have entered the dialysis or transplant state, they were ineligible to return to the CKD states.

The model was able to recreate the trial CKD distribution very satisfactorily considering that only four independent transition matrices were used throughout the period. As well as supporting the use of constant transition intensities, this was also supportive of the assumption of proportional hazards between CKD stages in the modelling of all-cause mortality, as patients were being appropriately moved from the CKD stages to the death state according to the hazard ratio associated with their CKD stage.

Figure 7: Health state occupancy, observed patient data versus modelled results using DAPA-CKD patient profile



B31. Please provide a plot of observed overall survival in DAPA-CKD versus modelled overall survival with and without adjustment for baseline covariates. Please do not break the axes in the plots.

The requested plot of the observed overall survival in DAPA-CKD, the modelled overall survival without adjustment to patient baseline characteristics, and the modelled overall survival with adjustment to patient baseline characteristics (as in the company base case) is provided in Figure 8.

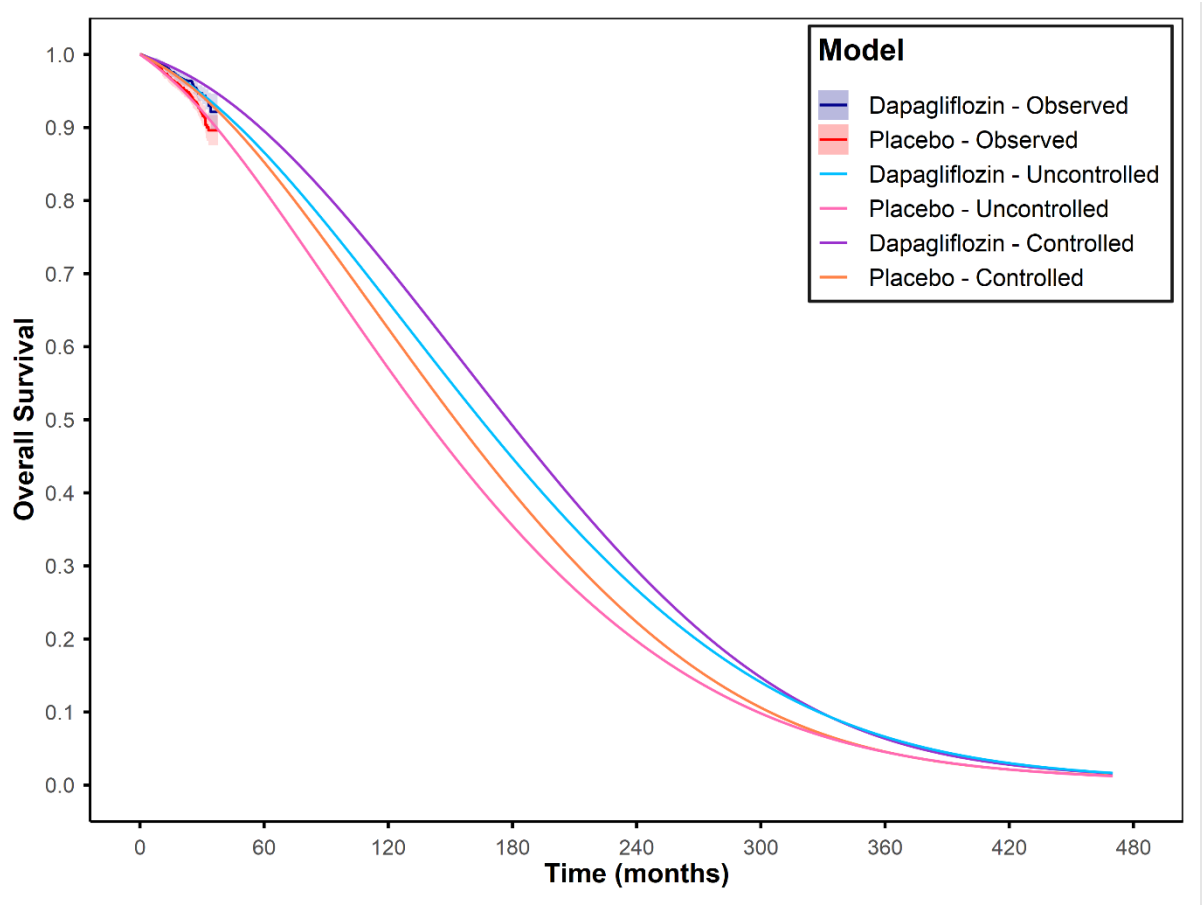
The "unadjusted"/"uncontrolled" overall survival model was fitted as a new Gompertz parametric model of all-cause mortality, which is conditional upon treatment and time-updated CKD stage *only.* This model predicts overall survival whilst disaggregating mortality risk among the CKD states and uses the CKD stage distribution from the cost-effectiveness model. This survival model can be selected in the cost-effectiveness model by selecting "Gompertz Simple" in cell K29 of the 'Model Interface' sheet.

The "adjusted"/"controlled" overall survival model is the parametric survival model applied in the company base case, which adjusts for time-updated CKD stage as well as baseline patient characteristics. In Figure 8, this model is applied to the patient baseline characteristics from DAPA-CKD.

Figure 8 shows that the "unadjusted" model reconstructed the observed data better than the fully "adjusted" model. However, predictions for overall survival on both the placebo and dapagliflozin arms were reduced in the "unadjusted" model compared to the "adjusted" and therefore there was no substantial difference in incremental survival in the two model. Whilst the reduced model ("unadjusted") does provide better calibration to the DAPA-CKD population, it is considered necessary for face validity that age and sex at least are included as controlling variables when applying this model to alternative populations due to the dependence of overall survival prognosis on these measures.

Results from scenario analyses using the “unadjusted” model are outlined in Table 31, based on implementation of the “unadjusted” model to scenario #1 of the company submission, which represents the DAPA-CKD overall population. Scenario analyses have been implemented in both the original company model and in the revised company model.

Figure 8: Observed survival in DAPA-CKD versus model OS, controlling for multiple baseline covariates and for time-varying CKD stage alone



Footnotes: “Observed” – Kaplan-Meier estimator of OS from DAPA-CKD; “Uncontrolled” – Gompertz model of OS dependent only upon time, eGFR and treatment status (i.e. without baseline adjustment). “Controlled” – Company base case Gompertz model with adjustment cofactors, configured for the DAPA-CKD population. OS predictions from models are economic model outputs and are dependent upon the time-varying CKD state occupation predicted by CKD health state transition matrices in the cost-effectiveness model.
Abbreviations: OS, overall survival.

Table 31: Scenario analysis B31 – all-cause mortality model without adjustment for baseline covariates (company submission scenario analysis #1: DAPA-CKD overall population)

	Dapagliflozin + SOC (intervention)	Placebo + SOC (comparator)	Incremental	ICER (£/QALY)
Company submission scenario analysis #1 (DAPA-CKD overall population) – fully adjusted survival model				
Life years	11.587	10.505	1.082	£5,457
QALYs	8.437	7.601	0.836	
Costs (£)	£78,758	£74,195	£4,563	
Scenario when implemented to scenario analysis #1 (DAPA-CKD overall population) – "unadjusted" survival model				
Life years	11.073	9.906	1.166	£6,072
QALYs	8.070	7.177	0.894	
Costs (£)	£74,385	£68,958	£5,427	
Company submission scenario analysis #1 (DAPA-CKD overall population) in revised model† – fully adjusted survival model				
Life years	11.529	10.461	1.068	£5,841
QALYs	8.057	7.288	0.768	
Costs (£)	£78,399	£73,910	£4,489	
Scenario when implemented to scenario analysis #1 (DAPA-CKD overall population) in revised model† – "unadjusted" survival model				
Life years	11.011	9.866	1.145	£6,493
QALYs	7.708	6.889	0.819	
Costs (£)	£74,015	£68,698	£5,317	

Footnote: † The revised model refers to the cost-effectiveness model in which the requests from B7, B17, B24, B25, B27 and B29 have been applied.
Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years; SOC: standard of care.

Subgroup analyses

B32. Priority question. CS, Section B.3.8.3.2, pages 119 to 122. The CS includes a number of economic subgroup analyses which involve adjusting the baseline characteristics of the model population. However, the same unadjusted transition matrices are applied in every subgroup analysis:

(a) Please comment on whether transition rates would be expected to vary between the subgroups.

(b) If possible, update the model to include subgroup-specific transition matrices.

The treatment effect of dapagliflozin on the primary endpoint was positive and consistent across all pre-specified subgroup of DAPA-CKD. The only subgroup with a p-value of interaction <0.05 was the subgroup by systolic BP, although these results are likely to be a chance finding (see Section B.2.7 of company submission). As such, the transition probabilities generated from the overall DAPA-CKD population is expected to be generalisable across all subgroups.

The approach used in the company base case to derive transition probabilities from the overall DAPA-CKD trial population (4,304 patients in overall trial population) provides the greatest power to most accurately define the transition probabilities and to reduce uncertainty. The transition probabilities were then supplemented by adjusted risk equations and survival equations to allow for adjustment to any variables expected to significantly impact outcomes.

To the company's knowledge, there are no methods for the derivation of adjusted transition probabilities that are equivalent to those used to generate the adjusted survival equations. The only alternative would be to generate transition probabilities using a subset of the data available for subgroups of interest. The exact transition probability matrix generated using this approach is expected to differ slightly compared with the base case transition probabilities, predominantly due to chance, and be associated with greater uncertainty.

To demonstrate this point, alternative transition probabilities have been derived for the three subgroups specified within the final scope for this appraisal:

- People in T2DM subgroup (2,906 patients)
- People with comorbid CVD (1,625 patients)
- People without comorbid T2DM and without comorbid CVD (1,064 patients)

The cost-effectiveness results of these subgroups when using the transition probabilities from the original company base case and when using the subgroup-specific transition probabilities are

summarised in Table 32: Scenario analysis B32 – subgroup-specific transition probabilities

		Dapagliflozin + SOC (intervention)	Placebo + SOC (comparator)	Incremental	ICER (£/QALY)
Scenario #6 (with comorbid T2DM)	**Original company submission scenario**				
	Life years	11.042	9.968	1.074	£5,648
	QALYs	8.048	7.221	0.828	
	Costs (£)	£74,225	£69,550	£4,675	
	Scenario analysis B32 when implemented to original company model				
	Life years	11.017	9.936	1.081	£5,619
	QALYs	8.016	7.184	0.832	
	Costs (£)	£75,313	£70,639	£4,674	
	Scenario analysis B32 when implemented to revised company model†				
	Life years	10.944	9.879	1.064	£5,929
	QALYs	7.646	6.881	0.764	
	Costs (£)	£74,794	£70,262	£4,532	
Scenario #9 (with comorbid CVD)	**Original company submission scenario**				
	Life years	10.090	9.023	1.067	£5,971
	QALYs	7.364	6.545	0.819	
	Costs (£)	£66,894	£62,003	£4,891	
	Scenario analysis B32 when implemented to original company model				
	Life years	10.104	9.021	1.084	£4,411
	QALYs	7.357	6.512	0.845	
	Costs (£)	£68,307	£64,581	£3,726	
	Scenario analysis B32 when implemented to revised company model†				
	Life years	10.023	8.953	1.070	£4,560
	QALYs	7.022	6.240	0.782	
	Costs (£)	£67,825	£64,258	£3,567	
Scenario #11 (without comorbid T2DM and without comorbid CVD)	**Original company submission scenario**				
	Life years	13.159	12.050	1.109	£4,979
	QALYs	9.559	8.698	0.861	
	Costs (£)	£91,785	£87,498	£4,287	
	Scenario analysis B32 when implemented to original company model				
	Life years	13.018	12.074	0.944	£8,683
	QALYs	9.424	8.713	0.710	
	Costs (£)	£93,399	£87,232	£6,167	
	Scenario analysis B32 when implemented to revised company model†				
	Life years	12.958	12.032	0.926	£9,706
	QALYs	8.997	8.351	0.646	
	Costs (£)	£93,729	£87,454	£6,275	

Footnote: † The revised model refers to the cost-effectiveness model in which the requests from B7, B17, B24, B25, B27 and B29 have been applied.
Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years; SOC: standard of care.

. The ICERs for these subgroups are comparable to the subgroup analyses using the transition probabilities from the company base case, with the ICERs remaining highly cost-effective and below £10,000/QALY gained for all subgroups.

Table 32: Scenario analysis B32 – subgroup-specific transition probabilities

		Dapagliflozin + SOC (intervention)	Placebo + SOC (comparator)	Incremental	ICER (£/QALY)
Scenario #6 (with comorbid T2DM)	**Original company submission scenario**				
	Life years	11.042	9.968	1.074	£5,648
	QALYs	8.048	7.221	0.828	
	Costs (£)	£74,225	£69,550	£4,675	
	Scenario analysis B32 when implemented to original company model				
	Life years	11.017	9.936	1.081	£5,619
	QALYs	8.016	7.184	0.832	
	Costs (£)	£75,313	£70,639	£4,674	
	Scenario analysis B32 when implemented to revised company model†				
	Life years	10.944	9.879	1.064	£5,929
	QALYs	7.646	6.881	0.764	
	Costs (£)	£74,794	£70,262	£4,532	
Scenario #9 (with comorbid CVD)	**Original company submission scenario**				
	Life years	10.090	9.023	1.067	£5,971
	QALYs	7.364	6.545	0.819	
	Costs (£)	£66,894	£62,003	£4,891	
	Scenario analysis B32 when implemented to original company model				
	Life years	10.104	9.021	1.084	£4,411
	QALYs	7.357	6.512	0.845	
	Costs (£)	£68,307	£64,581	£3,726	
	Scenario analysis B32 when implemented to revised company model†				
	Life years	10.023	8.953	1.070	£4,560
	QALYs	7.022	6.240	0.782	
	Costs (£)	£67,825	£64,258	£3,567	
Scenario #11 (without comorbid T2DM and without comorbid CVD)	**Original company submission scenario**				
	Life years	13.159	12.050	1.109	£4,979
	QALYs	9.559	8.698	0.861	
	Costs (£)	£91,785	£87,498	£4,287	
	Scenario analysis B32 when implemented to original company model				
	Life years	13.018	12.074	0.944	£8,683
	QALYs	9.424	8.713	0.710	
	Costs (£)	£93,399	£87,232	£6,167	
	Scenario analysis B32 when implemented to revised company model†				
	Life years	12.958	12.032	0.926	£9,706
	QALYs	8.997	8.351	0.646	
	Costs (£)	£93,729	£87,454	£6,275	

Footnote: † The revised model refers to the cost-effectiveness model in which the requests from B7, B17, B24, B25, B27 and B29 have been applied.
Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years; SOC: standard of care.

The consistency in the cost-effectiveness of dapagliflozin in these subgroup when applying transition probabilities derived from the overall trial population and when applying subgroup-specific transition probabilities confirms that the transition probabilities are not a key driver of the cost-effectiveness outcomes and that the results are robust to variation in transition probabilities.

Given the increased uncertainty associated with subgroup-specific transition probabilities and limited impact of subgroup-specific transition probabilities on the cost-effectiveness conclusion, the transition probabilities from the overall DAPA-CKD trial population were considered as the most appropriate transition probabilities for the base case and for all subgroup analyses.

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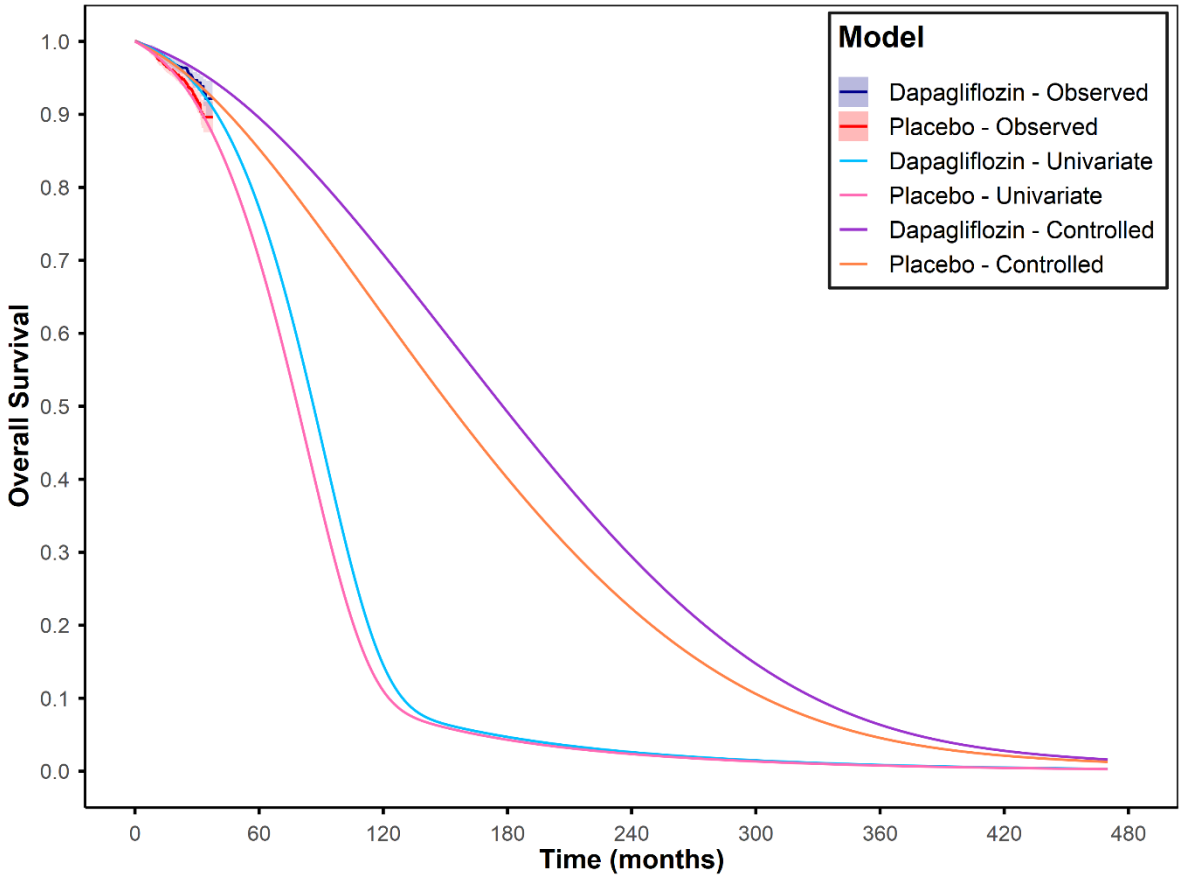
B31. Please provide a plot of observed overall survival in DAPA-CKD versus modelled overall survival with and without adjustment for baseline covariates. Please do not break the axes in the plots.

Additional clarification from the ERG: 'There is one question (B31) which the company hasn't addressed in the way that we were hoping, and it's quite an important issue. We wanted the company to provide a visual comparison of the full multivariable Gompertz model fitted to DAPA-CKD based on the statistical model output (without any adjustment to the CPRD and without including external data or transitions between states) versus the observed Kaplan-Meier OS function from DAPA-CKD. Instead, in their response to B31, the company has fitted a new simpler Gompertz model to the trial data - but this isn't the same parametric survival model which is used in the economic model, so it doesn't help us. Please can you ask the company if they are able to reconsider their response and provide the requested analysis as this would be helpful for judging how well the model represents the observed trial data and so that we can comment on the plausibility of the extrapolation.'

Following further clarifications of this request from the ERG, an updated figure has been provided (Figure 1). This figure contains the following three components:

- The observed overall survival in DAPA-CKD (labelled as "observed")
- The statistical model output from fitting survival models to the trial data, with dapagliflozin treatment as the only covariate (labelled as "univariate"); the Gompertz distribution has been provided as requested by the ERG
- The multivariate adjusted survival model from fitting survival models to the trial data, taking into account multiple covariates, including time-varying covariates, that impact the hazard of death (labelled as "controlled")

Figure 1. Observed survival in DAPA-CKD, univariate unadjusted survival curves (Gompertz) and multivariable adjusted survival curves (Gompertz)



Footnotes: "Observed" – Kaplan-Meier estimator of OS from DAPA-CKD. "Univariate" – Gompertz model of OS dependent only upon time and treatment status (i.e. without baseline or time-varying CKD adjustment). "Controlled" – Company base case Gompertz model with adjustment cofactors, configured for the DAPA-CKD population. OS predictions from models are economic model output and are dependent upon the time-varying CKD state occupation, including non-Gompertz mortality hazard in transplant and dialysis states.

Because of the strong association between CKD stage (disease severity) and mortality hazard,[1, 2] it is particularly important that time-varying CKD stage is taken into account when modelling all-cause mortality (see "uncontrolled" survival model provided in original response to B31).

Whilst the univariate unadjusted survival model provides better calibration to the within DAPA-CKD trial data compared to the multivariate adjusted model, it is not able to provide valid predictions of long-term survival in a heterogenous CKD population with varying disease severities. This is because more advanced stages of CKD are associated with an increased mortality risk[1, 2] and as such, the mortality hazard in the DAPA-CKD trial population is a weighted average of the mortality hazard associated with each of the CKD stages (and categories of other covariates) within the trial. Over time, patients with more severe stages of CKD are more likely to die compared patients with less severe stages of CKD. Consequently, the composition of patients and therefore the weighted average hazards in the population shift in two opposing ways: as more severe CKD patients die, the overall hazard shifts towards the hazard associated with the less severe CKD stages (main effect); and as patient experience CKD progression, the overall hazard shifts towards the hazard associated with more severe CKD stages (smaller effect). Additionally, within each

CKD stage, the mortality hazard is also likely to advance over time due to effects associated with aging and comorbidity, as reflected by the use of the baseline Gompertz hazard profile within each CKD stage.

When using the univariate unadjusted survival model, the weighted average mortality hazard is applied to all CKD stages. This means that the mortality hazard in more severe CKD health states is underestimated, resulting in an accrual of severe CKD patients in the cost-effectiveness model who would be expected to have died. Similarly, the mortality hazard in less severe CKD health states is overestimated with the univariate unadjusted survival model, resulting in a loss of less severe CKD patients in the cost-effectiveness model who would be expected to survive for longer. Because the CKD severity composition of the population remains constant with this approach (all patients have same mortality hazard) and because the univariate unadjusted survival model does not adjust for changes in CKD severity composition, the modelled hazard profile of the population is limited to describing a monotonically increasing hazard. In contrast, the multivariate adjusted survival model takes these shifts in CKD stage composition into account to ensure the predicted mortality hazard is reflective of the CKD stage composition of the population at any given time, allowing the survival effect favouring lower CKD stages to be captured.

The validity of using the multivariate adjusted survival model in conjunction with CKD state transition probabilities derived from DAPA-CKD has been confirmed by a clinical expert elicitation exercise, which found that the long-term survival predicted using the adjusted survival model (especially when using the Gompertz distribution) closely matched the long-term survival of DAPA-CKD patients expected by clinical experts Figure 2.[3] Details of the clinical expert elicitation exercise for long-term survival in CKD patients have been provided in response to B4d.

Figure 2*:* Risk equation-based overall survival predictions for patients in the placebo arm of the DAPA-CKD trial

Source: Willigers et al. 2021.[3]

The univariate survival model for the overall DAPA-CKD trial population can be selected within the cost-effectiveness model ('Model Interface' sheet, cell E29) to model all-cause mortality. The cost-effectiveness results of dapagliflozin when applying the univariate (unadjusted) survival model are shown in Table 1. The ICER for the DAPA-CKD overall population (scenario #2 in original company submission) reduced from £5,457/QALY gained to £4,759/QALY gained when applying the univariate unadjusted survival model. This is likely because patients in scenario B31 die earlier on and therefore are less likely to progress to the costly and low HRQoL dialysis health state, resulting in a reduction in the

incremental costs which more than offset the increase in QALYs compared to scenario #2 in the original company submission. When the unadjusted survival equation is applied to the revised company model, the ICER (£5,154/QALY gained) is also lower compared with scenario #2 in the original company submission.

The results of a scenario analysis using an univariate unadjusted survival model with a Weibull distribution are provided in Table 2. The Weibull distribution has been selected as an alternative to the aggressively monotonically increasing hazard associated with the Gompertz distribution, for better face validity with the more slowly increasing hazard associated with the shift in the CKD population composition to less severe patients. When using the Weibull distribution, dapagliflozin became dominant over placebo.

Table 1: Scenario analysis B31a – univariate unadjusted survival equation (Gompertz)

	Dapagliflozin + SOC (intervention)	Placebo + SOC (comparator)	Incremental	ICER (£/QALY)
Original company submission scenario #2 (DAPA-CKD overall population, adjusted survival equation)				
Life years	11.587	10.505	1.082	£5,457
QALYs	8.437	7.601	0.836	
Costs (£)	£78,758	£74,195	£4,563	
Scenario analysis B31a when implemented to original company model				
Life years	6.608	6.123	0.484	£4,759
QALYs	4.834	4.451	0.382	
Costs (£)	£42,581	£40,762	£1,820	
Scenario analysis B31a when implemented to revised company model†				
Life years	6.596	6.112	0.484	£5,154
QALYs	4.728	4.359	0.369	
Costs (£)	£42,622	£40,721	£1,901	

Footnote: † The revised model refers to the cost-effectiveness model in which the requests from B7, B17, B24, B25, B27 and B29 have been applied.
Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years; SOC: standard.

Table 2: Scenario analysis B31b – univariate unadjusted survival equation (Weibull)

	Dapagliflozin + SOC (intervention)	Placebo + SOC (comparator)	Incremental	ICER (£/QALY)
Scenario analysis B31b when implemented to original company model				
Life years	10.192	9.286	0.906	Dominant
QALYs	7.470	6.711	0.760	
Costs (£)	£64,725	£66,561	-£1,836	
Scenario analysis B31b when implemented to revised company model†				
Life years	10.110	9.231	0.880	Dominant
QALYs	7.131	6.440	0.691	
Costs (£)	£64,244	£66,186	-£1,942	

Footnote: † The revised model refers to the cost-effectiveness model in which the requests from B7, B17, B24, B25, B27 and B29 have been applied.
Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years; SOC: standard.

In summary, we firmly believe that the multivariate adjusted survival model should be used in the base case, as it captures the changes in mortality hazard overtime, reflects the changes in the CKD stage composition of the population and aligns with long-term survival estimates as elicited from clinical experts. Nevertheless, the scenario analyses using the univariate unadjusted survival model show that dapagliflozin remains cost-effective or becomes dominant when this unadjusted modelling approach is taken.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Dapagliflozin for treating chronic kidney disease [ID3866]

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 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 manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.] If so, please state the name of manufacturer, amount, and purpose of funding.	£32,055 to fund Kidney Care UK's Kidney Kitchen project https://www.kidneycareuk.org/about-kidney-health/living-kidney-disease/kidney-kitchen/ This is web based support to enable people with kidney disease to enjoy eating and drinking while following the diet plans given to them by their renal dietician. The funds covered costs including, staff time, filming costs, web development costs (more details available if required). Kidney Care UK also receives a grant of £200 per meeting for consultancy to an international think tank hosted by AZ which meets quarterly.

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	n/a
5. How did you gather information about the experiences of patients and carers to include in your submission?	The information and views represented in this submission has been gathered through a range of sources: Kidney Care UK advocacy services and Facebook support group, the views of Kidney Care Staff who are kidney patients, our Patient Advisory Group. 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.
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?	Many cases of CKD are mild or moderate and risks can be managed by patients and their GPs without ever visiting a hospital. However, for people with CKD that progresses and requires specialist input from the renal team it can be extremely serious and require life changing treatment. 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 patients 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 five hours a day, three days a week, every week, at hospital. Fiona Loud, our policy director and a kidney patient, explains "dialysis meant drinking just 500 ml of fluid a day, an almost impossible diet where chocolate, coffee, bananas, cheese, and so many others things are banned or restricted. And you must spend 5 or 6 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." Kidney transplant, while not a cure, is the best form of treatment for kidney disease. However there are more people waiting for a transplant than there are available organs and people from Black and Minority Ethnic communities have to wait considerably longer than people from White British 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.[ii] 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 patients. 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 transplant patients, 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?	The most recent Patient Reported Experience Measures found that overall patients rate the overall experience of the service provided by their renal unit highly.[ix] People who progress to kidney failure often find the burden of treatment is very significant. As described above, many patients can find living with five 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.
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.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	The development of a new way of treating kidney disease, that shows real benefits, has been of huge interest to patients. The benefits identified in the DAPA-CKD trial, of delaying further decline in kidney function and progression to end stage kidney failure, as well reducing the risk of death from renal causes would clearly be significant advantages for kidney patients in the context of a progressive and currently incurable condition such as CKD. Progress in the development of new treatments for kidney disease is perceived to be very slow and the positive findings for this technology offer real hope to patients. Kidney patients are at very high risk of death from cardiovascular causes and therefore the evidence that SLGT2 inhibitors lower 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?	Some patients with CKD and diabetes have reported unpleasant side effects, particularly UTIs and yeast infections. 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.
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.	Not to our understanding.

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	CKD impacts most on people from BAME backgrounds and socio-economically deprived groups. People from these groups are also more likely to progress quicker to kidney failure and die earlier with CKD.
Other issues	
13. Are there any other issues that you would like the committee to consider?	We would like to see estimations of the length of time over which people are likely to be prescribed Dapagliflizon and a discussion regarding what is currently known about longer term effects, in terms of efficacy and safety profile.
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. • It is currently incurable with limited pharmacological options for delaying progression. Treatments for kidney failure very burdensome with access to the gold standard of kidney transplant limited	

- The findings that this drug can delay progression of CKD in patients with and without diabetes offer real hope and could lead to a real step change in treatment of kidney patients
- Drug treatments such as Dapagliflozin must be accompanied by information and support about dietary, exercise and lifestyle interventions that can help to delay the progression of kidney disease.
- Patients must be supported to report side effects as the ongoing monitoring and evaluation of adverse events is important.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Dapagliflozin for treating chronic kidney disease [ID3866]

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	London Kidney Network

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	The core objective of the London Kidney Network (LKN) is to deliver the NHS "triple aims" for kidney patients in London: improving quality and outcomes, experience and value. This will be delivered by a multi-professional network of experts who will engage with and respond to our partners including patients, service providers, expert advisory bodies, commissioners and research bodies. We are accountable to the NHSE London Specialised Commissioning Team and hosted by St Georges University Hospital Trust.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last	Disclosures by respondents within the LKN: [redacted] Grant Holder: AstraZeneca, Cheisi. Speaker Honoraria: Napp, AstraZeneca, Vifor Fresenius, Bayer, Pharmacosmos [redacted] Grant Holder: BI Honraria: AZ, BI, Lilly, Napp, Vifor

12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.] If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No.
The aim of treatment for this condition	

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	We are encouraged by significant study outcomes in this area, with reference to the recently published DAPA-CKD trial demonstrating a NNT of only 19 to prevent one primary outcome event. We feel assured by the data that Dapagliflozin has proven to be of equal benefit in non-diabetic and diabetic CKD populations, with respect to the following clinically important endpoints: • Decreased risk of kidney failure • Decreased risk of death from CV causes or hospitalisation for HF • Prolonged survival We understand that economic modelling is likely to support projected health system savings associated with a reduction of patients reaching RRT. Additional health system savings are forecast related to cardiovascular morbidity. These benefits are in addition to those seen in patients on ACEi/ARBs only.
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.)	Clinically significant outcomes can best be described at a population level. We consider that there is no reason that patients with proteinuric CKD in England would not achieve the magnitude of benefits seen in the DAPA CKD trial.

8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. We assert that with current best practice for the management of proteinuric kidney disease, there is still a significant incidence of end-stage renal failure - with RAAS inhibitors only providing a 16 to 20% reduction in risk. In England, there are approximately 1.9 million people (4% of adults) on primary care CKD registers (QoF 2019/20), plus an estimated further 560 thousand who have biochemical evidence of CKD stage 3-5 (vie eGFR results in their primary care record) but are not present on CKD registers (National CKD Audit 2017). This estimation of primary care prevalence of CKD (5.2%) aligns well with the estimated true community prevalence of 5.4% as measured by the Health Survey for England 2016, indicating that most people with CKD stage 3-5 are recognised in some way by primary care services. Whilst not all of these estimated 2.5 million patients will require or be eligible for Dapagliflozin, we support the notion that through its effective implementation, significant numbers of people stand to have their lives improved due to prevention or delaying end-stage kidney disease and death from renal or cardiovascular causes. Current guidance for managing proteinuric kidney disease includes people with diabetes only. Outcomes from the clinical trials demonstrate that there is a benefit of SGLT2i that is distinct from a blood glucose lowering effect. Consequently, it is particularly important that non-diabetic CKD patients are not excluded from the benefits of Dapagliflozin in the outcome of this appraisal. Failure to include recommendations for this group would significantly impair confidence of integrated care systems to include them in local prescribing protocols.
What is the expected place of the technology in current practice?	

9. How is the condition currently treated in the NHS?	Diabetic and non-diabetic kidney disease treatment is supported by a number of agents to manage the multi-morbid presentations seen in these conditions; hypertension, hyperglycaemia, proteinuria, obesity and cardiovascular disease. Goals of treatment are to slow CKD progression and to reduce cardiovascular morbidity and mortality. However, despite optimal care many patients continue to progress (as stated above) resulting in considerable clinical and economic burden of this disease.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	During LKN engagement with primary and secondary care in London and Surrey Heartlands, we have noticed widespread awareness of the benefits of SGLT2i in proteinuric kidney disease, but without the same confidence and clarity with respect to prescribing or treatment guidelines. In regions where primary and secondary care links are enhanced, clinical guidance on SGLT2i in diabetic kidney disease have been produced based on previous trials in this area. Direction from this NICE TA would be a meaningful facilitator in expanding the potential of this drug through clinical pathways. We are aware that this has been reviewed in the NICE CKD Guidelines presently in development. We are aware that the UK Kidney Association is currently producing national guidance in this area.
• 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	There is agreement that the pathway of care should enable maximal cardiorenal protection in people with documented albuminuria. We consider that this now includes SGLT2i down to their lowest licensing boundary. Our experience is in engaging with primary and secondary care organisations in London and the Surrey Heartlands. There is desire for recommendations at a national level which can shape both commissioning decisions and to guide explicit pathways of care.

experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	We assert that the use of Dapagliflozin in appropriate cohorts of proteinuric kidney disease patients would have significant clinical benefit which is above and beyond that seen with current utilised agents. Recognition by NICE as an agent of choice in this technological appraisal would support ICS' nationally to incorporate Dapagliflozin into prescribing pathways for patients with proteinuric kidney disease (crucially, with or without diabetes). This has potential to limit prescribing variation and ensure that patients, no matter their geographical location, will have access to this important medication.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Dapagliflozin is currently used within its licence: in treating people with diabetes to improve glycaemic control reduce cardio renal complications (down to a GFR of 45ml/min) and also in patients with symptomatic heart failure with reduced ejection fraction to prevent worsening heart failure or cardiovascular death. We assert that Dapagliflozin should be utilised in line with the DAPA CKD trial criteria given the outstanding clinical outcomes, as well as being well tolerated and safe.
• How does healthcare resource use differ between the technology	Extending Dapagliflozin use, in line with published studies will allow it to be used in people with diabetes primarily as a drug to prevent renal complications in more advanced CKD and will extend its use in patients without diabetes who have CKD to prevent cardiorenal complications and improve survival.

and current care?	
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	We recommend that Dapagliflozin should be prescribed in line with trial criteria, i.e. eGFR < 75ml/min (and >25ml/min) and proteinuria. This would mean that for most individuals, treatment would commence in primary care. There may be patients who are 'hard to reach' who present to healthcare settings with more advanced CKD (3a-4). They may commence Dapagliflozin in primary care or following advice from secondary care, therefore these clinicians should also be aware of how to appropriately use this medication.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Education will be required to ensure that primary care prescribers particularly, feel able to safely and effectively use this medication. This includes, but is not limited to the production of prescribing pathways. Appropriate use of this medication also requires identification of the cohort in scope to benefit. At present, there is not consistent practice nationally with respect to identifying people with CKD proteinuria. Investment in technologies to improve this practice are underway such as the exploration of algorithmic trigger tools and remote technologies to support uACR capture. Investment to improve identification and treatment of proteinuric kidney disease must have particular focus on groups presently shown to experience health inequities.
11. Do you expect the technology to provide clinically meaningful benefits	We assert that with current best practice for the management of proteinuric kidney disease, there is still a significant incidence of end-stage renal failure - with RAAS inhibitors only providing a 16 to 20% reduction in risk. Dapagliflozin offers equivalent or greater benefits in proteinuric CKD when compared to the introduction of RAASi agents and will impact outcomes such as reduction in number reaching end stage kidney disease,

compared with current care?	number developing diabetes (in non-diabetic CKD), reduction in heart failure hospitalisations, cardiovascular mortality.
• Do you expect the technology to increase length of life more than current care?	Yes, the DAPA CKD trial supports this assertion by significantly reduced rates of cardiovascular and renal deaths, as well as significant impact on eGFR decline and number reaching ESKD.
• Do you expect the technology to increase health-related quality of life more than current care?	Reducing the number of people who progress to end stage kidney disease will bear considerable impact to HRQOL, as will the impact of reduced HF related hospital admissions.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than	The number needed to treat (NNT) is only 19 in the DAPA CKD trial, which confirms this is a very effective therapy in this area. There are no groups who benefit less from this intervention in terms of age/gender/race/kidney function or proteinuria. Patients with a history of diabetic ketoacidosis (DKA) may be at a slightly increased risk of DKA using this drug. We wish to emphasise that the very small risk of DKA seen in patients with diabetes is **not** seen in the non-diabetic population (nil DKA).

the general population?	
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,	We do not support additional monitoring of eGFR following commencement as decline is small and anticipated. Recovery is seen and not linked with an increased risk of AKI. Indeed, multiple studies in SGLT2i have demonstrated less AKI events on treatment than placebo. Practical implications: • Patients need optimised RAAS blockade therapy first – it would be important that any pathways defined supported clinicians to do this. • Need to be identifying people set to benefit from Dapaglifozin by measuring uACR in all relevant cohorts.

factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	• We recommend that RAAS inhibitor agent dosing is optimised in those who tolerate this prior to commencing Dapagliflozin. • When starting this medication we do not support additional eGFR monitoring as there is no evidence that the small, transient drop in eGFR causes harm, and in fact AKI rates are reduced in cohorts prescribed Dapagliflozin. • We would like to highlight the importance of clear sick day rules when using this medication.
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	Reaching ESKD and renal replacement therapy significantly impacts life expectancy and therefore reducing the number of people who progress to end stage kidney disease or slowing the rate of eGFR decline offers a substantial benefit of treatment.

quality-adjusted life year (QALY) calculation?	
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?	We consider that the indication for Dapagliflozin in proteinuric CKD management is a major therapeutic breakthrough, with unique benefits to the non-diabetic population. As stated above, the impact is likely to exceed that seen with the introduction of RAAS inhibitors several decades ago.
• Is the technology a 'step-change' in the management of the condition?	Yes, please see above for our rationale.

• Does the use of the technology address any particular unmet need of the patient population?	ESKD confers huge reductions in patient QoL, and as such any agents demonstrated to significantly impact this will address this.
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?	We assert that Dapagliflozin has demonstrated a good safety profile and is globally well tolerated, even at the lower end of the studied eGFR range (25-30ml/min). There is some data around the development of genitourinary infections in patients treated with dapagliflozin; Bacterial UTI: Type 2 DM 1.6% vs 0.9% non-diabetic (0.6% placebo non-diabetic) Mycotic infection: Type 2 DM 0.2% v 0.0% in non-diabetic population Urinary tract bacterial infection: non-diabetic (0%) on dapa vs 0.1% in type 2 DM Indeed, in patients with type 2 diabetes any risk of DKA can be prevented by: a) patient selection: exclusion of patients with type 1 DM or Latent Autoimmune Diabetes of Adult (LADA), patients with a previous history of DKA and patients with likely insulin deficiency such as those with pancreatic exocrine disease (pancreatitis, pancreatic cancer) b) Appropriate sick-day rule advice – as would currently be appropriate for patients with CKD and with or without diabetes.
Sources of evidence	

18. Do the clinical trials on the technology reflect current UK clinical practice?	Trials with dapagliflozin reflect UK practice up to the point of the addition of dapagliflozin and that the patients included in the concomitant standard of care are equivalent to that which would be used in the UK.
• If not, how could the results be extrapolated to the UK setting?	Trials included UK sites.
• What, in your view, are the most important outcomes, and were they measured in the trials?	The primary outcome in the DAPA CKD trial was a composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes.
• If surrogate outcome measures were used, do they adequately	

predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. How do data on real-world experience compare with the trial data?	Dapagliflozin is not being used as per the DAPA CKD trial parameters; therefore real world data is unlikely to exist in any significant amount.

Equality	
21a. Are there any potential equality issues that should be taken into account when considering this treatment?	
21b. Consider whether these issues are different from issues with current care and why.	

22. In up to 5 bullet points, please summarise the key messages of your submission.

- It is the view of the LKN that Dapagliflozin represents a significant therapeutic breakthrough in the management of proteinuric CKD.
- We assert that there are unique benefits observed in the non-diabetic population, hence we urge the TA to include this patient group in recommendations.
- We consider that significant numbers of people with proteinuric CKD in England stand to benefit in line with the results achieved in the DAPA CKD trial.
- Clear recommendations for use will minimise the very small risk of DKA in diabetic individuals.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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Dapagliflozin for treating chronic kidney disease: A Technology Appraisal

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Declared competing interests of the authors

None of the authors have any conflicts of interest to declare.

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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.

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Contributions of authors

Mark Clowes critiqued the company's search strategy. Edith Poku summarised and critiqued the clinical effectiveness data reported within the company's submission. Jean Hamilton critiqued the statistical aspects of the submission. Paul Tappenden and Aline Navega Biz critiqued the health economic analysis submitted by the company. All authors were involved in drafting and commenting on the final report.

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Abbreviations

ACE	Angiotensin converting enzyme
ACM	All-cause mortality
AE	Adverse event
AF	Acceleration factor
AFT	Acceleration failure time
AIC	Akaike Information Criterion
AKI	Acute kidney injury
ANCA	Anti-neutrophil cytoplasmic antibody
ARB	Angiotensin receptor blocker
ASA	Additional scenario analysis
BIC	Bayesian Information Criterion
BMI	Body mass index
CEAC	Cost-effectiveness acceptability curve
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence interval
CKD	Chronic kidney disease
CMU	Commercial Medicines Unit
CPRD	Clinical Practice Research Datalink
CRD	Centre for Reviews and Dissemination
CS	Company's submission
CSR	Clinical Study Report
CV	Cardiovascular
CVD	Cardiovascular disease
DARE	Database of Abstracts of Reviews of Effects
DKA	Diabetic ketoacidosis
dL	Decilitre
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
eGFR	Estimated glomerular filtration rate
EHR	Electronic health record
Embase	Exerpta Medica Database
eMIT	Electronic Market Information Tool
EPO	Erythropoietin
EQ-5D	EuroQol 5-Dimensions
ERG	Evidence Review Group
ESA	Erythropoiesis stimulating agent
ESKD	End-stage kidney disease
ESS	Effective sample size
EVPI	Expected Value of Perfect Information
FAS	Full Analysis Set
FPG	Fasting plasma glucose
FTA	Fast Track Appraisal
g	Gram
GEE	Generalised estimating equations
GP	General practitioner
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
HTN	Hypertension
ICER	Incremental cost-effectiveness ratio

ICTRP	International Clinical Trials Registry Platform
IPD	Individual patient data
IQR	Inter-quartile range
ITC	Indirect treatment comparison
ITT	Intention-to-treat
KDIGO	Kidney Disease Improving Global Outcomes
KDQoL-36	Kidney Disease Quality of Life 36-Item Short Form Survey
L	Litre
LOCF	Last observation carried forward
m^2	Metre squared
MAIC	Matching-adjusted indirect comparison
MEDLINE	Medical Literature Analysis and Retrieval System Online
mg	Milligram
MI	Myocardial infarction
mmol	Millimole
MRA	Mineralocorticoid receptor antagonist
N/a	Not applicable
NG	NICE Guideline
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NR	Not reported
ONS	Office for National Statistics
OR	Odds ratio
OS	Overall survival
PH	Proportional hazards
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QIC	Quasi-Information Criterion
RAAS	Renin-angiotensin-aldosterone system
RCT	Randomised controlled trial
RDI	Relative dose intensity
RMM	Repeated measures model
RRT	Renal replacement therapy
SA	Scenario analysis
SAE	Serious adverse event
SAS	Safety Analysis Set
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error
SGLT2	Sodium-glucose cotransporter-2
SIGN	Scottish Intercollegiate Guidelines Network
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SoC	Standard of care
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TSD	Technical Support Document
uACR	Urine albumin-to-creatinine ratio
ULN	Upper limit of normal
UTI	Urinary tract infection
VBA	Visual Basic for Applications
WTP	Willingness-to-pay

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the Evidence Review Group (ERG) as being potentially important for decision-making. It also includes a summary of the incremental cost-effectiveness ratios (ICERs) from the company's updated base case model and scenario analyses undertaken by the company and the ERG.

Section 1.1 provides 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 1.5 provide a brief summary of the evidence presented by the company and explain the key issues in more detail. Section 1.6 summarises the results of the economic analyses presented by the company and the ERG. Section 1.7 summarises the ERG's view regarding the company's case for appraising dapagliflozin for treating chronic kidney disease (CKD) through the National Institute for Health and Care Excellence's (NICE) Fast Track Appraisal (FTA) route. Background information on the condition, technology and evidence and information on non-key issues are in the main ERG report.

All issues identified represent the ERG's view, not the opinion of NICE.

1.1 Overview of the ERG's key issues

The company's submission (CS) presents the methods and results of a model-based economic analysis of dapagliflozin plus standard of care (SoC) versus SoC alone for the treatment of CKD from the perspective of the NHS and Personal Social Services (PSS) over a lifetime horizon. Results are presented in terms of the incremental cost per quality-adjusted life year (QALY) gained. Health outcomes and costs are discounted at a rate of 3.5% per annum. The event risks included in the model are estimated using data from the DAPA-CKD trial; risks of mortality, hospitalisation for heart failure (hHF) and acute kidney injury (AKI) are adjusted to the UK population based on population characteristics from a bespoke dataset of CKD patients obtained from the Clinical Practice Research Datalink (CPRD).

The key issues identified by the ERG are summarised in Table 1.

Table 1: Overview of the ERG's key issues

ID13866	Summary of issue	Report sections
Issue 1	Uncertainty surrounding the target population and the effectiveness of dapagliflozin in patients excluded from DAPA-CKD	5.3.4
Issue 2	Concerns regarding the company's overall modelling approach and OS predictions	5.3.4

OS - overall survival

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival [OS]) and quality of life in a QALY. An ICER is the ratio of the extra cost for every QALY gained.

Based on the company's model, dapagliflozin is assumed to affect QALYs by:

- Increasing OS
- Increasing the amount of time patients spend alive in better health states (prior to receiving renal replacement therapy [RRT] or transplant).

Dapagliflozin is assumed to affect costs by:

- Increasing total costs as a consequence of the acquisition cost of dapagliflozin
- Increasing lifetime costs of CKD management (pre-RRT) due to extended OS
- Increasing the lifetime costs of dialysis
- Increasing the total costs of managing transient events and other AEs.

The modelling assumptions that have the greatest effect on the ICER are:

- The probabilities of transitioning between the model health states in each treatment group, and the risk of death applied within each health state.

1.3 The decision problem: Summary of the ERG's key issues

The decision problem addressed in the CS is generally in line with the final NICE scope. The ERG has some concerns regarding the definition of the target population in whom dapagliflozin would be used in clinical practice; this issue is discussed in the context of the company's economic analysis (see Section 1.5, Issue 1).

1.4 The clinical effectiveness evidence: Summary of the ERG's key issues

The key evidence for the clinical effectiveness and safety of dapagliflozin in treating CKD is the DAPA-CKD trial. DAPA-CKD was an event-driven, multicentre, international double-blind randomised controlled trial (RCT) which included adult patients with CKD with or without comorbid type 2 diabetes mellitus (T2DM). The trial was conducted across 386 study centres. Eligible patients had an eGFR of ≥25 to ≤75ml/min/1.73m^2 and a urine albumin-to-creatinine ratio (uACR) of ≥22.6mg/mmol (200mg/g) to ≤565mg/mmol (5,000mg/g). Patients were randomised in a 1:1 ratio to receive oral dapagliflozin 10mg (n=2,152) or a matched film-coated placebo tablet (n=2,152), in addition to SoC. Concomitant medications during the trial included treatments for CKD, T2DM, cardiovascular (CV) risk factors and T2DM or CKD complications. The anticipated study duration and estimated mean treatment period of

DAPA-CKD was 45 months and 33 months, respectively. The trial was terminated prematurely based on a determination of overwhelming efficacy by the independent data monitoring committee.

Dapagliflozin was associated with a statistically significant risk reduction of 39% (hazard ratio [HR] 0.61; 95% confidence interval [CI]: 0.51, 0.72; $p<0.001$) in the primary endpoint (a composite endpoint of sustained decline in eGFR ≥50%, end-stage kidney disease (ESKD) or death from renal or CV causes) compared with placebo. Statistically significant benefits for dapagliflozin were observed for most of the individual components of the primary outcome (where assessed) as well as for secondary outcomes. These included the renal-specific composite outcome of ≥50% sustained decline in eGFR, ESKD, and renal death (HR 0.56; 95% CI: 0.45, 0.68; $p<0.001$); the composite outcome of risk of hospitalisation for HF or CV death (HR 0.71; 95% CI: 0.55, 0.92; $p=0.0089$) and all-cause mortality (HR 0.69; 95% CI: 0.53, 0.88; $p=0.004$). Dapagliflozin demonstrated a consistent treatment benefit in all pre-specified analyses of relevant subgroups, although a p-value for interaction of <0.05 was observed for systolic blood pressure (SBP; ≤130 mmHg versus >130 mmHg). [redacted]. Safety outcomes in DAPA-CKD were generally consistent with available safety data for dapagliflozin in other indications (diabetes and HF).

The ERG considers DAPA-CKD to be at low risk of bias. The ERG's advisors suggested that the DAPA-CKD trial reflects many of the types of patients who might be treated with dapagliflozin in clinical practice; however, several groups of patients were excluded due to the trial eligibility criteria, including patients with urine albumin excretion <22.6mg/mmol, those with prior organ transplant, and those with type 1 diabetes mellitus (T1DM). Also, whilst almost all patients in the trial were receiving angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) therapy, many patients with CKD do not receive these therapies in clinical practice. The limitations of the available evidence are highlighted as part of Issue 1 (see Section 1.5).

1.5 The cost-effectiveness evidence: Summary of the ERG's key issues

The company submitted a cohort-level state transition model which assesses the cost-effectiveness of dapagliflozin plus SoC versus SoC alone in people with CKD [redacted]. The model estimates the trajectory of patients through health states defined by CKD stages 1-5 (all pre-RRT, with separate states for CKD stages 3a and 3b), with additional states for dialysis, transplant and death. Each alive health state is associated with a health utility value and cost. Transient events (hHF and AKI) and AEs are assumed to result in additional QALY losses and costs. The relative effectiveness of dapagliflozin is modelled via three separate mechanisms: (i) arm-specific transition matrices are applied

to each treatment group; (ii) a treatment-related log HR is applied to the per-cycle survival probability in all health states except for the transplant state, and (iii) a treatment-related log odds ratio (OR) is applied to the risk of hHF and AKI in each state except for the transplant state. Transition probabilities were estimated using observed patient count data from DAPA-CKD. State-specific mortality risks were estimated using a multivariable survival model fitted to OS data from DAPA-CKD, which includes time-updated CKD stage and a treatment-related HR as covariables. Risks of hHF and AKI were estimated using generalised estimation equations (GEE) models fitted to data from DAPA-CKD. Health utility was estimated using a linear mixed effects model fitted to EQ-5D data collected in the trial. The company's updated base case model and scenario analyses suggest that the ICER for dapagliflozin versus SoC is consistently below £10,000 per QALY gained.

The ERG notes that there are no previous NICE appraisals of treatments for slowing the progression of CKD. However, the ERG considers the general structure of the model to be appropriate and believes that it includes events, outcomes and costs which are relevant to treatment for CKD. The health state utility values included in the model are similar to those reported in the literature. The ERG also considers that the cost assumptions are generally reasonable. The ERG's critical appraisal of the company's original model identified a number of issues; several of these have been resolved in the company's updated model which was provided as part of the company's clarification response, or have been explored through the use of scenario analyses in the CS and the company's clarification response. The ERG has identified two outstanding issues: Issue 1 relates to the target population in whom dapagliflozin would be used and the populations not represented in DAPA-CKD, whilst Issue 2 relates to the ERG's concerns regarding the way in which the company's model combines evidence from DAPA-CKD and the resulting impact of this approach on the model's OS predictions.

Issue 1: Uncertainty surrounding the target population and the effectiveness of dapagliflozin in patients excluded from DAPA-CKD

Report section	5.3.4
Description of issue and why the ERG has identified it as important	The anticipated wording of the CKD indication in the marketing authorisation is expected to relate to use of dapagliflozin for [redacted] However, there are some CKD populations for whom DAPA-CKD does not provide evidence of efficacy for dapagliflozin. These include: people with urine albumin excretion <22.6mg/mmol; people with ESKD; people with prior organ transplantation, and people with T1DM. Whilst the CS presents further evidence from DAPA-HF and DECLARE-TIMI 58 which is intended to demonstrate the generalisability of the treatment effect of dapagliflozin regardless of uACR or eGFR, the company's economic model is based on effectiveness evidence drawn exclusively from DAPA-CKD. The ERG also notes that it is unclear whether the CPRD dataset, which is used to inform baseline patient characteristics and to adjust event risks in the economic model, reflects the target population in whom dapagliflozin would

	be used in clinical practice. The CS states that dapagliflozin is expected to be used *"in addition to optimised SoC, which may include ACE inhibitors and ARBs."* In DAPA-CKD, 97% of patients were receiving an ACE inhibitor or ARB at baseline. However, in the CPRD dataset, only [redacted] of people were receiving these therapies. The ERG's clinical advisors commented that many patients with CKD do not receive ACE inhibitor/ARB therapy in practice for a variety of reasons, but that the strongest evidence for the effectiveness of dapagliflozin in treating CKD is from DAPA-CKD, in which almost all patients were receiving ACE inhibitors/ARBs. They considered it possible that the benefits of sodium-glucose cotransporter-2 (SGLT2) inhibitors might be similar in people with CKD and proteinuria who are not treated with ACE inhibitors/ARBs, but commented that the evidence is much less certain in these groups, and that the use of dapagliflozin in this context would be going beyond the available trial data from DAPA-CKD. They also commented that the supporting evidence for people not treated with ACE inhibitors/ARBs from DECLARE-TIMI 58 and DAPA-HF is uncertain. The advisors further commented that of those patients in the CPRD dataset who were receiving ACE inhibitors/ARBs, many may not have met the inclusion criteria for the trial. The ERG notes that these issues raise questions regarding the suitability of the adjustment of baseline characteristics and event risks to the CPRD population.
What alternative approach has the ERG suggested?	This issue largely relates to restrictions around the characteristics of the patient population for whom a NICE recommendation will be made.
What is the expected effect on the cost-effectiveness estimates?	The company's scenario analyses indicate that the ICER is expected to be less than £10,000 per QALY gained across all populations considered, including the unadjusted DAPA-CKD overall population.
What additional evidence or analyses might help to resolve this key issue?	If the Appraisal Committee considers a recommendation only in people who are already receiving ACE inhibitor or ARB therapy, and/or in those with a urine albumin excretion of ≥22.6mg/mmol, it may be appropriate to amend the company's model to reflect this narrower subgroup of the CPRD dataset.

Issue 2: Concerns regarding the company's overall modelling approach and OS predictions

Report section	5.3.4
Description of issue and why the ERG has identified it as important	The company's model estimates the transition probabilities between health states for CKD1-5 (pre-RRT) based on unadjusted probabilities obtained from DAPA-CKD. The risk of death in each CKD state in each model cycle is based on the outputs of a multivariable survival model fitted to OS data from DAPA-CKD (applying a value of 1.0 to the relevant eGFR category and retaining the mean values for all other covariates). Relative treatment effects on OS are modelled via two mechanisms: (i) directly – through the application of an HR to each state-specific OS model except transplant, and (ii) indirectly – through the application of transition matrices which lead to slower disease progression for dapagliflozin compared with SoC. The ERG has several concerns with this approach: (i) The company's multivariable survival model includes both a treatment effect indicating covariate (an HR) and a time-updated covariate for CKD stage. The ERG has concerns that including post-randomisation covariates can lead to problems in determining causality. If part of the causal effect of treatment is through CKD stage, this approach will

	block that effect, and the resulting model coefficients may not be meaningful. (ii) The company's economic model estimates state-specific mortality risks using a "mean of covariates" approach. The ERG considers that this reflects a misinterpretation of the outputs of the multivariable survival model, which has been shown to lead to bias when estimating survival distributions. (iii) The company's unadjusted economic model, which does not include adjustment to the CPRD population, overestimates observed OS in DAPA-CKD in both treatment groups. This is likely to be a consequence of issues (i) and/or (ii) above. This raises some doubts regarding the confidence that should be placed on the model results.
What alternative approach has the ERG suggested?	The ERG believes 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).
What is the expected effect on the cost-effectiveness estimates?	The impact of resolving the poor fit of the model is not fully clear. An exploratory analysis undertaken by the ERG which inflates estimated mortality risks using an HR to force the unadjusted model to better fit the observed OS data has little impact on the ICER. However, this analysis is not rigorous and should be interpreted with caution.
What additional evidence or analyses might help to resolve this key issue?	As described above, it may be possible to achieve a better model fit to OS using an alternative modelling approach. However, this would involve a considerable amount of additional analysis by the company. It is unclear whether such an analysis would significantly alter the overall economic conclusions drawn from the analysis.

1.6 Summary of key cost-effectiveness results

The ICERs for the range of scenarios presented by the company and the ERG are summarised in Table 2. It should be noted that the ERG's exploratory analyses include one scenario analysis in which transition probabilities were assumed equal between the groups; this analysis generated an ICER which was greater than £10,000 per QALY gained. Whilst this scenario analysis demonstrates that the transition probabilities (and the resulting impact on mortality risks) are key drivers of the ICER, the ERG does not consider this scenario to be plausible given the changes in CKD stage observed in DAPA-CKD.

Table 2: Summary of key cost-effectiveness results based on the company's updated model

Scenario	ICER
Company's updated base case model (probabilistic)	**£5,827 per QALY gained**
Company's original scenario and subgroup analyses reported in the CS	**Dominating** to **£6,916 per QALY gained**
Company's additional scenario and subgroup analyses presented in the clarification response	**Dominating** to **£9,706 per QALY gained**
ERG's additional analyses	**Dominating** to **£28,862 per QALY gained**

ICER - incremental cost-effectiveness ratio; QALY - quality-adjusted life year; ERG - Evidence Review Group

1.7 Summary of ERG view on the company's FTA case

At the decision problem meeting, the company suggested that dapagliflozin satisfies the criteria for NICE's Fast Track Appraisal (FTA) process on the basis that the ICER for dapagliflozin versus SoC is consistently low in the company's base case analysis and across all scenario analyses considered. The economic analyses presented by the company and the ERG are summarised as follows:

- Based on the updated model submitted following the clarification round, the company's probabilistic base case ICER is expected to be £5,827 per QALY gained. The deterministic estimate from the updated base case model is slightly higher (ICER = £6,158 per QALY gained).
- Based on the company's updated model, the highest ICER from the scenario analyses presented in the CS is £6,916 per QALY gained. The highest ICER estimated within the additional scenario analyses provided in the company's clarification response is £9,706 per QALY gained.
- All but one of the ERG's additional exploratory analyses result in ICERs which are lower than £10,000 per QALY gained. The scenario which generated a higher ICER shows the importance of the transition probabilities on the model results, but is not plausible given the data observed in DAPA-CKD.
- The analysis of the consequences of decision uncertainty suggests very high net health effects and a low global Expected Value of Perfect Information (EVPI).

However, the ERG has some concerns regarding the company's approach to separately modelling health state transitions and mortality risks. The ERG notes that the unadjusted model for the DAPA-CKD overall population over-predicts OS in both treatment groups compared with OS observed in the trial. As such, the ERG believes that the economic analyses presented by the company and the ERG should be interpreted with some degree of caution.

The appropriateness of a referral to FTA ultimately depends whether an Appraisal Committee would expect that an alternative modelling approach, which appropriately estimates event risks in each treatment group, and which leads to unadjusted OS predictions which are consistent with observed data from DAPA-CKD, would change the conclusions of the economic analysis. Such an analysis would require a considerable amount of additional work by the company. The ERG believes that even if the issues identified in the company's model were resolved, the ICER for dapagliflozin would probably remain below £20,000 per QALY gained.

2. BACKGROUND

This chapter presents a brief summary and critique of the company's description of the disease and the current treatment pathway for chronic kidney disease (CKD) in England.

2.1 Critique of the company's description of the underlying health problem

Section B.1.3.1 of the company's submission (CS)[1] contains a useful and accurate overview of CKD. The disease is often, but not always, characterised by a progressive decrease in kidney function over time. CKD is diagnosed through laboratory measures of kidney function and/or markers of kidney damage, such as the estimated glomerular filtration rate ([eGFR], an indicator of overall kidney function) and the urine albumin-to-creatinine ratio ([uACR], which is used for initial detection of proteinuria). Current guidelines define CKD as decreased eGFR or other markers of kidney damage for at least three months regardless of underlying cause.[1, 2] Type 2 diabetes mellitus (T2DM), hypertension (HTN) and cardiovascular disease (CVD) such as heart failure (HF) frequently co-occur with CKD.[1] The risk of developing CKD increases with age.[3]

CKD can be classified in terms of disease severity and risk of adverse outcomes using a combination of eGFR and uACR categories (see Table 3), using six categories for eGFR (G1 to G5, with G3 being subdivided into 3a and 3b to reflect increased CVD risk) and three categories for uACR (A1-A3), based on predefined thresholds.[1, 4, 5] Increased uACR and decreased eGFR are associated with an increased risk of adverse outcomes in adults, with a multiplicative effect when present in combination. Complications resulting from reduced kidney function include dyslipidaemia and electrolyte imbalances, anaemia, acute kidney injury (AKI) and infections.[1] A small but significant percentage of patients with CKD progress to kidney failure, which is defined as an eGFR that is consistently lower than 15ml/min/1.73m^2; the late presentation of kidney failure is associated with increased morbidity, mortality and healthcare costs.[1, 3]

In 2016, the Health Survey for England (HSE) reported an estimated prevalence of CKD (at any stage) in people aged 35 years and older of 15%.[6] However, a substantial proportion of patients with CKD may remain undiagnosed or are diagnosed at an advanced stage as a result of the disease typically being asymptomatic at early stages or not presenting with specific symptoms. As a consequence, lower prevalence rates of diagnosed disease are usually reported in official general practice databases. According to the CS,[1] approximately 1.9 million adults in England were reported by the NHS Quality and Outcomes Framework in 2020 as having a diagnosis of CKD with an eGFR category of G3a to G5, which corresponds to an estimated prevalence of 4.05%;[7] the prevalence of people with G1 and G2 is not reported in the CS.[1]

Table 3: Classification of CKD by risk of adverse outcomes in adults, based on eGFR and uACR categories (adapted from CS, Table 3 and KDIGO guidelines 2012)

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

ACR – albumin-to-creatinine ratio; CKD - chronic kidney disease; eGFR - glomerular filtration rate
** No CKD if there are no other markers of kidney damage*
Source: KDIGO[5] and CS[1]

CKD impacts both on patients' expected survival and health-related quality of life (HRQoL). People with CKD are at a higher risk of CV events and CV-related/all-cause death, which increases with worsening of kidney function.[2] Compared to individuals without CKD, decreased renal function is also associated with an increase in the risk of hospitalisation due to conditions such as AKI (hazard ratio [HR]: 4.90; 95% confidence interval [CI]: 4.47, 5.38), HF (HR 1.66; 95% CI: 1.59, 1.75) and myocardial infarction ([MI] - HR: 1.40; 95% CI: 1.34, 1.46).[8]

CKD is also associated with significant impacts on HRQoL for patients and caregivers, which increase with disease progression. Patients with later stage CKD have reported significantly reduced HRQoL across multiple domains of the EuroQol 5-Dimensions (EQ-5D) when compared to patients with CKD stage 1 or normal kidney function.[9] The CS[1] highlights that the requirement for dialysis, in which patients may have to attend lengthy appointments three times a week and follow strict dietary and fluid restrictions, can be distressing and places a significant impact on patients, caregivers and families, thus having further negative impacts on HRQoL.

The CS[1] highlights the considerable economic burden associated with CKD and related complications as a consequence of high rates of hospitalisation and outpatient visits, which increases with declining eGFR and higher uACR levels. The CS refers to an analysis of 99,186 patients with CKD included in the UK Clinical Practice Research Datalink (CPRD) which estimated the median annual cost of hospitalisations to be £1,342 per patient.[10] In 2015, Kent *et al.* estimated a 12-fold increase in hospitalisation costs between CKD stage 5 (pre-dialysis) and CKD stages 3, based on an analysis of the SHARP cohort.[11] Kerr *et al*. estimated the costs of CKD management for patients with CKD stages 3 to 5 for the NHS in England to be around £1.45 billion in 2009/2010.[12] The ERG's clinical advisors commented that the current costs of CKD in the NHS are likely to be substantially higher due to the increase in the prevalence of end-stage kidney disease (ESKD) over the last decade. Renal replacement therapy (RRT) and major vascular events are the main contributors to the high hospital care costs in moderate-to-severe CKD.[11] As such, preventing or delaying disease progression would be important in reducing this high economic burden associated with advanced CKD and ESKD.[1]

2.2 Critique of the company's overview of current service provision

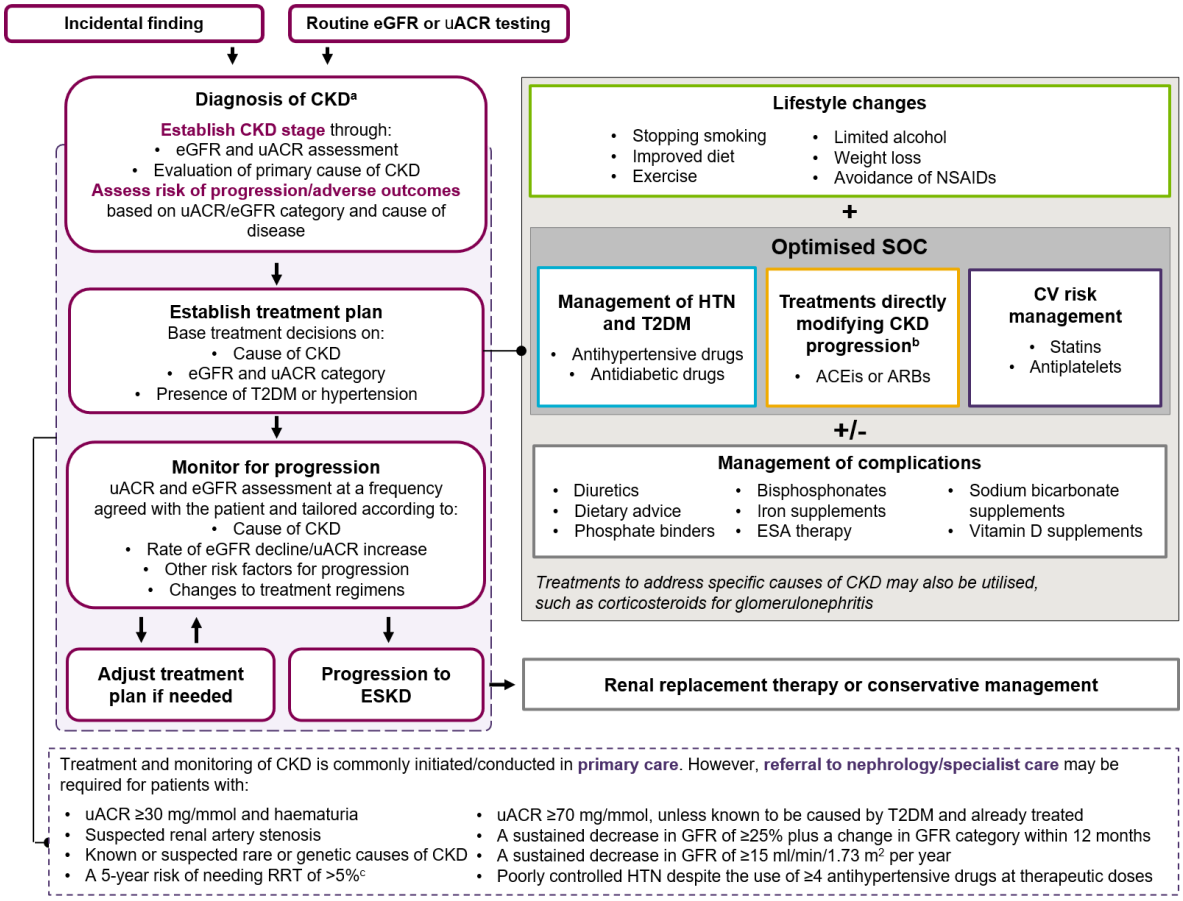
An overview of the treatment pathway is presented in Section B.1.3.3 of the CS.[1] This refers to NICE Clinical Guideline 182 (Chronic kidney disease in adults: assessment and management)[3] and the revised guideline draft for consultation, which is expected to be published in August 2021.[4] The company's view of the pathway is shown in Figure 1. The clinical advisors to the Evidence Review Group (ERG) considered the company's description of the treatment pathway to be a generally reasonable representation of the current treatment pathway for patients with CKD and noted that it is in line with current guidelines for CKD management.

As described in the CS,[1] the management of patients with CKD consists of a variety of treatment strategies with the aims of slowing disease progression, and consequently delaying ESKD, and reducing the risk of CV events and premature death. Therefore, these treatments focus on slowing CKD progression, as well as managing other comorbid conditions such as T2DM, HTN or CVD and treating complications.[2, 13] The ERG's clinical advisors commented that many patients never reach ESKD and for these patients, reducing CV risk is more important than delaying CKD progression.

Patients with CKD are usually managed in primary care or through specialist nephrology clinics, depending on the individual patient's needs and the severity of their disease.[1] In 2020, approximately [redacted] of patients with CKD stage 3 to 5 were managed in primary care.[14] The CS suggests that managing CKD in the primary care setting would provide increased convenience for patients at early disease stages, and would enable resources in the specialist care setting to be reserved for patients at advanced stages of the disease.

Patients with CKD require routine follow-up and regular monitoring of disease progression, and the number of appointments increases with disease severity.[4] Pharmacological standard of care (SoC) comprises individually optimised therapy, which may include angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) for the management of disease progression, statins and antiplatelets for the management of CV risk, management of underlying T2DM and HTN with antidiabetic and antihypertensive drugs, and treatments for the management of complications such as anaemia or mineral and bone disorders.[3, 4]

Figure 1: Current treatment pathway for CKD in the UK (reproduced from the CS, Figure 3)



ACE inhibitors and ARBs are recommended in the UK only for patients with high levels of uACR (>70mg/mmol regardless of underlying comorbidities or >30 mg/mmol and comorbid HTN) or patients with comorbid T2DM and uACR >3mg/mmol. Sodium-glucose cotransporter (SGLT2) inhibitors, such as dapagliflozin and canagliflozin, may also be recommended for patients with T2DM and uACR >30mg/mmol if they meet the criteria in the respective marketing authorisation, as stated in the draft NICE guidelines for CKD management.[4] For patients who are not eligible for or cannot tolerate treatment with ACE inhibitors or ARBs, or are not eligible for SGLT2 inhibitors, no specific disease-modifying treatments are recommended to prevent CKD progression.

The CS[1] indicates that [redacted] of CKD patients in the UK may receive statins, which are recommended for the primary prevention of CVD in patients at risk of developing CVD (≥10%) or for secondary prevention in patients with established CVD. Antiplatelets, which are recommended for secondary prevention of CVD, or anticoagulant therapies, are received by an estimated [redacted] of patients in the UK.[1, 15] Colecalciferol or ergocalciferol may be offered to patients with vitamin D deficiency to treat symptoms of CKD-related mineral and bone disorders, and bisphosphonates may be used for the prevention and treatment of osteoporosis in patients with eGFR≥30 ml/min/1.73m^2, if indicated.[3]

According to the CS,[1] dapagliflozin will be positioned as an additional treatment option for [redacted]. The treatment may be offered in addition to ACE inhibitors and ARBs, meeting an unmet need for patients receiving optimised SoC alone, particularly those without T2DM or HF, or those with diabetes and lower eGFR levels (<45ml/min/1.73m^2, corresponding to categories G3b to G5).[1] The company's clarification response indicates that the target population for dapagliflozin includes people who are not receiving ACE inhibitor or ARB therapy.[16]

3 CRITIQUE OF COMPANY'S DEFINITION OF THE DECISION PROBLEM

This chapter provides a summary and critique of the decision problem addressed in the CS.[1] A summary of the decision problem as outlined in the final NICE scope[17] and addressed in the CS is presented in Table 4, together with brief comments from the ERG. The ERG's critique of the decision problem addressed within the CS is presented in the subsequent sections.

Table 4: The decision problem (reproduced from CS, Table 1, with comments from the ERG)

Element of decision problem	Final scope issued by NICE[17]	Decision problem addressed in CS[1]	Rationale if different from the final NICE scope	ERG's comments
Population	Adults with CKD who are receiving individually optimised standard care.	As per scope	[redacted]	In line with scope. However, some patient groups are not represented in DAPA-CKD.
Intervention	Dapagliflozin in combination with optimised standard care (including treatment with an ACE inhibitor or ARB).	As per scope	Intervention aligned with NICE final scope.	Generally in line with scope. However, the economic analysis reflects a population in whom only [redacted] of patients are receiving ACE inhibitor/ARB therapy. In DAPA-CKD, 97% of patients were receiving ACE inhibitors/ARBs. It is unclear how many patients in the CPRD dataset would have been eligible for the trial.
Comparator	Established clinical management without dapagliflozin.	As per scope	Comparator aligned with NICE final scope. Established clinical management without dapagliflozin comprises individually optimised SoC alone, which is represented by the placebo arm of the dapagliflozin clinical trial.	
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 • Adverse effects of treatment • Health-related quality of life	As per scope	N/a	In line with scope
Economic analysis	• The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY gained • The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be	As per scope	N/a	In line with scope

Element of decision problem	Final scope issued by NICE[17]	Decision problem addressed in CS[1]	Rationale if different from the final NICE scope	ERG's comments
	sufficiently long to reflect any differences in costs or outcomes between the technologies being compared • Costs will be considered from an NHS and PSS perspective			
Subgroups to be considered	• People with diabetes • People with CVD • People with other causes of CKD	• People with comorbid T2DM • People with comorbid CVD • People without comorbid T2DM and without comorbid CVD	It is most relevant in clinical practice to group patients by comorbidity rather than by cause of CKD, as it is difficult to accurately establish the cause of CKD in most cases. The third subgroup requested in the final scope has been clarified during the decision problem meeting to be the subgroup of patients without comorbid T2DM and without comorbid CVD.	Definition of subgroups based on comorbidity agreed with NICE
Special considerations including issues related to equity or equality	None stated.	Considerations related to current use and availability of dapagliflozin in primary and secondary care for patients with T2DM, T1DM and HFrEF.	Dapagliflozin is currently available across primary and secondary treatment settings for patients with T2DM, T1DM and HFrEF.[18] A positive recommendation for dapagliflozin in CKD is expected to extend the benefits of dapagliflozin to all eligible patients with CKD, including patients with CKD but without T2DM or HFrEF. A NICE recommendation that permitted the initiation of dapagliflozin for the treatment of CKD in the primary care setting is needed to deliver equitable access to treatment, given access to specialist CKD care varies considerably by geography.	The final NICE scope did not list any special considerations. The ERG's clinical advisors agreed that most patients with early stages of CKD would be managed in a primary care setting.

ACE - angiotensin-converting enzyme; ARB - angiotensin II receptor blockers; CKD - chronic kidney disease; CV - cardiovascular; CVD - cardiovascular disease; eGFR - estimated glomerular filtration rate; HFrEF - heart failure with reduced ejection fraction; N/a - not applicable; NICE - National Institute for Health and Care Excellence; T1DM - type 1 diabetes mellitus; T2DM - type 2 diabetes mellitus; SoC - standard of care

3.1 Population

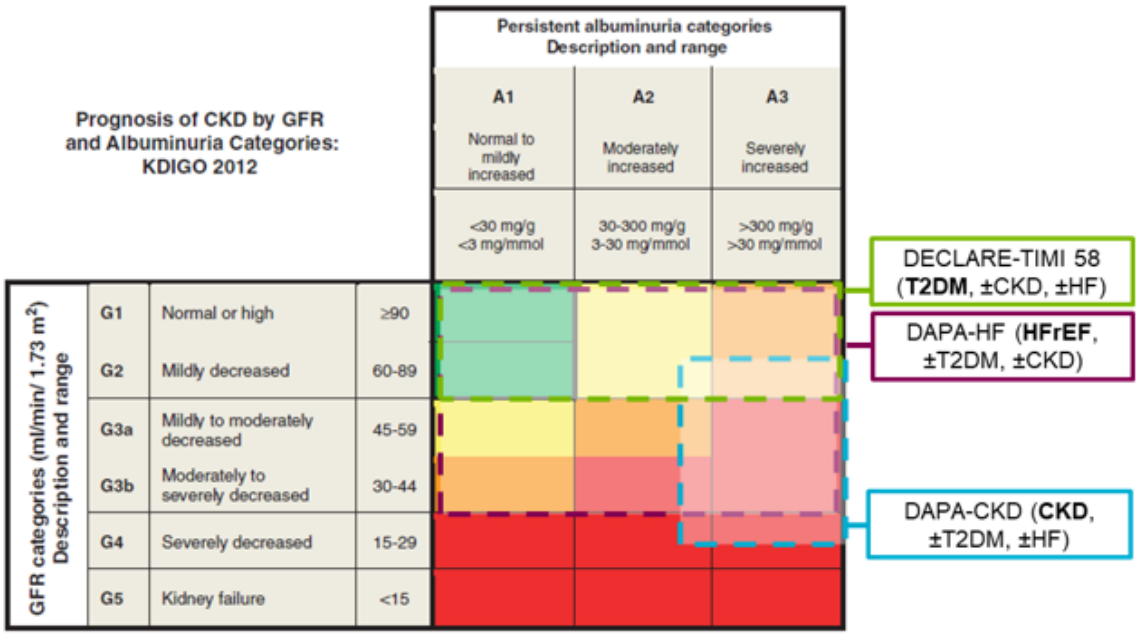
Decision problem: The CS[1] defines the population of interest as adults with CKD who are receiving individually optimised SoC. This is line with the final NICE scope.[17]

Relevance of clinical evidence: The pivotal trial supporting the CS[1] is the DAPA-CKD trial.[19] This is a multicentre, international, event-driven, double-blind, parallel-group, placebo-controlled randomised controlled trial (RCT) comparing dapagliflozin 10mg with placebo, once daily, in addition to SoC, in adults with CKD (eGFR ≥25 and ≤75mL/min/1.73m^2) with albuminuria (uACR ≥200 and ≤5000mg/g), with or without T2DM. The trial included adult patients who were on stable doses of ARBs or ACE inhibitors, although a small proportion of patients were unable to take either treatment. Patients requiring more focused treatment (e.g. for anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis or lupus nephritis) and those with common genetic conditions (e.g. autosomal dominant or autosomal recessive polycystic disease) or those with kidney transplant were excluded from the trial. The ERG's advisors suggested that the DAPA-CKD trial is broadly representative of many of the types of patients who might be treated with dapagliflozin in clinical practice; however, the trial protocol excluded several groups of patients e.g. those with urine albumin excretion <22.6mg/mmol, those with prior organ transplant, and those with type 1 diabetes mellitus (T1DM). Also, whilst almost all patients in the trial were receiving ACE inhibitor or ARB therapy, many patients with CKD do not receive these therapies in clinical practice.

The CS[1] (Section B.2.13.2, page 69) states that the [redacted]. The CS refers to additional supporting data from the DECLARE-TIMI 58 (n=17,160 patients) and DAPA-HF (n=4,744 patients) trials.[20, 21] Both of these studies were large Phase III RCTs which included some patients with comorbid CKD. DECLARE-TIMI 58 included patients with T2DM who had or were at risk of atherosclerotic CVD, whereas DAPA-HF included patients with heart failure with reduced ejection fraction (HFrEF), regardless of the presence or absence of comorbid T2DM. In relation to renal function at baseline, more patients in DAPA-CKD[19] had CKD Stage 3 compared with patients in DAPA-HF and DECLARE-TIMI 58 (44% versus 14% and 7%, respectively). Approximately, 50% of patients randomised to each treatment arm in DAPA-CKD had severe albuminuria (uACR >1,000 mg/g [113 mg/mmol]). In contrast, the proportion of patients with albuminuria in DECLARE-TIMI 58 varied widely (normoalbuminuria n=11,644 [69.1%]; microalbuminuria n=4,030 [23.9%] or macroalbuminuria n=1,169 [6.9%]), while uACR measurements were not undertaken in DAPA-HF. The CS outlines the range of eGFR and uACR values in the relevant study populations with CKD enrolled in the DAPA-CKD, DAPA-HF and DECLARE-TIMI 58 to support the full anticipated marketing authorisation of dapagliflozin (Figure 2). DAPA-CKD excluded patients with very low eGFR (25mL/min/1.73m^2 or

less) and patients with urine albumin excretion <22.6mg/mmol, whereas DECLARE-TMI 58 included only 7% of patients with uACR >30mg/mmol and 69.1% of patients with normoalbuminuria. It should be noted that except for assumptions around certain adverse events (AEs) associated with dapagliflozin, data from DAPA-HF and DECLARE-TIMI 58 are not used to inform the company's economic model (see Section 5.2).

Figure 2: Supporting data for the efficacy and safety of dapagliflozin with the full expected marketing authorisation (reproduced from CS, Figure 16)



Text in bold indicates primary trial population in studies
CKD - chronic kidney disease; GFR - glomerular filtration rate; HFrEF - heart failure with reduced ejection fraction; T2DM - type 2 diabetes mellitus

3.2 Intervention and comparator:

Decision problem: The intervention assessed within the clinical section of the CS[1] is dapagliflozin in combination with optimised SoC (including treatment with an ACE inhibitor or ARB, unless contraindicated), whilst the comparator is placebo with optimised SoC. This is in line with the final NICE scope.[17] As described in the CS, dapagliflozin is a selective and reversible SGLT2 inhibitor. The anticipated effects of SGLT2 inhibition in people with CKD are wide-ranging and include improvement in renal outcomes related to a variety of CKD causes and modification of risk factors for CKD progression. Dapagliflozin does not currently have a marketing authorisation in the UK for the treatment of [redacted] (this is expected in [redacted]). The expected dosing of dapagliflozin is 10mg once daily, taken orally. The list price for 28 x 10mg tablets of dapagliflozin is £36.59.[22] Treatment with dapagliflozin is expected to be used on long-term basis or until the treatment is discontinued at the discretion of the patient's physician. The CS[1] indicates that General Practitioners (GPs) will be the most appropriate health care professionals to initiate treatment in most cases.

Relevance of clinical evidence: The intervention and comparator in DAPA-CKD[19] are in line with the final NICE scope.[17] The CS[1] (Section B.2.3.4, page 38) mentions that within DAPA-CKD, patients received dapagliflozin 10mg or placebo with permitted CKD-related treatments including renin-angiotensin-aldosterone system (RAAS) inhibitors; treatments for cardiovascular (CV) risk factors, T2DM and CKD complications and other appropriate medications at the discretion of the attending physician.[1] The ERG notes that almost all patients in DAPA-CKD received ACE inhibitor/ARB therapy as background therapy. However, the company's economic analysis is intended to reflect the CKD population included in a CPRD dataset in which [redacted] of patients were not receiving these therapies. The ERG also notes that it is unclear how many patients in the CPRD dataset would have been eligible for recruitment into the DAPA-CKD trial. The ERG therefore believes there is uncertainty regarding the company's intended target population and the relevance of the company's adjustment to the CPRD population. This issue is discussed further in Section 5.3.4.

3.3 Outcomes

Decision problem: The final NICE scope[17] lists the following outcomes: morbidity including CV outcomes and renal outcomes (such as kidney replacement and kidney failure); markers of disease progression (such as eGFR and albuminuria); mortality; AEs and HRQoL. The CS[1] reports relevant data from DAPA-CKD[19] on all of these outcomes.

Relevance of clinical evidence: The clinical outcomes data from DAPA-CKD[19] presented in the CS[1] are relevant to the decision problem. The primary outcome in DAPA-CKD was a composite endpoint of time to first occurrence of: sustained decline in the eGFR of at least 50%; ESKD, and death from renal or cardiovascular causes. Secondary and additional outcomes from DAPA-CKD included:

- A composite endpoint of time to first occurrence of: ≥50% sustained decline in eGFR, ESKD, and renal death
- A composite endpoint of time to first occurrence of CV death or hospitalisation for heart failure (hHF)
- Time to death from any cause
- A composite endpoint of time to first occurrence of chronic dialysis, renal transplant or renal death
- Rate of decline in the eGFR
- Doubling of serum creatinine or AKI
- AEs
- HRQoL, as measured by the Kidney Disease Quality of Life Instrument (KDQoL-36) and the EQ-5D index.

The company's economic model includes data from DAPA-CKD[19] relating to: progression of kidney disease (based on transitions between health states defined by CKD stage (pre-RRT), dialysis and transplantation); overall survival (OS), HRQoL measured by EQ-5D; incidence of hHF and AKI, and AEs.

3.4 Economic analysis

The CS[1] reports the methods and results of a model-based health economic analysis which estimates the incremental cost-effectiveness of dapagliflozin plus SoC versus SoC alone from the perspective of the NHS and Personal Social Services (PSS) over a lifetime horizon. Further details of the company's economic analyses are presented in Chapter 5.

3.5 Subgroups

Decision problem: The final NICE scope[17] specifies subgroups of interest as: people with diabetes; people with CVD and people with other causes of CKD. The CS[1] includes clinical subgroup analyses of the primary endpoint including: (i) people with comorbid T2DM; (ii) people with comorbid CVD and (iii) people without comorbid T2DM and without comorbid CVD. The CS also includes economic subgroup analyses for these three populations. The CS explains that defining patient subgroups by comorbidity is more appropriate than defining subgroups by cause of CKD as accurately establishing the cause of CKD in clinical practice is complex.

Relevance of clinical evidence: DAPA-CKD[19] enrolled patients with CKD, with or without T2DM. People with T1DM were excluded. The ERG's clinical experts commented that excluding patients with T1DM from the trial is acceptable due to the anticipated risk of ketoacidosis associated with the use of a SGLT2 inhibitors in these patients.[23] The ERG's clinical experts stated that there is a lack of evidence for dapagliflozin in adults with CKD with co-existing T1DM.

4 CLINICAL EFFECTIVENESS

This chapter presents a summary and critique of the clinical effectiveness evidence presented within the CS.[1] The company performed a systematic literature review (SLR) of pharmacological treatments for CKD and a summary of the relevant head-to-head trial of dapagliflozin versus placebo, together with SoC (DAPA-CKD[19, 24]) for people with or without comorbid T2DM. The CS presents supporting data related to three trials (DELIGHT[25], DERIVE[26] and Kohan 2014[27]) evaluating dapagliflozin in patients with T2DM and comorbid CKD and two trials (DECLARE-TIMI 58[21] and DAPA-HF[20]) in patients with T2DM with or at risk for atherosclerotic CVD, and in patients with HFrEF regardless of the presence of T2DM, respectively.

4.1 Critique of the methods of systematic literature review

4.1.1 Searches

CS Appendix D[28] reports an SLR of pharmacological treatments for CKD. The ERG considers the company's reporting of the literature searches to be somewhat confusing – whilst the finalised search strategy was run in August 2020 (and updated in November 2020), screening had already begun based on an earlier iteration of the search from March 2020 (which is also reported in CS Appendix D). When the ERG queried the reason for this (see clarification response,[16] question A5), the company clarified that an independent systematic review team had critically appraised the search strategy and recommended a number of amendments. The ERG recognises the value of peer review of search strategies but notes that it is only necessary to report the final agreed search strategies rather than any prototype searches which were subsequently superseded.

Searches covered relevant conference proceedings and trials registers as well as the core databases required by NICE (CENTRAL, MEDLINE and Embase), with the last two of these searched together as a multi-file search on Embase.com (using a single strategy).

The ERG comments that one of the reasons that the STA template requires companies to reproduce their search strategies is so that these can be verified by the ERG. This typically involves checking a sample of strings to ensure that the numbers retrieved have been accurately reported, and to confirm that the correct subject headings for each database have been used. However, as the ERG does not have access to Embase.com, it was not possible to reproduce these searches exactly as run by the company. By using a single strategy across MEDLINE and Embase, the company is effectively entrusting a closed-box proprietary system to appropriately map and translate their search terms. The ERG accepts that this functionality may be an attractive option to save time, but its use also significantly reduces the transparency of the search process. Furthermore, since the ERG is unaware of any peer-reviewed studies validating this approach, manufacturers are advised to use multi-file searching with caution or -

preferably - to search databases one at a time, optimising the search string for each source. The full implications of the approach taken by the company are difficult to ascertain, as the time constraints of the NICE appraisal process mean that it is not feasible for the ERG to conduct its own independent SLR and to compare the findings. However, the ERG did not identify any additional studies eligible for inclusion which have been omitted from the company's SLR.

4.1.2 Inclusion criteria and study selection

The company undertook an SLR to identify published RCTs of pharmacological treatments in patients with CKD. The ERG acknowledges that the broad scope and eligibility criteria of the SLR were appropriate to identify potentially relevant studies for the decision problem addressed in the CS.[1] The ERG considers the review eligibility criteria to be acceptable.

As detailed in CS Appendix D [28] (Section D.1.2), two independent reviewers completed study selection. Disagreements were resolved by consensus or referral to a third reviewer. The ERG considers that this approach reflects good practice.

Figure 1 of CS Appendix D[28] shows that 20,529 unique records were identified. Subsequently, 89 studies, relating to 100 records were included. All 89 studies are presented in CS Appendix D[28] (Table 13) by study name, trial number and reference to related publications. Table 5 summarises the available evidence according to the different pharmacological treatments for CKD included in the SLR.

Table 5: Summary of included studies according to pharmacological treatments for CKD (adapted from CS Appendix D, Table 13)

Intervention	Number of included studies
Dapagliflozin	4
Other SGLT2 inhibitors[a] - Canagliflozin - Bexagliflozin - Ertugliflozin - Empagliflozin	5 - 2 - 1 - 1 - 1
ACE inhibitors	12
ACE inhibitor combination therapies	4
ARBs	13
Other therapies[b]	51

[a] *E.g. linagliptin, dulaglutide and liraglutide*
ACE - angiotensin converting enzyme; ARB - angiotensin receptor blockers; SGLT2 - sodium-glucose co-transporter 2

CS Appendix D[28] (Section D.2) states that included studies were further filtered to exclude trials of ACE inhibitors, ARBs and therapies still in development. This was done to ensure that the focus of the review remained on primary trials of interest for the CS which were aligned with the decision problem (RCTs of dapagliflozin). A summary of the four identified RCTs evaluating dapagliflozin in patients

with CKD (DAPA-CKD,[19] DELIGHT,[25] DERIVE[26] and Kohan 2014[27]), together with the rationale for their use (or non-use) in the economic model, is presented in Table 6. The CS[1] (Section B.2.2) states that DAPA-CKD[24] is the pivotal trial that provides clinical evidence related to the current appraisal, while the three other dapagliflozin RCTs[25-27] provide supporting data only. The CS notes that DELIGHT, DERIVE and Kohan 2014 were smaller studies, which assessed surrogate markers of kidney disease (e.g. change from baseline in eGFR, uACR or creatinine clearance). The CS also notes that DERIVE and Kohan 2014 were designed primarily to assess the effect of dapagliflozin on glycaemic control, rather than the outcomes listed in the final NICE scope.[17] The ERG agrees with the company that DAPA-CKD[24] is the key source of evidence for the clinical efficacy and safety of dapagliflozin in treating people with CKD with or without T2DM. The ERG also agrees with the reasons provided for not using the remaining three studies to inform the economic model.

Table 6: RCTs of dapagliflozin for treating CKD (reproduced from CS, Table 7 and CS Appendix D, Table 14)

Study	DAPA-CKD[19]	DERIVE[26]	DELIGHT[25]	Kohan 2014[27]
Study Details	• Double-blind randomised Phase III trial • Multicentre, international (21 countries) • NCT03036150	• Double-blind randomised Phase III trial • Multicentre, international (8 countries) • NCT02413398	• Double-blind randomised Phase II/III trial • Exploratory, parallel design, international (9 countries) • NCT02547935	• Double-blind randomised Phase II/III trial • Multicentre, international (13 countries) • NCT00663260
Population	• Adults (≥18 years) with CKD • With or without comorbid T2DM • eGFR ≥25 and ≤75ml/min/1.73m^2 • uACR ≥200mg/g to ≤5,000mg/g (≥22.6 to ≤565mg/mmol) • Stable dose of ACE inhibitor or ARB for ≥4 weeks before screening (patients who were documented to be unable to take ACE inhibitors or ARBs were allowed to participate)	• Adults (18–75 years) with T2DM for >12 months, inadequate glycaemic control and CKD Stage 3a • eGFR ≥45 and ≤59ml/min/1.73m^2 • Stable glucose-lowering treatment regimen	• Adults (≥18 years) with T2DM for >12 months • eGFR ≥25 and ≤75ml/min/1.73m^2 • uACR ≥30 to ≤3,500mg/g (≥3.4 to ≤395.5mg/mmol) • Stable glucose-lowering and anti-hypertensive treatments for ≥12 weeks before randomisation	• Adults (≥18 years) with T2DM and inadequate glycaemic control (HbA1c ≥7.0 and ≤11.0%) • eGFR ≥30 and ≤59ml/min/1.73m^2 • Stable antidiabetic regimen
Therapies used and number of patients per treatment arm	• Dapagliflozin 10mg (n=2,152) • Placebo (n=2,152)	• Dapagliflozin 10mg (n=160) • Placebo (n=161)	• Dapagliflozin 10mg (n=145) • Dapagliflozin 10mg + saxagliptin 2.5mg (n=155) • Placebo (n=148)	• Dapagliflozin 10mg (n=85) • Dapagliflozin 5mg (n=83) • Placebo (n=84)

Study	DAPA-CKD[19]	DERIVE[26]	DELIGHT[25]	Kohan 2014[27]
Reported outcomes specified in the decision problem Outcomes incorporated in the model are marked in bold	• Morbidity including CV outcomes (**hospitalisation for HF**) • **Disease progression (such as renal replacement, ESKD**) and markers of disease progression (such as eGFR, albuminuria) • **All-cause mortality**, CV mortality, renal mortality • **Adverse effects of treatment** • **HRQoL**	• Change from baseline in uACR • Change from baseline in eGFR	• Change from baseline in uACR • Change from baseline in eGFR	• Change from baseline in eGFR and creatinine clearance • Change in uACR category
Other outcomes reported in this submission	**Doubling of serum creatinine (AKI)**	N/a	N/a	N/a
Rationale for use/non-use in the model	DAPA-CKD represents the primary source of efficacy and safety data for dapagliflozin in this indication. Data reported from DAPA-CKD are relevant to the decision problem and have been used in the model	Not used. DERIVE was conducted in a small population, exclusively in patients with CKD and comorbid T2DM, and evaluated only surrogate markers of kidney disease.	Not used. DELIGHT was conducted in a small population, exclusively in patients with CKD and comorbid T2DM, and evaluated only surrogate markers of kidney disease.	Not used. Kohan 2014 was conducted in a small population, exclusively in patients with CKD and comorbid T2DM, and evaluated only surrogate markers of kidney disease.

Bold text indicates outcomes used in the economic model (see Section 5.2)

ACE - angiotensin-converting enzyme; AKI - acute kidney injury; ARB - angiotensin receptor blocker; CKD - chronic kidney disease; CV - cardiovascular; eGFR - estimated glomerular filtration rate; ESKD - end-stage kidney disease; HbA1c - glycated haemoglobin; HF - heart failure; HRQoL – health-related quality of life; N/a - not applicable; T2DM - type 2 diabetes mellitus; uACR - urine albumin-to-creatinine ratio

4.1.3 Inclusion criteria for the indirect comparison

CS Appendix D[28] (D.3, page 49) states that it was not necessary to undertake an indirect treatment comparison (ITC) because DAPA-CKD[19] provides relevant direct evidence to inform the base case economic analysis. Despite this, the CS[1] reports on a matching-adjusted indirect comparison (MAIC) between dapagliflozin and canagliflozin in a subgroup of patients with comorbid T2DM; the results of this MAIC are used to inform an economic scenario analysis (see Section 5.2). Canagliflozin is licensed in patients with CKD with comorbid T2DM, but is not listed as a relevant comparator in the final NICE scope.[17] Two trials, DAPA-CKD[19] and CREDENCE[29] were used to inform the MAIC. The CS did not explain why CREDENCE was selected out of the two identified studies of canagliflozin in patients with T2DM and comorbid CKD.[29-31] The primary outcome in CREDENCE was a composite of ESKD (dialysis, transplantation, or a sustained estimated GFR of <15ml per minute per 1.73m^2), a doubling of the serum creatinine level, or death from renal or CV causes. Efficacy outcomes in the other canagliflozin trial (Yale 2014[30, 31]) related to outcomes of glycaemic control, e.g. changes in glycated haemoglobin (HbA1c) and fasting plasma glucose (FPG). The key eligibility criteria of the DAPA-CKD and CREDENCE trials are reported in the CS Appendix D (Table 16). A summary and critique of this MAIC is reported in Section 4.3.

4.1.4 Critique of data extraction

Section D.1.2 of CS Appendix D[28] states that data extraction was performed using a pre-designed extraction table in Microsoft Excel.® Whilst the CS[1] does not provide information about the methods or processes used to validate the abstracted data, the ERG believes that the key study characteristics and outcomes data from DAPA-CKD[19] have been comprehensively reported in the CS and accompanying appendices.

4.1.5 Quality assessment

Section B.2.5 of the CS[1] states that the quality assessment of DAPA-CKD[19] was performed using the checklist recommended by NICE for assessing bias in RCTs. No details are provided regarding how many reviewers conducted the quality assessment or how the process was validated. The ERG considers this checklist to be appropriate and agrees with the overall quality assessment reported in the CS.[1]

4.1.6 Evidence synthesis

Section B.2.8 of the CS[1] states that a meta-analysis was not conducted because of the inherent differences in eligibility criteria and reported outcomes of the dapagliflozin trials identified by the SLR. The ERG considers this reasonable. DAPA-CKD[19] provides direct head-to-head clinical efficacy evidence of dapagliflozin plus SoC versus placebo plus SoC.

4.1.7 Additional trials evaluating dapagliflozin in patients with CKD

Section B.2.1 of the CS[1] notes that, in addition to DAPA-CKD,[19] the SLR identified three additional trials (DELIGHT[25], DERIVE[26] and Kohan 2014[27]) which evaluated the clinical efficacy of dapagliflozin in patients with T2DM and comorbid CKD. The CS[1] also refers to two further trials, DECLARE-TIMI 58[21] and DAPA-HF,[20] which included patients with a wide range of eGFR and uACR categories and some patients with comorbid CKD, who either had or were at risk of atherosclerotic CVD, or who had HF. CS Appendix L[28] outlines the study methodology, key efficacy and safety outcomes of these five clinical trials which provide supporting data.

4.1.8 Ongoing studies

Section B.2.11 of the CS[1] states that no relevant ongoing studies were identified. The ERG believes this is statement is accurate. The ERG undertook additional searches of the International Clinical Trials Registry Platform (ICTRP), clinicaltrials.gov and Google Scholar using the search term 'dapagliflozin' (search date 10 June 2021). The ERG did not identify any additional relevant recently completed or ongoing studies.

4.2 Critique of the key clinical study

4.2.1 Trial design: DAPA-CKD

Section B.2.3 of the CS[1] describes the methodology of the key clinical trial - DAPA-CKD.[19] DAPA-CKD was an event-driven, multicentre, international double-blind RCT that included adults patients with CKD, with or without comorbid T2DM. The study was conducted across 386 study centres. The company's clarification response[16] (question A13) indicates that [redacted] participants (dapagliflozin arm, n=[redacted]; placebo arm, n=[redacted]) were recruited from nine study sites in the UK. Remaining study sites were located in Argentina, Brazil, Canada, China, Denmark, Germany, Hungary, India, Japan, Korea, Mexico. Peru, Philippines, Poland, Russia, Spain, Sweden, Ukraine, United States and Vietnam.[1] The ERG's clinical advisors suggested that the management of CKD across these study settings is likely to be broadly generalisable to UK clinical practice.

The eligibility criteria for DAPA-CKD[19] are presented in Table 7. Patients were eligible if they were adult patients with CKD (n=4,304) with or without comorbid T2DM, with an eGFR of ≥25 to ≤75ml/min/1.73m^2 and uACR of ≥22.6mg/mmol (200mg/g) to ≤565mg/mmol (5,000mg/g). The trial design excluded patients with other kidney conditions or genetic pathologies that may require more focused treatment. The ERG's clinical advisors noted that DAPA-CKD included a broad and heterogeneous population, but the extent to which the trial is representative of clinical practice is limited in that all patients in DAPA-CKD had albuminuria with a uACR of ≥22.6mg/mmol (200mg/g), whilst a substantial proportion of the overall CKD population in England does not.

Table 7: Eligibility criteria, DAPA-CKD (reproduced from CS, Table 8)

Inclusion criteria	Exclusion criteria
• ≥18 years of age at the time of consent • eGFR ≥25 to ≤75ml/min/1.73m^2 at screening • uACR ≥200mg/g (≥22.6mg/mmol) to ≤5,000mg/g (≤565mg/mmol) at screening • Stable and, for the patient, maximum tolerated labelled dose of an ACE inhibitor or ARB for at least four weeks before screening, if not medically contraindicated	• T1DM • Autosomal dominant or autosomal recessive polycystic kidney disease, lupus nephritis or ANCA-associated vasculitis • Receiving cytotoxic therapy, immunosuppressive therapy or other immunotherapy for primary or secondary renal disease within six months prior to enrolment • New York Heart Association Class IV congestive HF at time of enrolment • Myocardial infarction, unstable angina, stroke or transient ischaemic attack within 12 weeks prior to enrolment • History of organ transplantation • Receiving therapy with an SGLT2 inhibitor within eight weeks prior to enrolment or previous intolerance of an SGLT2 inhibitor • Coronary revascularisation (percutaneous coronary intervention or coronary artery bypass grafting) or valvular repair/replacement within 12 weeks prior to enrolment or is planned to undergo any of these procedures after randomisation • Any condition outside the renal and cardiovascular study area with a life expectancy of <2 years based on investigator's clinical judgement • Active malignancy requiring treatment at the time of Visit 1 (with the exception of successfully treated basal cell or treated squamous cell carcinoma) • Known blood-borne diseases • Hepatic impairment (aspartate transaminase or alanine transaminase >3 times the ULN or total bilirubin >2 times the ULN at the time of enrolment)

ACE - angiotensin-converting enzyme; ANCA - anti-neutrophil cytoplasmic antibody; ARB - angiotensin receptor blocker; eGFR - estimated glomerular filtration rate; HF - heart failure; SGLT2 - sodium glucose co-transporter 2; T1DM - type 1 diabetes mellitus; uACR - urine albumin-to-creatinine ratio; ULN - upper limit of normal

The CS[1] states that recruitment aimed to *"ensure a minimum of 30% of patients were recruited to either the diabetic or non-diabetic subpopulation and the number of patients with an eGFR between 60-75 ml/min/1.73m^2 was capped so that no more than 10% of patients started the trial with an eGFR range corresponding to stage 2 CKD"* (CS, Section B.2.3.1). The company's clarification response[16] (question A12) indicates that the 10% cap was applied to ensure that the DAPA-CKD population *"included a range of risk profiles which could adequately demonstrate the impact of dapagliflozin on these*

outcomes." The company's response (question A12) also highlights the very low risk of progression to ESKD (dialysis or transplantation) in a prevalent population of individuals with eGFR 60–75mL/min/1.73 m^2 (CKD stage 2).

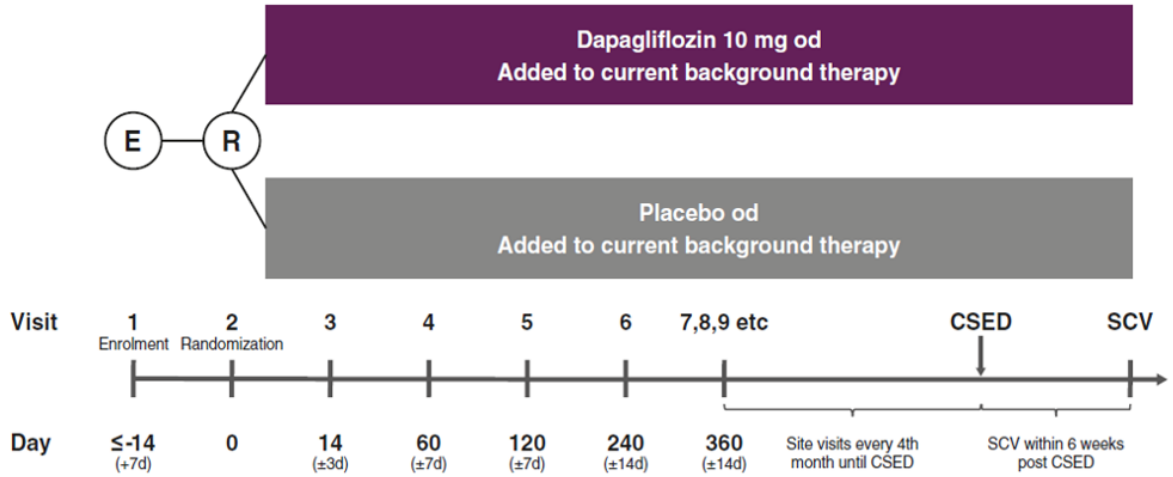
Trial interventions and concomitant treatments

Patients were randomised in a 1:1 ratio to each treatment group using a web-based system.[1, 24] Randomisation was stratified to achieve a balance between treatment groups in relation to the proportions of patients with or without comorbid T2DM and by baseline uACR (≤113 or >113mg/mmol [1,000 mg/g]). Patients received the trial treatments, oral dapagliflozin 10mg (n=2,152) or a matched film-coated placebo tablet (n=2,152), once daily, at similar times each day, in addition to SoC.[1, 24] Other permitted medications included treatments for CKD, T2DM, CV risk factors, complications of T2DM and CKD as well as other concomitant treatments deemed necessary for the patient's safety. The use of non-steroidal anti-inflammatory medications was restricted whilst the use of fixed dose combined preparations and open-label SGLT2 inhibitors were not permitted.[1]

Study visits and study duration: DAPA-CKD

An overview of the trial design is presented in Figure 3. Planned study visits after randomisation were at 2 weeks, 2 months, 4 months, 8 months and then 4-monthly intervals.

Figure 3: Study design: DAPA-CKD (reproduced from CS, Figure 5)



CSED - common study end date (date when the predetermined number of adjudicated primary events are anticipated; E - enrolment; od - once daily; R - randomisation; SCV - study closure visit

DAPA-CKD was stopped early because dapagliflozin demonstrated a positive treatment effect relating to the primary outcome. The median follow-up was 2.4 years (interquartile range [IQR], 2.0 to 2.7 years). No future data analyses are expected for DAPA-CKD.[16]

Outcomes

The CS[1] presents a wide range of study endpoints from DAPA-CKD,[19] in order of hierarchical testing sequence, as follows:

1. Primary endpoint:
    - Composite endpoint of ≥50% sustained decline in eGFR, reaching ESKD, CV or renal death
2. Composite and specific secondary endpoints:
    - Incidence of ≥50% sustained decline in eGFR, reaching ESKD and renal death
    - Incidence of CV death or hospitalisation due to HF
    - Death from any cause
3. Exploratory outcomes relevant to the appraisal:
    - Effect of treatment on eGFR over time
    - Proportion of patients with eGFR >40ml/min/1.73m^2 at baseline that progress to eGFR <30ml/min/1.73m^2 (i.e., CKD stage 4) over the study period
    - Time to the first occurrence of AKI (defined as an event of doubling of serum creatinine in relation to the most up-to-date central laboratory measurements)
    - Change in overall KDQoL-36 score, from baseline
    - Change in EQ-5D-5L score, from baseline
    - Time to first occurrence of chronic dialysis, renal transplantation or renal death
    - Change in uACR, from baseline
4. Safety outcomes as follows:
    - Serious AEs
    - Discontinuation of study treatment due to AEs
    - Changes in biochemical/ haematology parameters
    - AEs of special interest
5. Subgroup analyses

    The CS[1] (Section B.2.3.6) lists eight pre-specified subgroups of interest. Reported outcomes of the subgroup analyses are presented in Section 4.2.3.

Statistical analyses

The CS[1] (Section B.2.4) and CS Appendix D[28] report the statistical analyses for DAPA-CKD.[19] The objective of the trial was to test the assumption that dapagliflozin was superior to placebo in reducing the risk of renal and CV events in patients with CKD (with or without comorbid T2DM) who were already receiving a stable dose of an ACE inhibitor or an ARB (unless ACE inhibitors/ARBs were contraindicated).

The analysis of the primary composite endpoint was based on the Full Analysis Set (FAS).[1, 19] The FAS was comprised of all patients randomised to either treatment arm, irrespective of their adherence to the study protocol and continued participation in the study (i.e. the intention-to-treat [ITT] population). For patients with no observed outcome event, the date of their last assessment was used as the censoring date. Treatment arms were compared using a Cox proportional hazards (PH) regression, stratified by the presence of T2DM and uACR values at baseline and adjusted by eGFR.[1] Table 13 of the CS[1] reports the power calculation for estimating the study sample size. The ERG notes that DAPA-CKD had adequate power to detect differences between treatment groups. The ERG requested clarification[16] (question A14) with regard to the lack of adjustments to CIs relating to the analyses of individual components of the primary outcome and the possible impact on the study results if adjustments were made. The company's clarification response[16] stated that CIs were presented only for the descriptive interpretation of the component variables and that these should only be used as a measure of precision. Similarly, *p*-values were not adjusted or included in the hierarchical testing sequence.

Changes from baseline in KDQoL and EQ-5D-5L scores for treatment groups were also reported in the CS[1], (Section B.2.6.3.4). These outcomes were analysed using a repeated measures model (RMM), without imputation of missing data.[16]

The analysis of safety outcomes was based on the actual treatment received during the study. The primary analysis of all safety outcomes used the Safety Analysis Set (SAS), which included all patients who received at least one dose of dapagliflozin.[1]

Patient disposition and treatment duration in DAPA-CKD

Table 8 summarises the patient flow in DAPA-CKD.[1] Four thousand, two hundred and eighty-nine patients (99.7%) completed DAPA-CKD. Treatment discontinuation was reported in 583 patients over the duration of the trial (dapagliflozin arm: 12.7%; placebo arm, 14.4%). DAPA-CKD was stopped early following the clinical efficacy of dapagliflozin based on 408 primary outcome events. Data were censored at the study closure visit (Figure 3) or "*on the date of the date of the last central laboratory assessment, clinical assessment, or known contact, depending on the specific outcome."*[24] The median time spent by participants in DAPA-CKD until the censoring date for the primary analysis was [redacted] months (range [redacted] months).[1]

Table 8: Patient disposition: DAPA-CKD (adapted from CS, Figure 6)

Description	Dapagliflozin N	Placebo N	Total N
All randomised patients	2,152	2,152	4, 304
Did not receive treatment	3	3	6
Completed treatment	2,142	2,147	4,289
Discontinued treatment: - Patient decision - Adverse event - Other[a]	274 142 118 14	309 160 123 26	583
Discontinued study: - Withdrew consent - Lost to follow-up	10 8 2	5 3 2	[redacted] 11 [redacted]
Median time until last visit	[redacted] months (range [redacted] months)		
Median time in study until the primary analysis censoring date	[redacted] months (range [redacted] months)		

[a]*Severe non-compliance to protocol, development of study specific discontinuation criteria (confirmed DKA, positive pregnancy test, other).*

Quality assessment: DAPA-CKD

A summary of the methodological quality assessment of DAPA-CKD[19] using the NICE-recommended checklist for assessing bias in RCTs is reported in Table 14 of the CS.[1] Quality assessment items related to: randomisation; allocation concealment; comparability of treatment groups in terms of prognostic factors and drop-outs; blinding of care providers, participants and outcome assessors; selective outcome reporting; appropriateness of outcome analysis and potential competing interests of the authors of the published study. The company's quality assessment suggests that DAPA-CKD is associated with a low risk of bias. The ERG agrees with this assessment.

4.2.2 Baseline characteristics: DAPA-CKD

Overall population

Baseline patient characteristics for the overall population of DAPA-CKD are summarised in Table 9. The ERG identified a recent publication, Wheeler 2021,[32] which provided additional information for subgroups of patients with T2DM and patients without diabetes; data split by presence/absence of T2DM are also presented in Table 9. For the entire population, the proportion of patients with T2DM was 67.5%,[19] whereas more than 30% had comorbid CVD.[1] More patients had CKD stage 3, i.e. eGFR ≥30–<60 ml/min/1.73 m^2 (dapagliflozin, 75.5%; placebo 74.4%), compared with those with either CKD stage 2 or CKD stage 4 (Table 9).[1, 32] Baseline median uACR was 107.3mg/mmol (949mg/g); approximately half of the patients in each treatment group presented with severely increased albuminuria (uACR >1,000mg/g [113mg/mmol]).[24] ARBs and statins were the most common preceding treatments in the study population (dapagliflozin versus placebo: 67.1% versus 66.3%; 64.8%, versus 65.0%, respectively).[1] The ERG considers that the study groups are well-balanced in terms of baseline characteristics.

The ERG's clinical advisors noted that the reported baseline characteristics for the overall population were broadly representative of many types of patients who might be treated with dapagliflozin in clinical practice in England. However, they also commented that several groups of patients were excluded due to the trial eligibility criteria, including patients with urine albumin excretion <22.6mg/mmol, those with prior organ transplant, and those with T1DM. Also, whilst almost all patients in the trial were receiving ACE inhibitor or ARB therapy, many patients with CKD do not receive these therapies in clinical practice. One clinical advisor also mentioned that the blood pressure of patients seen in the clinical setting was generally less controlled compared to those enrolled in DAPA-CKD (i.e. baseline mean systolic blood pressure [SBP] = 137.1 mmHg). Additionally, the ERG's clinical advisors noted slight variations in background medications in the trial compared with clinical practice in England.

Subgroups of patients with T2DM and patients without diabetes

Compared to those without T2DM, patients with T2DM had somewhat higher eGFR, uACR and body mass (Table 9).[32] More patients in the T2DM subgroup received a diuretic and statin compared with those without T2DM. In the dapagliflozin arm, more patients with T2DM compared with those without diabetes received prior treatment with a diuretic (49%; n=718 versus 30%; n=210, respectively) or a statin (71%; n=1,039 versus 51%; n=356). The placebo arm followed a similar trend for both background medications (Table 9).[32] The proportions of patients with T2DM and patients without diabetes who had CKD stage 4 were 13.8% and 16%, respectively. Overall, the ERG considers that most baseline characteristics were balanced between the subgroups. The ERG's clinical advisors commented that the proportion of patients with T2DM (67.5%) is considerably higher than would be expected in clinical practice.

Table 9: Baseline patient characteristics: DAPA-CKD (adapted from CS, Table 11 and Wheeler 2021, Table 1)

	Overall population		Patients with T2DM		Patients without T2DM	
Characteristic	**Dapagliflozin (n=2,152)**	**Placebo (n=2,152)**	**Dapagliflozin (n=1455)**	**Placebo (n=1451)**	**Dapagliflozin (n=697)**	**Placebo (n=701)**
Age, years (SD)	61.8 (12.1)	61.9 (12.1)	64.1 (9.8)	64.7 (9.5)	56.9 (14.6)	56.0 (14.6)
Female sex, n	709 (32.9%)	716 (33.3%)	494 (34%)	471 (32%)	215 (31%)	245 (35%)
Race, n						
White	1,124 (52.2%)	1,166 (54.2%)	751 (52%)	790 (54%)	373 (54%)	376 (54%)
Black	104 (4.8%)	87 (4.0%)	76 (5%)	61 (4%)	28 (4%)	26 (4%)
Asian	749 (34.8%)	718 (33.4%)	481 (33%)	451 (31%)	268 (38%)	267 (38%)
Other	175 (8.1%)	181 (8.4%)	147 (10%)	149 (10%)	28 (4%)	32 (5%)
Weight, kg (SD)	81.5 (201.1)	82.0 (20.9)	83·2 (20·9)	83·8 (21·2)	77·9 (17·8)	78·3 (19·9)
BMI (SD)	29.4 (6.0)	29.6 (6.3)	NR	NR	NR	NR
Current smoker, n	283 (13.2%)	301 (14.0%)	195 (13%)	200 (14%)	88 (13%)	101 (14%)
Blood pressure, mmHg (SD)						
Systolic	136.7 (17.5)	137.4 (17.3)	138.8 (17.6)	139.6 (17.1)	132·3 (16.4)	132·9 (16.9)
Diastolic	77.5 (10.7)	77.5 (10.3)	76.5 (10.4)	76.5 (9.9)	79·6 (10.9)	79·6 (10.8)
Estimated GFR (ml/min/1.73 $m^{2,}$ (SD)						
Mean	43.2 (12.3)	43.0 (12.4)	44.0 (12.6)	43.6 (12.6)	41.7 (11.5)	41.8 (11.9)
≥60	234 (10.9%)	220 (10.2%)	179 (12%)	169 (12%)	55 (8%)	51 (7%)
≥45–<60	646 (30.0%)	682 (31.7%)	450 (31%)	468 (32%)	196 (28%)	214 (31%)
≥30–<45	979 (45.5%)	919 (42.7%)	636 (44%)	603 (42%)	343 (49%)	316 (45%)
<30	293 (13.6%)	331 (15.4%)	190 (13%)	211 (15%)	103 (15%)	120 (17%)
Haemoglobin (g/l)	128.6±18.1	127.9±18.0	126.3 (17.8)	125.6 (18.0)	133.4 (17.9)	132.7 (17.2)
Serum potassium (mEq/l)	4.6±0.5	4.6±0.6	4·7 (0.6)	4·7 (0.6)	4·6 (0.5)	4·6 (0.5)
uACR (mg/g)						
Median (IQR)	965 (472 to 1,903)	934 (482 to 1,868)	1024.5 (472.5 to 2111.0)	1004.5 (493.3 to 2017.0)	870.5 (472.0 to 1533.5)	841.5 (458.5 to 1554.5)
>1,000, n	1,048 (48.7%)	1,031 (47.9%)	741 (51%)	732 (50%)	307 (44%)	299 (43%)
T2DM, n (%)	1,455 (67.6%)	1,451 (67.4%)	N/a	N/a	N/a	N/a
Cardiovascular disease, n (%)	813 (37.8) [a]	797 (37.0) [a]	NR	NR	NR	NR
Heart failure, n	235 (10.9%)	233 (10.8%)	177 (12%)	184 (13%)	58 (8%)	49 (7%)

	Overall population		Patients with T2DM		Patients without T2DM	
Characteristic	**Dapagliflozin (n=2,152)**	**Placebo (n=2,152)**	**Dapagliflozin (n=1455)**	**Placebo (n=1451)**	**Dapagliflozin (n=697)**	**Placebo (n=701)**
Background medication at randomisation, n						
ACE inhibitors	673 (31.3%)	681 (31.6%)	451 (31%)	443 (31%)	222 (32%)	238 (34%)
ARB	1,444 (67.1%)	1,426 (66.3%)	984 (68%)	974 (67%)	460 (66%)	452 (64%)
Diuretic	928 (43.1%)	954 (44.3%)	718 (49%)	747 (51%)	210 (30%)	207 (30%)
Statin	1,395 (64.8%)	1,399 (65.0%)	1039 (71%)	1043 (72%)	356 (51%)	356 (51%)
Metformin (biguanides)	NR	NR	629 (44%)	613 (43%)	NR	NR
Sulfonylurea derivative	NR	NR	389 (27%)	385 (27%)	NR	NR
DPP-4 inhibitor	NR	NR	364 (25%)	378 (26%)	NR	NR
GLP-1 analogue	NR	NR	63 (4%)	59 (4%)	NR	NR
Insulin	NR	NR	814 (56%)	784 (54%)	NR	NR

[a] *History of peripheral artery disease, angina pectoris, myocardial infarction, percutaneous coronary intervention, coronary-artery bypass grafting, heart failure, valvular heart disease, abdominal aorta aneurysm, atrial fibrillation, atrial flutter, ischemic stroke, transient ischemic attack, haemorrhagic stroke, carotid artery stenosis, cardiac-pacemaker insertion, vascular stent, coronary-artery stenosis, ventricular arrhythmia, implantable cardioverter–defibrillator, noncoronary revascularization, or surgical amputation*

ACE - angiotensin-converting enzyme; ARB - angiotensin receptor blocker; BMI - body mass index; GFR - glomerular filtration rate; IQR – inter-quartile range; Na - not applicable; NR - not reported; SD, standard deviation; T2DM; type 2 diabetes mellitus; uACR: urine albumin-to-creatinine ratio

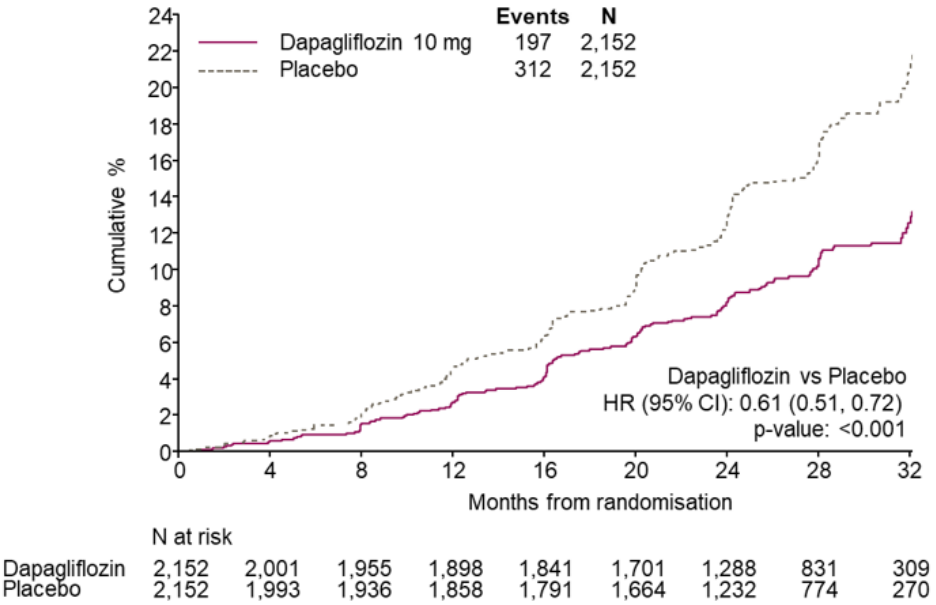
4.2.3 Effectiveness results: DAPA-CKD

Overall population

Primary outcome

The primary outcome of DAPA-CKD was a composite endpoint of sustained decline in eGFR ≥50%, ESKD or death from renal or CV causes. Dapagliflozin was associated with a statistically significant risk reduction of 39% (HR 0.61; 95% CI: 0.51, 0.72; p<0.001) in the composite endpoint and fewer events occurred in the dapagliflozin treatment arm (n=197 events, 9.2%) compared with placebo (n=312 events, 14.5%).[1, 24] The cumulative incidence plot for the primary composite outcome (see Figure 4) indicates an early and sustained separation between the treatment arms over the study period.

Figure 4: Cumulative incidence plot of primary outcome: DAPA-CKD (reproduced from CS, Figure 7)



Exploratory analyses of individual components of the primary composite outcomes

Exploratory analyses of components of the primary composite outcomes are summarised in Table 10. The analyses indicate that dapagliflozin demonstrated a significant benefit across almost all components of the primary composite endpoint (where assessed).

Table 10: Primary composite outcome, individual components of the primary outcome and death from any cause: DAPA-CKD (reproduced from CS, Tables 15 and 16)

Outcome, n (%)	Dapagliflozin (N=2,152)	Placebo (N=2,152)	Hazard ratio (95% CI)	*p*-value (primary outcome)	*p*-value (exploratory analysis)
Primary composite outcome	197 (9.2)	312 (14.5)	0.61 (0.51, 0.72)	<0.001	N/a
Exploratory analysis – individual components of the primary outcome					
Sustained ≥50% decline in eGFR	112 (5.2)	201 (9.3)	0.53 (0.42, 0.67)	N/a	[redacted]
End-stage kidney disease	109 (5.1)	161 (7.5)	0.64 (0.50, 0.82)	N/a	[redacted]
eGFR of <15 ml/min/1.73 m^2	84 (3.9)	120 (5.6)	0.67 (0.51, 0.88)	N/a	[redacted]
Chronic dialysis	68 (3.2)	99 (4.6)	0.66 (0.48, 0.90)	N/a	[redacted]
Kidney transplantation	3 (0.1)	8 (0.4)	N/a[a]	N/a	N/a[b]
Death from renal causes	2 (<0.1)	6 (0.3)	N/a[a]	N/a	N/a[b]
Death from CV causes[c]	65 (3.0)	80 (3.7)	0.81 (0.58, 1.12)	N/a	[redacted]
Death from any cause					
All deaths	101 (4.7)	146 (6.8)	0.69 (0.53–0.88)	0.004	N/a
CV death	41 (1.9)	50 (2.3)	NR	NR	N/a
Non-CV death	36 (1.7)	66 (3.1)	NR	NR	N/a
Undetermined cause of death	24 (1.1)	30 (1.4)	NR	NR	N/a

*Footnotes: [a]Not calculated for this endpoint due to an insufficient number of events, [b]N/a denotes not applicable because p-values for efficacy outcomes are reported only for outcomes that were included in the hierarchical testing strategy .*c *Deaths adjudicated as "cause undetermined" with regard to CV death or non-CV death were included in as CV deaths in the analysis of the primary endpoint. Undetermined cause of death refers to a death not attributable to a CV or non-CV cause due to the lack of information or insufficient supporting information to assign the cause of death.*
CI - confidence interval; eGFR - estimated glomerular filtration rate; N/a - not applicable; NR - not reported

Secondary outcomes

Secondary outcomes were as follows:

- Time to first event of the composite of ≥50% sustained decline in eGFR, ESKD, and renal death
- Time to first event of the composite of CV death and hospitalisation for heart failure
- Time to death from any cause.

Compared with placebo, treatment with dapagliflozin resulted in a significant risk reduction in the secondary outcomes: renal-specific composite outcome of ≥50% sustained decline in eGFR, ESKD, and renal death (HR 0.56; 95% CI: 0.45, 0.68; p<0.001); composite outcome of risk of hospitalisation

for HF or CV death (HR 0.71; 95% CI: 0.55, 0.92; *p*=0.0089) and all-cause mortality (HR 0.69; 95% CI: 0.53, 0.88; *p*=0.004) (Table 11) .[1, 24]

Table 11: Secondary outcomes: DAPA-CKD (adapted CS, Table 16, Heerspink *et al.*, 2020, Table 2)

Outcome, n (%)	Dapagliflozin (N=2,152)	Placebo (N=2,152)	Hazard ratio (95% CI)	*p*-value
Composite of decline in estimated GFR of ≥50%, end-stage kidney disease, or death from renal cause	142 (6.6)	243 (11.3)	0.56 (0.45–0.68)	<0.001
Composite of death from cardiovascular causes or hospitalisation for heart failure	100 (4.6)	138 (6.4)	0.71 (0.55–0.92)	0.0089
All cause mortality CV death Non-CV death Undetermined cause of death	101 (4.7) 41 (1.9) 36 (1.7) 24 (1.1)	146 (6.8) 50 (2.3) 66 (3.1) 30 (1.4)	0.69 (0.53–0.88)	0.004

CI - confidence interval; VC - cardiovascular; GFR - glomerular filtration rate; N - number

Additional outcomes

The CS[1] (Section 2.6.3) reports outcomes based on further exploratory analyses. Compared with placebo, dapagliflozin demonstrated treatment benefit in relation to a reduced rate of deterioration in renal function (between-group difference 0.93 ml per minute per 1.73 m^2 per year (95% CI, 0.61, 1.25; [redacted]); proportion of early-stage patients (eGFR >40 ml/min/1.73m^2 at baseline) reaching CKD stage 4 ([redacted]) and time to the composite endpoint of chronic dialysis, renal transplant and renal death ([redacted]).

The CS[1] (Section 2.6.3.) also describes additional outcomes relating to the positive treatment effect of dapagliflozin versus placebo on AKI ([redacted], n=[redacted] versus [redacted] of patients, respectively) and [redacted] The CS[1] explains that the findings show that dapagliflozin delays worsening of renal damage in patients with CKD.

Health-related quality of life

The CS[1] (Section B.2.6.3.4) presents a brief summary of HRQoL outcomes in DAPA-CKD.[19] [redacted] The ERG requested additional information from the company regarding HRQoL outcomes in the trial (see clarification response,[16] question A15). The company's response provides

more detailed results of the changes in KDQoL (by sub-scale) and EQ-5D utility in the trial, as well as mean baseline EQ-5D-5L utility scores in the dapagliflozin and placebo arms ([redacted]) and baseline scores for KDQoL subscales.[16]

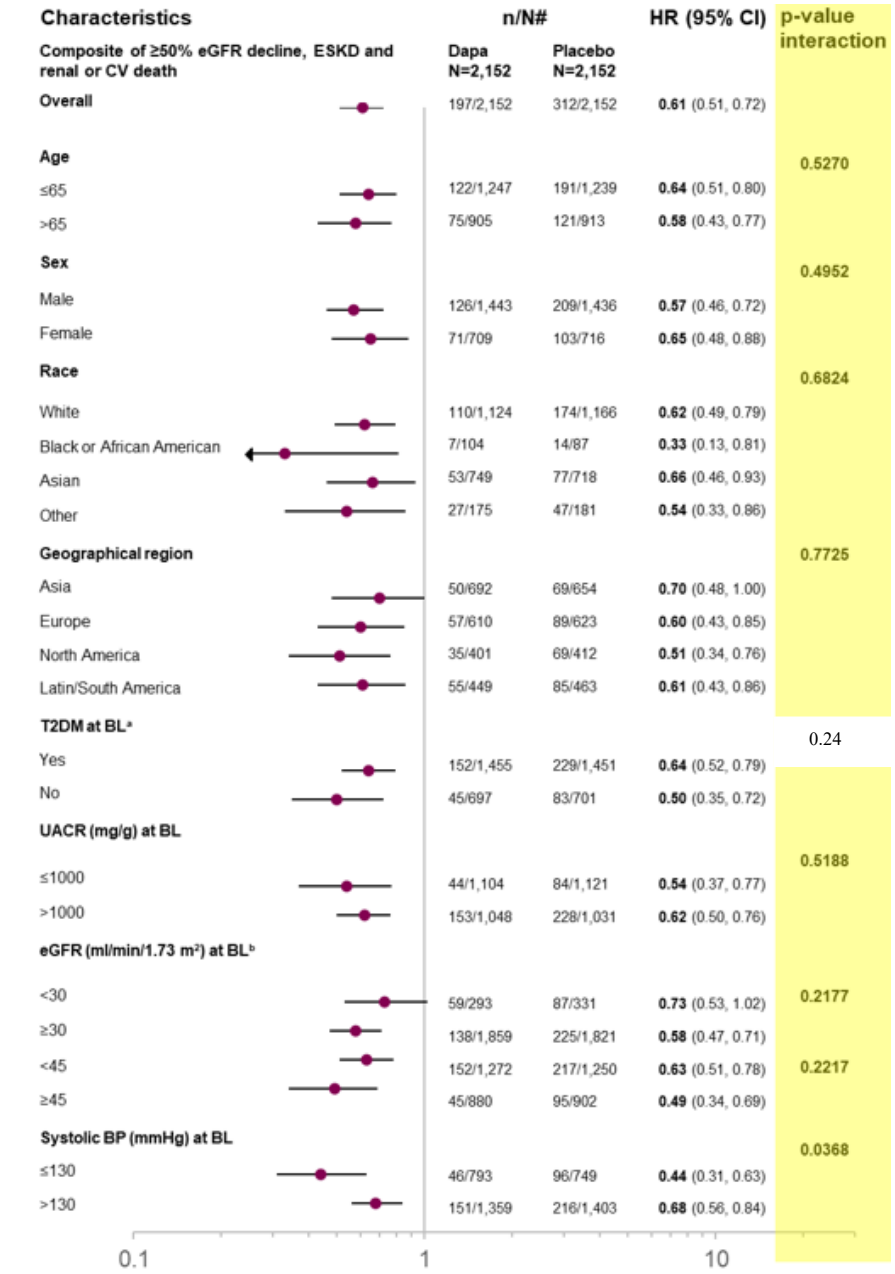
[redacted]

Subgroup analyses

Overall population

The CS[1] (Section B.2.3.6 and Section B.2.7) presents pre-specified analyses (see Figure 5) and *post hoc* subgroup analyses (see Figure 6). The CS[1] explains that the *post hoc* analyses were undertaken to obtain effectiveness data for all the relevant subgroups in line with the final NICE scope.[17] The CS[1] states that with the exception of SBP, whereby patients with SBP of ≤130 mmHg at baseline experienced a greater benefit ([redacted]), the treatment benefit for dapagliflozin was consistent in all pre-specified analyses of relevant subgroups. Similarly, *post hoc* analyses demonstrated a consistent treatment benefit for dapagliflozin in the analyses of patients with or without comorbid CVD (*p*-value for interaction=[redacted]) and in patients without comorbid T2DM and without comorbid CVD versus those with comorbid CVD and/or T2DM (*p*-value for interaction, [redacted]).[1]

Figure 5: Forest plots of primary efficacy outcome according to pre-specified subgroups for DAPA-CKD (reproduced from CS, Figure 14)



CI - confidence interval; CV - cardiovascular; eGFR - estimated glomerular filtration rate; ESKD - end stage kidney disease; HbA1c - glycated haemoglobin; N - number of patients; n - number of patients included in analysis; T2DM - type 2 diabetes mellitus; uACR - urine albumin-to-creatinine ratio

Figure 6: *Post hoc* analyses of primary efficacy outcome for DAPA-CKD (reproduced from CS, Figure 15)

[redacted]

CI - confidence interval; CVD - cardiovascular disease; HR - hazard ratio

Patients with T2DM and patients without diabetes

Primary composite outcome

Compared with placebo, dapagliflozin was associated with treatment benefits in patients with T2DM (HR, 0.64 (95% CI 0.52–0.79) and patients without diabetes (HR, 0.50 (95% CI 0.35–0.72).[32] Cumulative incidence plots reported in Wheeler *et al*., 2021[32] showed early and sustained separation over the duration of the study (not shown here). As observed in the overall population, treatment benefit of dapagliflozin was observed in the individual components of the primary outcome in patients with T2DM and in those without diabetes.[32] There were no observed differences in the components of the primary composite outcome by diabetes status or cause of CKD.[32]

Secondary renal-specific composite outcome (sustained eGFR decline ≥50%, ESKD, or renal-related death)

A beneficial treatment effect of dapagliflozin over placebo was reported by Wheeler *et al*., 2021[32] for the renal-specific composite secondary outcome of sustained eGFR decline ≥50%, ESKD, or renal-related death. This was consistent for patients with T2DM (HR=0.57; 95% CI 0.45, 0.73) and patients without diabetes (HR=0.51; 95% CI 0.34, 0.75). Compared to those without diabetes, patients with T2DM had higher incidence of the composite outcome of CV death or hospital admission for HF and all-cause mortality.[32] The authors state that there was '*no effect modification by diabetes status*.'[32]

4.2.4 Safety

Section B.2.10 of the CS[1] states that the safety outcomes in DAPA-CKD[19] are consistent with existing comprehensive safety data for dapagliflozin in other indications. In DAPA-CKD, the median duration of exposure for patients was [redacted] months (range: [redacted] months) for dapagliflozin and [redacted] months (range: [redacted] months) for placebo. Overall, there were [redacted] patient-years of exposure to dapagliflozin in DAPA-CKD. Table 17 of the CS presents an overview of safety data reported in DAPA-CKD; this is reproduced in Table 12.

The frequency of AEs with an outcome of death was lower in the dapagliflozin arm compared with the placebo arm ([redacted] versus [redacted], on-treatment; [redacted] versus [redacted], on- and off- treatment, respectively). The CS[1] (Section B.2.10) notes that *"similar numbers*" of AEs leading to discontinuation of the study drug, dose interruption and dose reduction were reported for both treatment arms. The proportion of AEs possibly related to the active treatment was [redacted] for dapagliflozin versus [redacted] for placebo (see Table 12).

Table 12: Summary of AEs: DAPA-CKD (reproduced from CS, Table 17)

AE category, n (%)	Dapagliflozin (N=2,149)	Placebo (N=2,149)
Any AE with outcome of death (on- treatment)	[redacted]	[redacted]
Any AE with outcome of death (on- and off- treatment)	[redacted]	[redacted]
Any SAE, including events with outcome of death (on-treatment)	[redacted]	[redacted]
Any SAE, including events with outcome of death (on- and off- treatment)	633 (29.5)	729 (33.9)
Any AE leading to discontinuation of study drug	118 (5.5)	123 (5.7)
Any AE leading to dose interruption	[redacted]	[redacted]
Any AE leading to dose reduction	[redacted]	[redacted]
Any AE possibly related to dapagliflozin	[redacted]	[redacted]
AEs of special interest (on- and off- treatment)		
Definite or probable diabetic ketoacidosis	0	2 (<0.1)
Major hypoglycaemic event	14 (0.7)	28 (1.3)
Volume depletion	127 (5.9)	90 (4.2)
Fracture	85 (4.0)	69 (3.2)
Renal-related AE	155 (7.2)	188 (8.7)
Amputation	35 (1.6)	39 (1.8)

AE - adverse event; SAE - serious AE; N - number

SAEs

For the overall population, serious adverse events (SAEs) were lower in the dapagliflozin arm compared with the placebo arm (see Table 12) for both the on-treatment (n=[redacted] versus n=[redacted] and on-and off-treatment analyses (n=633; 29.5% versus n=729; 33.9%).[1] Higher rates of SAEs were reported among patients with T2DM compared to those without T2DM.[32]

Most common AEs (≥0.5% of patients in either treatment group) in DAPA-CKD

Table 18 of the CS[1] presents SAEs occurring in ≥0.5% of all patients in either the dapagliflozin or placebo arms (on treatment analysis); this is reproduced in Table 13. The CS[1] states that the three most commonly reported SAEs for both treatment groups were [redacted].

Table 13*:* Summary of most common AEs, occurring in ≥0.5% of patients in either treatment group: DAPA-CKD (reproduced from CS, Table 18)

AE category, n (%)[a]	Dapagliflozin (N=2,149)	Placebo (N=2,149)
Patients with any SAE	[redacted]	[redacted]
Acute kidney injury	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Cardiac failure	[redacted]	[redacted]
Acute myocardial infarction	[redacted]	[redacted]
End stage renal disease	[redacted]	[redacted]

AE category, n (%)[a]	Dapagliflozin (N=2,149)	Placebo (N=2,149)
Ischaemic stroke	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]
Chronic kidney disease	[redacted]	[redacted]
Cellulitis	[redacted]	[redacted]
Angina unstable	[redacted]	[redacted]
Renal impairment	[redacted]	[redacted]
Transient ischaemic attack	[redacted]	[redacted]
Cardiac failure congestive	[redacted]	[redacted]
Cerebrovascular accident	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]
Osteomyelitis	[redacted]	[redacted]
Prostate cancer	[redacted]	[redacted]
Hypoglycaemia	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]
Death	[redacted]	[redacted]
Hyperkalaemia	[redacted]	[redacted]
Hyperglycaemia	[redacted]	[redacted]

SAE - serious adverse event

AEs of special interest

The CS[1] (Section B.2.10.2) presents pre-specified AEs of special interest: diabetic ketoacidosis (DKA), fracture, renal events, major hypoglycaemia and volume depletion (see Table 14). No patient in the dapagliflozin arm experienced DKA during both the on-treatment and on- and off-treatment periods. Generally, dapagliflozin was associated with lower rates of major hypoglycaemic events, renal events and amputation and higher rates of fracture and symptoms of volume depletion compared with placebo.[1]

Table 14: Rates of AEs of special interest (on-treatment and on- and off-treatment periods): DAPA-CKD (adapted from CS, Tables 17 and 19)

AE of special interest	Number (%) of patients			
	Dapagliflozin (N=2,149)	Placebo (N=2,149)	Dapagliflozin (N=2,149)	Placebo (N=2,149)
	On-treatment period		On- and off- treatment period	
Amputation	[redacted]	[redacted]	35 (1.6)	39 (1.8)
Definite or probable DKA	[redacted]	[redacted]	0	2 (<0.1)
Fracture	[redacted]	[redacted]	85 (4.0)	69 (3.2)
Renal-related AE	[redacted]	[redacted]	155 (7.2)	188 (8.7)
Major hypoglycaemic event	[redacted]	[redacted]	14 (0.7)	28 (1.3)
Volume depletion	[redacted]	[redacted]	127 (5.9)	90 (4.2)

AE- adverse event; DKA - diabetic ketoacidosis

Adverse drug reactions reported in the SmPC

AEs reported in the Summary of Product Characteristics (SmPC) of dapagliflozin in T1DM and T2DM are mentioned in the CS[1] (Section B.2.10.3). The ERG notes that AEs reported in CS Table 20 are similar to those reported in '*Table 1. Adverse reactions in placebo-controlled clinical studies and postmarketing experience'* presented in the draft SmPC.[33]

4.3 Summary and critique of company's indirect comparison

An ITC was conducted to estimate the comparative efficacy of dapagliflozin versus canagliflozin for patients with CKD and comorbid T2DM. Although canagliflozin is not listed as a comparator for this appraisal in the final NICE scope,[17] CS Appendix D[28] states that there may be a "*potential increase in use of canagliflozin in the future for patients with CKD and T2DM*" and the results were used to inform a scenario analysis in the company's economic model (see Section 5.2). However, Section B.1.3.3 of the CS[1] states that canagliflozin is not a relevant comparator for this appraisal.

4.3.1 Trials included in the indirect comparison

The DAPA-CKD and CREDENCE trials[19, 29] were used to inform the comparison of dapagliflozin plus SoC and canagliflozin plus SoC. The baseline characteristics of the two studies are compared in Section D.3.2.2 of CS Appendix D.[28] DAPA-CKD enrolled a broader population than CREDENCE, which included only patients with T2DM who were aged 30 years or older.

4.3.2 Summary of the indirect comparison

In the absence of head-to-head evidence comparing dapagliflozin and canagliflozin, an anchored MAIC was conducted. Although the studies share a common comparator arm (SoC) allowing an anchored comparison, simpler ITC methods were not considered appropriate due to differences between the trial populations.

Methods for the MAIC

MAIC is a population adjustment method that makes use of the available individual patient data (IPD) to adjust for between-trial imbalances in the distribution of observed covariates. Individuals in the IPD population (DAPA-CKD[19]) are weighted to balance the covariate distribution with that of the target aggregate population (CREDENCE[29]), thereby allowing meaningful comparisons to be derived. In order to make anchored comparisons, MAIC relies on the assumption of conditional constancy of *relative* effects. This is a weaker assumption than that made for unanchored comparisons (which require conditional constancy of *absolute* effects). Anchored MAICs require that all treatment effect modifiers are known and accounted for in the adjustment model but balance of prognostic variables is not necessary.[34]

Comparisons were conducted for eight outcomes: (1) CREDENCE primary; (2) CV death; (3) all-cause mortality (ACM); (4) ESKD; (5) hHF; (6); doubling of serum creatinine; (7) CREDENCE renal composite, and (8) CREDENCE exploratory renal.

Selection of baseline covariates

Twenty-one variables that were available in CREDENCE[29] were considered for inclusion in the weighting model (see CS Appendix D,[28] Section D.3.2.4). Clinical advisors to the company considered

that there were no additional treatment effect modifiers that were unreported by either trial (see company's clarification response,[16] question B14b). A selection procedure was conducted using a Cox PH model to select variables that exhibited conditional correlation with treatment effect. A total of thirteen adjustment sets were determined. Five of these were generic to all outcomes: (i) Primary (smoking status, history of hypertension, history of HF, history of MI, duration of diabetes, SBP, eGFR categorical, baseline concomitant RAAS inhibitors); (ii) Clinical A (SBP, eGFR categorical, uACR, baseline concomitant RAAS inhibitors); (iii) Clinical A/B (race, history of HF, SBP, eGFR categorical, uACR, baseline concomitant RAAS inhibitors); (iv) Clinical unranked (race, history of HF, duration of diabetes, BMI, SBP, eGFR categorical, UACR, baseline insulin, baseline RAASI inhibitors) and (v) all. An additional 8 sets of covariates (one for each endpoint) were selected based on statistical significance for the specific endpoint.

Estimation of weights

DAPA-CKD[19] enrolled a broader population than CREDENCE[29] and so this was trimmed prior to weighting, resulting in reduced sample sizes of 1,442 and 1,444 patients in the SoC and dapagliflozin plus SoC arms, respectively. The final sample size differed for each matching set and is detailed in Tables 19 and 20 of CS Appendix D[28] for the SoC and dapagliflozin arms, respectively.

Following methods described in NICE Decision Support Unit (DSU) Technical Support Document (TSD) 18,[34] patients in DAPA-CKD[19] were allocated a weight to ensure that baseline characteristics match those of CREDENCE.[29] Baseline characteristics before and after matching are shown in Table 18 of CS Appendix D[28] for the primary matching set. The effective sample size (ESS) was 714 patients (33%) and 738.3 patients (34%) for the SoC and dapagliflozin arms.

Results of the MAIC

HRs and 95% CIs for dapagliflozin versus canagliflozin are provided in Table 15 for the naïve unadjusted comparisons and the company's MAIC using the primary analysis set. [redacted]

Table 15: Results of MAIC, HR (95% CI) (adapted from CS Appendix D, Figures 4 and 5)

Outcome	Analysis set	
	Unweighted	Primary

CREDENCE Primary	[redacted]	[redacted]
CV death		
ACM		
ESKD		
hHF		
Doubling of serum creatinine		
CREDENCE renal composite		
CREDENCE exploratory renal		

CV - cardiovascular; ACM - all-cause mortality; ESKD - end-stage kidney disease; hHF - hospitalisation for heart failure

4.3.3 Summary of the indirect comparison

The ERG considers that the procedure used by the company to select covariates was overly complex. Potential treatment effect modifiers that did not exhibit correlation with treatment effect in DAPA-CKD[19] were not included on the basis that this "*would not un-bias the observed treatment effect and would increase its variance*" (CS Appendix D,[28] Section D.3.2.4). The ERG does not agree with this justification since the increase in variance is likely to be appropriate if there are additional treatment effect modifiers that are not balanced between trials. [redacted]

4.4 Additional work on clinical effectiveness undertaken by the ERG

No additional work on clinical effectiveness was undertaken by the ERG.

4.5 Discussion and conclusions for clinical effectiveness

DAPA-CKD[19] was an event-driven, multicentre, international double-blind RCT. The ERG considers that DAPA-CKD is a trial with a low risk of bias, that provides direct head-to head clinical effectiveness evidence in line with the final NICE scope.[17] Of the overall population of 4,304 participants, only [redacted] of these were recruited from the UK.[16] Eligible patients were adults patients with CKD with or without comorbid T2DM with an eGFR of ≥25 to ≤75ml/min/1.73m^2 and uACR of ≥22.6mg/mmol (200mg/g) to ≤565mg/mmol (5,000mg/g). Randomisation was capped to ensure that no more than 10% of patients started the trial with an eGFR range corresponding to CKD stage 2.

A statistically significant benefit for dapagliflozin was demonstrated for the primary endpoint of the trial (a composite outcome of sustained decline in eGFR ≥50%, ESKD or death from renal or CV causes), most individual components of the primary composite endpoint (where assessed) and secondary outcomes in the overall population and relevant subgroups. [redacted]

[redacted] Safety data were from DAPA-CKD and were generally similar between treatment groups.[1] The ERG notes that the reported AEs from DAPA-CKD were generally consistent with available safety data for dapagliflozin in other indications.

Overall, the ERG considers that DAPA-CKD provides robust direct head-to-head evidence of the clinical effectiveness and safety of dapagliflozin versus placebo, in addition to SoC in patients with CKD with T2DM or without diabetes. The ERG's advisors suggested that the DAPA-CKD trial reflects many of the types of patients who might be treated with dapagliflozin in clinical practice; however, several groups of patients were excluded due to the trial eligibility criteria, including patients with urine albumin excretion <22.6mg/mmol, those with prior organ transplant, and those with T1DM. Also, whilst almost all patients in the trial were receiving ACE inhibitor or ARB therapy, many patients with CKD do not receive these therapies in clinical practice.

5 COST EFFECTIVENESS

This chapter provides a summary and critique of the company's economic analyses of dapagliflozin for the treatment of CKD, together with additional exploratory analyses undertaken by the ERG. Section 5.1 summarises the company's SLR of existing economic analyses of treatments for CKD. Section 5.2 describes the methods and results of the company's *de novo* economic model. Section 5.3 presents the ERG's critical appraisal of the company's model. Section 5.4 presents the methods and results of additional exploratory analyses undertaken by the ERG. Section 5.5 presents a discussion of the available economic evidence for dapagliflozin.

5.1 Company's review of existing economic evaluations

5.1.1 *Summary of the company's search strategy and review methods*

The company's SLRs of economic evaluations; HRQoL studies and cost and resource use studies are reported in CS Appendices G, H and I,[28] respectively. These reviews were all based on the same set of searches, which were run in October 2020. These are reported in CS Appendix G. The searches covered: MEDLINE and Embase (separately, using appropriate index terms in each); CRD databases (the archives of the HTA database and NHS EED); relevant conference proceedings, registries and international HTA websites. Filters to identify the eligible study types for inclusion in each review were applied; these were based on those of the Scottish Intercollegiate Guidelines Network (SIGN). The searches are reported in full and the ERG is satisfied that they were well designed and executed.

The company's SLR of existing economic analyses adopted a broad scope, which included any intervention for the treatment of CKD stages 2 to 4, or treatments for a complication of CKD (e.g. hyperphosphatemia) modelled in a CKD patient population.[1, 28] Sifting was undertaken using a two-stage process, starting with sifting of titles and abstracts, followed by scrutiny of the full-texts of potentially relevant studies. Sifting was undertaken by two reviewers, with disagreements resolved by discussion or involvement of a third reviewer where necessary. Data extraction was undertaken by one reviewer and checked by a second reviewer. Included studies were critically appraised using the Drummond *et al.* checklist.[35]

5.1.2 Summary of company's review findings

The company's review identified a total of 17 publications describing 16 unique economic analyses which met the inclusion criteria for the review; these are summarised in CS Appendix G.[28] Nine of the included studies were identified from the electronic database searches; the other seven studies were identified from searching conference proceedings and HTA websites. The identified studies include several economic evaluations of treatments for CKD, as well as others which relate to treatments for other diseases and comorbid conditions which involve progression of kidney disease and ESKD. Further

details regarding the full set of included studies can be found in CS Appendix G (Section G.2.1). Of particular note, the company's review identified one existing economic analysis which assessed the cost-effectiveness of dapagliflozin for CKD which formed the basis for the model presented in the CS[1] (McEwan *et al*.[36]). This study reports the methods and results of a model-based economic analysis of dapagliflozin plus SoC versus SoC alone from the perspective of the NHS and PSS. The model adopted a cohort-level state transition approach, with health states defined by CKD progression (CKD stages 1-5, prior to RRT), with additional states for dialysis, kidney transplantation and death. The model abstract was published prior to the release of the results of the DAPA-CKD trial[19] trial and the model poster presentation was subsequently updated using results from the trial.[37] The authors report that the incremental cost-effectiveness ratio (ICER) for dapagliflozin plus SoC versus SoC was estimated to be £5,143 per quality-adjusted life year (QALY) gained. The other 15 studies included in the company's review are not directly relevant to this appraisal, but may provide some information regarding model structure and/or parameter values.

5.2 Summary of the company's submitted economic evaluation

This section describes the company's original submitted model, as described in the CS.[1] Following the clarification round, the company submitted an updated base case model. The revised model and its results are summarised separately in Section 5.3.5.

5.2.1 Scope of the company's economic analysis

As part of their submission to NICE,[1] the company submitted a *de novo* health economic model programmed in Microsoft Excel using Visual Basic for Applications (VBA). The scope of the company's model is summarised in Table 16. The model assesses the cost-effectiveness of dapagliflozin plus SoC versus SoC alone for patients with CKD in terms of the incremental cost per QALY gained. Health outcomes and costs for each treatment group are assessed from the perspective of the NHS and PSS over a lifetime horizon.

Table 16: Scope of company's model

Population	Patients with CKD ([redacted])
Time horizon	Lifetime ([redacted] years)
Intervention	Dapagliflozin plus SoC
Comparator	SoC alone
Economic analysis approach	Cost-utility analysis
Outcome	Incremental cost per QALY gained
Perspective	NHS and PSS
Discount rate	3.5% for health outcomes and costs
Price year	2019/20

CKD - chronic kidney disease; SoC - standard of care; QALY - quality-adjusted life year; NHS - National Health Service; PSS - Personal Social Services; RRT - renal replacement therapy

Population

The target population is assumed to reflect the population of patients with CKD included in a bespoke analysis of the CPRD[15] conducted by the company, rather than the population of patients recruited into the DAPA-CKD trial.[19] The risks of death, hHF and AKI are based on statistical models fitted to data from DAPA-CKD which are then adjusted to reflect the characteristics of the CPRD population. At baseline, patients are assumed to have an initial age of [redacted] years and [redacted] of the population is female. [redacted]

Alongside the base case analysis, the CS[1] also reports on the cost-effectiveness of dapagliflozin in the overall DAPA-CKD population and across nine subgroups of the CPRD and DAPA-CKD populations:

(i) CPRD subgroup with comorbid T2DM
(ii) CPRD subgroup without comorbid T2DM
(iii) CPRD subgroup with uACR <200mg/g
(iv) CPRD subgroup with uACR ≥200mg/g
(v) DAPA-CKD subgroup with comorbid T2DM
(vi) DAPA-CKD subgroup without comorbid T2DM
(vii) DAPA-CKD subgroup with comorbid CVD
(viii) DAPA-CKD subgroup without comorbid CVD
(ix) DAPA-CKD subgroup without comorbid T2DM and without comorbid CVD.

The patient characteristics applied in the company's base case and subgroup analyses are described in Section 5.2.4.

Comparator

The comparator included within the company's model is SoC, which is assumed to include ramipril (an ACE inhibitor), losartan and irbesartan (ARBs), atorvastatin (a statin) and aspirin (an antiplatelet). Only a proportion of patients is assumed to receive each of these drugs in each model cycle, based on the reported usage in the CPRD dataset.[15] These proportions are applied uniformly across all model health states and are assumed to remain constant over time.

The company's scenario analyses include an economic comparison of dapagliflozin versus canagliflozin for patients with CKD and comorbid T2DM, [redacted]

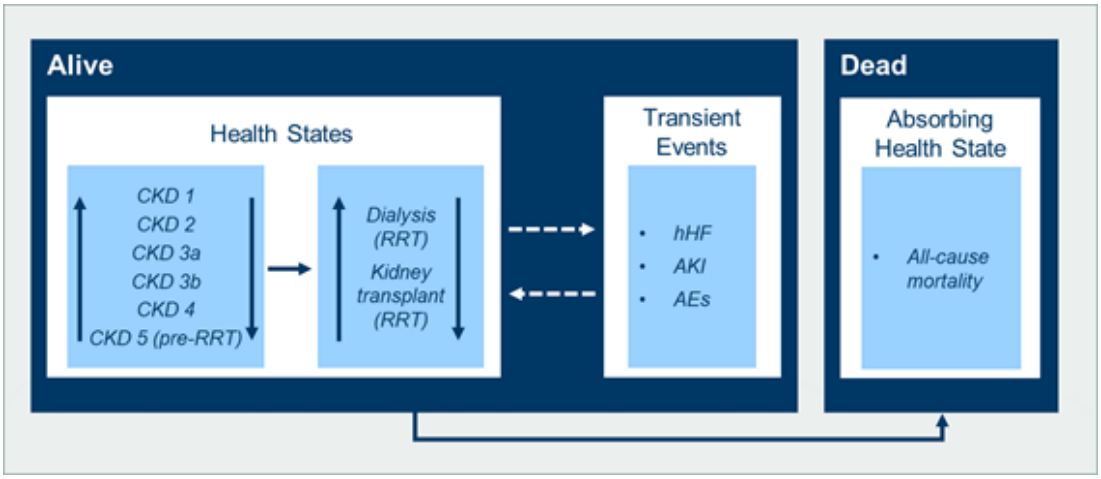
Intervention

The intervention assessed within the company's economic analysis is dapagliflozin given alongside SoC. Dapagliflozin is assumed to be given orally at a dose of 10mg once daily. The model does not include a treatment discontinuation rule based on exposure or response to dapagliflozin, although patients are assumed to discontinue treatment if they undergo kidney transplantation. The model also assumes that a proportion of patients discontinue in each model cycle. The company's clarification response[16] (question B8) states that [redacted] and the draft SmPC for dapagliflozin[33] [redacted]. Following discontinuation of dapagliflozin, patients are assumed to continue to receive SoC alone.

5.2.2 Company's model structure and logic

The company's model structure is shown in Figure 7. The model adopts a cohort-level state transition approach with six health states defined according to CKD stage (1-5 [pre-RRT]), with additional states for dialysis, kidney transplant and death.

Figure 7: Company's model structure (reproduced from CS, Figure 22)



CKD - chronic kidney disease; RRT - renal replacement therapy; hHF - hospitalisation for heart failure; AKI - acute kidney injury; AE - adverse event

The company's model logic operates as follows. Patients enter the model according to the distribution of CKD stage at baseline in the CPRD dataset.[15] During each monthly model cycle, patients in the CKD 1-5 states can transition to any other CKD state, progress to dialysis, undergo a kidney transplant or die. Patients who have previously undergone a kidney transplant or who are receiving dialysis cannot transition back to the other CKD states. The model includes two sets of transition matrices for each treatment group: the first matrix relates to the initial period between months 0 and 4, whilst the second

matrix is applied to all subsequent model cycles after month 4. Separate matrices are applied in each treatment group. The risk of death during each model cycle is assumed to be conditional on the patient's current CKD stage and treatment group, with higher mortality risks applied to more advanced CKD states and to the dialysis state, and lower mortality risks applied to dapagliflozin-treated patients in all states except for the transplant state. HRQoL is also assumed to be dependent on health state; lower utility values are applied to the CKD stage 5, transplant and dialysis health states relative to the states for CKD stages 1-4. The same utility values are applied to equivalent states in each treatment group. The model includes the incidence of two transient events, hHF and AKI, which lead to QALY losses. The risks of experiencing these events are assumed to be conditional on CKD stage and treatment group, with lower risks applied in the dapagliflozin group. The model also includes AEs which are assumed to lead to further QALY losses. Health utility is not adjusted for increasing age (although this was amended in the updated model - see Section 5.3.5).

The relative effectiveness of dapagliflozin versus SoC is modelled via three separate mechanisms:

(i) Arm-specific transition matrices are applied to each treatment group;

(ii) A treatment-related log HR is applied to the per-cycle conditional probability of survival in all health states except for the transplant state;

(iii) A treatment-related log OR is applied to the risk of hHF and AKI in each health state except for the transplant state.

In the intervention group, patients are assumed to discontinue dapagliflozin at a constant rate over time. Relative treatment effects are assumed to remain constant whilst the patient is still receiving dapagliflozin, but are immediately lost upon treatment discontinuation. Patients who have discontinued dapagliflozin are assumed to revert to the risks of CKD progression, mortality, hHF and AKI for the SoC group.

The model includes costs associated with: drug acquisition; health state resource use; dialysis; transplantation; the treatment of transient events, and the management of AEs.

The model predicts that dapagliflozin generates more QALYs than SoC as a consequence of slower disease progression and extended OS. Total costs are higher for the dapagliflozin group principally due to the additional costs of drug acquisition and slightly higher lifetime costs associated with CKD management compared with SoC.

5.2.3 Key model assumptions

The company's model applies the following key assumptions:

- SoC is assumed to include a mix of treatments including an ACE inhibitor, ARBs, a statin and an antiplatelet
- Dapagliflozin is assumed to be used as an adjunct to SoC
- The disease is modelled according to 9 mutually exclusive and jointly exhaustive health states: CKD stages 1, 2, 3a, 3b, 4 and 5 [pre-RRT]; dialysis, transplant and dead.
- More advanced CKD stage is assumed to be associated with higher mortality risk.
- HRQoL is dependent on the model health state. Utility values are assumed to be similar for most CKD states; dialysis is assumed to be associated with comparably lower HRQoL.
- hHF and AKI lead to QALY losses and costs, but are not causally related to mortality.
- AEs result in HRQoL decrements and additional costs.
- Relative treatment effects are applied to (i) transitions between the model health states; (ii) mortality risks within each health state and (iii) risks of hHF and AKI. Treatment effects on mortality and transient events are applied to the dialysis state, but are not applied to the transplant health state. These apply indefinitely whilst the patient is still receiving dapagliflozin but are lost upon discontinuation.
- The risk of discontinuing dapagliflozin is assumed to be constant over time.
- The model includes the following cost components:
    - Drugs (dapagliflozin in the intervention group, SoC [both groups] = ramipril [redacted], losartan [redacted], irbesartan [redacted], atorvastatin [redacted] and aspirin [redacted]).
    - Health state costs by CKD stage
    - Transplant costs
    - Dialysis costs
    - Costs of managing transient events (hHF and AKI)
    - Costs of managing AEs
- No costs are included for antidiabetic drugs, treatments for CKD complications (e.g. vitamin D, erythropoietin stimulating agents and phosphate binders), prescribing, routine outpatient appointments or primary care visits.
- Dapagliflozin is assumed to require no additional tests or follow-up appointments.

5.2.4 Evidence used to inform the model parameters

Table 17 summarises the evidence sources used to inform the parameter values used in the company's base case model. These are discussed in detail in the subsequent sections.

Table 17: Evidence sources used to inform the company's model parameters

Model parameter / group	Source
Patient characteristics	CPRD dataset[15]
Transition probabilities, CKD stages 1-5, months 0-4	DAPA-CKD[19]
Transition probabilities, CKD stages 1-5, month 5 plus	DAPA-CKD[19]
Transition probabilities, transplant and dialysis	Sugrue *et al*.[38]
Mortality risk for individual CKD stages 1-5 (risk conditional on each stage)	Multivariable Gompertz model fitted to data from DAPA-CKD[19] adjusted to CPRD population characteristics[15]
Mortality risk, transplant and dialysis states	Sugrue *et al*.[38]
Probability of hHF (conditional on CKD stage)	GEE model fitted to data from DAPA-CKD,[19] adjusted to CPRD population characteristics[15]
Probability of AKI (conditional on CKD stage)	GEE model fitted to data from DAPA-CKD,[19] adjusted to CPRD population characteristics[15]
Discontinuation probability	DAPA-CKD[19]
AE frequency	DAPA-CKD[19] and DECLARE-TIMI 58[21]
Health utility by CKD stage	Linear mixed model fitted to data from DAPA-CKD[19]
Health utility – dialysis	Lee *et al.*[39]
Health utility - transplant	Lee *et al.*[39]
Disutility - hHF	DAPA-CKD[19]
Disutility – AKI	DAPA-CKD[19]
Disutility - AEs	DAPA-CKD,[19] DAPA-HF,[20] and Currie *et al*.[40]
Drug acquisition costs	Unit costs from eMIT[41] and MIMS.[22] Percentages of patients receiving individual drugs from CPRD[15]
CKD1-5 health state costs	Kent *et al*.[11]
Transplant cost	NHS Reference Costs 2018/19[42]
Dialysis cost	NICE NG107[43]
hHF cost	NHS Reference Costs 2018/19[42]
AKI cost	NHS Reference Costs 2018/19[42]
AE costs	PSSRU,[44] Hammer *et al*.,[45] NHS Reference Costs,[42] Dhatariva *et al.*[46] and Alva *et al*.[47]

CKD - chronic kidney disease; CPRD - Clinical Practice Research Datalink; LOCF - last observation carried forward; hHF - hospitalisation for heart failure; AKI - acute kidney injury; AE - adverse event; GEE - generalised estimation equations; NICE - National Institute for Health and Care Excellence; NG - NICE Guideline; PSSRU - Personal Social Services Research Unit

Patient characteristics

The CS[1] highlights that the clinical experts consulted by the company identified discrepancies between the characteristics of patients recruited into DAPA-CKD[19] and patients who would be seen in UK clinical practice. In particular, the experts highlighted differences in terms of race (with fewer Black/African American [redacted]), younger age and better controlled blood pressure in patients recruited to DAPA-CKD compared with the CKD population in the UK. In order to improve the generalisability of the economic analysis to the UK setting, the baseline characteristics of the modelled patient population were assumed to reflect the population of patients

included in a bespoke dataset obtained from the CPRD.[15] The economic model includes the adjustment of predicted event risks (mortality, hHF and AKI) derived from DAPA-CKD to this CPRD population.

[redacted] The company's base case economic analysis reflects the overall CPRD population. The CS[1] presents additional scenario analyses for the overall DAPA-CKD population and for subgroups of the CPRD and DAPA-CKD populations, defined according to the presence/absence of one or more comorbidities or uACR level. The population values applied in the base case and subgroup analyses are summarised in Table 18.

Table 18: Baseline characteristics for base case analysis (CPRD population) and subgroup analyses (CPRD and DAPA-CKD)

Characteristic	CPRD overall CKD population and subgroups					DAPA-CKD overall CKD population and subgroups					
	Overall population (base case)	Comorbid T2DM	Without comorbid T2DM	uACR <200mg/g	uACR ≥200mg/g	Overall population	Comorbid T2DM	Without comorbid T2DM	Comorbid CVD	Without comorbid CVD	Without comorbid T2DM or CVD
Age (years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	61.841	64.436	56.447	66.350	59.263	53.766
Female	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.331	0.332	0.329	0.292	0.354	0.352
BMI (kg/m2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	29.518	30.296	27.904	30.708	28.837	27.469
Race: White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.532	0.530	0.536	0.670	0.453	0.480
Race: Black or African American	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.044	0.047	0.039	0.052	0.040	0.040
Race: Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.083	0.102	0.043	0.072	0.089	0.044
Smoker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.136	0.136	0.135	0.130	0.139	0.137
CKD 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.000	0.000	0.000	0.000	0.000	0.000
CKD 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.105	0.120	0.076	0.115	0.100	0.081
CKD 3a	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.309	0.316	0.293	0.300	0.313	0.302
CKD 3b	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.441	0.426	0.471	0.442	0.440	0.458
CKD 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.145	0.138	0.160	0.143	0.146	0.159
CKD 5 (pre-RRT)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.000	0.000	0.000	0.000	0.000	0.000
Dialysis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.000	0.000	0.000	0.000	0.000	0.000
Transplant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.000	0.000	0.000	0.000	0.000	0.000
uACR: 30-300 mg/g	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.103	0.106	0.097	0.107	0.101	0.094
uACR: >=300 mg/g	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.897	0.894	0.903	0.893	0.899	0.906
T2DM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.675	1.000	0.000	0.793	0.608	0.000
Glomerulonephritis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.161	0.033	0.428	0.060	0.220	0.490
ACE inhibitor	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.274	0.269	0.285	0.333	0.240	0.277
ARB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.556	0.554	0.558	0.513	0.580	0.564
MRA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.045	0.050	0.036	0.078	0.026	0.023
Diuretic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.371	0.426	0.255	0.482	0.307	0.209
Potassium (mmol/L)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	4.647	4.674	4.591	4.651	4.645	4.581
SBP (mmHg)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	137.083	139.227	132.625	139.160	135.894	131.331
Haemoglobin (g/dL)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	12.825	12.594	13.307	12.921	12.770	13.220
Prior HF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.109	0.124	0.077	0.299	0.000	0.000
Prior MI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.091	0.110	0.051	0.250	0.000	0.000
Prior stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.069	0.079	0.049	0.190	0.000	0.000

CPRD - Clinical Practice Research Datalink; CKD - chronic kidney disease; T2DM - type 2 diabetes mellitus; CVD – cardiovascular disease; uACR - urine albumin-to-creatinine ratio; BMI - body mass index; ACE - angiotensin-converting enzyme; ARB - angiotensin II receptor blocker; MRA - mineralocorticoid receptor antagonist; SBP - systolic blood pressure; HF - heart failure; MI - myocardial infarction

Health state transition probabilities (excluding mortality)

Transition probabilities are based on a monthly cycle length. The probabilities of transitioning between the alive health states in the dapagliflozin and SoC groups of the model are shown in Table 19 and Table 20, respectively. These probabilities were derived from two sources: (i) transitions from CKD1-5 (pre-RRT) to any other state were estimated using IPD from DAPA-CKD;[19] (ii) transitions between the transplant and dialysis states were obtained from a review of published economic models of kidney disease reported by Sugrue *et al*.[38]

Transitions from CKD1 to CKD5 (pre-RRT) to any other health state

The transition probabilities were estimated using patient-level count data from DAPA-CKD.[19] The model applies treatment-dependent transition probabilities over two time periods: the initial period relates to each cycle in Months 0 to 4, whilst the subsequent period relates to each cycle from Month 5 onwards. The observed data were sub-divided into monthly observation intervals, with last observation carried forward (LOCF) applied to intervals in which no change in state was observed. Non-informative priors of 1.0 were applied to each transition. Transition probabilities were estimated using WinBUGS based on three chains of 10,000 iterations and the results were checked for convergence. Further details regarding the data structure and the WinBUGS code are provided in the company's clarification response[16] (question B2). The CS[1] justifies the use of treatment-dependent transition matrices through reference to the statistically significant difference in sustained decline in eGFR of ≥50% in DAPA-CKD.[19] In addition, the CS states that separate matrices were applied in the initial and subsequent periods to represent the initial eGFR drop followed by a nominal increase in eGFR associated with dapagliflozin initiation observed in the trial (see CS,[1] Figure 11). The CS does not explain why it was necessary to use this piecewise approach for the SoC group.

Unlike most of the other model parameters relating to clinical event risks, the transition probabilities are not adjusted to account for differences in baseline characteristics between the DAPA-CKD and CPRD populations,[15, 19] either within the base case or subgroup analyses.

Transitions between dialysis and transplant health states

Transition probabilities between the dialysis and transplant health states were taken from Sugrue *et al.*[38] as there were insufficient events observed in DAPA-CKD[19] to reliably derive these probabilities. The company's clarification response[16] (question B10) states that 2 patients on dapagliflozin and 4 patients on placebo moved from dialysis to transplant. The same transition probabilities are applied in each treatment group in both the initial and subsequent periods. The model assumes that once patients undergo a kidney transplant or dialysis, they cannot regress back to the other CKD health states.

Table 19: Monthly transition probabilities, dapagliflozin

Dapagliflozin, initial period (months 0-4)								
From\To	CKD1	CKD2	CKD3a	CKD3b	CKD4	CKD5 (pre-RRT)	Dialysis	Transplant
CKD1	0.586	0.219	0.049	0.049	0.024	0.024	0.024	0.025
CKD2	0.018	0.709	0.246	0.019	0.003	0.003	0.001	0.001
CKD3a	0.001	0.079	0.749	0.162	0.008	0.000	0.000	0.000
CKD3b	0.001	0.005	0.079	0.812	0.102	0.001	0.000	0.000
CKD4	0.001	0.003	0.006	0.143	0.843	0.004	0.001	0.001
CKD5 (pre-RRT)	0.063	0.125	0.062	0.124	0.375	0.125	0.063	0.062
Dialysis	0.000	0.000	0.000	0.000	0.000	0.000	0.995	0.005
Transplant	0.000	0.000	0.000	0.000	0.000	0.000	0.007	0.993
Dapagliflozin, subsequent period (months 5 onwards)								
From\To	CKD1	CKD2	CKD3a	CKD3b	CKD4	CKD5 (pre-RRT)	Dialysis	Transplant
CKD1	0.891	0.070	0.009	0.015	0.006	0.003	0.003	0.003
CKD2	0.005	0.909	0.078	0.006	0.002	0.000	0.000	0.000
CKD3a	0.001	0.025	0.913	0.059	0.002	0.000	0.000	0.000
CKD3b	0.000	0.001	0.025	0.938	0.035	0.000	0.000	0.000
CKD4	0.000	0.000	0.001	0.035	0.952	0.010	0.001	0.000
CKD5 (pre-RRT)	0.001	0.002	0.002	0.001	0.027	0.920	0.045	0.002
Dialysis	0.000	0.000	0.000	0.000	0.000	0.000	0.995	0.005
Transplant	0.000	0.000	0.000	0.000	0.000	0.000	0.007	0.993

Probabilities rescaled to ensure that the sum of each row is equal to 1.0. Non-permitted transitions shown with grey shading
CKD - chronic kidney disease; RRT - renal replacement therapy

Table 20: Monthly transition probabilities, SoC

SoC, initial period (months 0-4)								
From\To	CKD1	CKD2	CKD3a	CKD3b	CKD4	CKD5 (pre-RRT)	Dialysis	Transplant
CKD1	0.375	0.313	0.156	0.031	0.031	0.031	0.031	0.031
CKD2	0.009	0.770	0.195	0.016	0.004	0.002	0.002	0.001
CKD3a	0.002	0.070	0.774	0.149	0.004	0.000	0.000	0.000
CKD3b	0.002	0.004	0.084	0.826	0.082	0.001	0.001	0.000
CKD4	0.001	0.002	0.005	0.127	0.856	0.007	0.001	0.001
CKD5 (pre-RRT)	0.043	0.174	0.043	0.044	0.175	0.348	0.130	0.043
Dialysis	0.000	0.000	0.000	0.000	0.000	0.000	0.995	0.005
Transplant	0.000	0.000	0.000	0.000	0.000	0.000	0.007	0.993
SoC, subsequent period (months 5 onwards)								
From\To	CKD1	CKD2	CKD3a	CKD3b	CKD4	CKD5 (pre-RRT)	Dialysis	Transplant
CKD1	0.884	0.075	0.015	0.011	0.004	0.004	0.004	0.004
CKD2	0.004	0.915	0.072	0.008	0.002	0.000	0.000	0.000
CKD3a	0.000	0.023	0.910	0.064	0.003	0.000	0.000	0.000
CKD3b	0.000	0.001	0.026	0.931	0.041	0.000	0.001	0.000
CKD4	0.000	0.001	0.001	0.028	0.954	0.014	0.002	0.000
CKD5 (pre-RRT)	0.001	0.001	0.001	0.002	0.038	0.910	0.044	0.003
Dialysis	0.000	0.000	0.000	0.000	0.000	0.000	0.995	0.005
Transplant	0.000	0.000	0.000	0.000	0.000	0.000	0.007	0.993

Probabilities rescaled to ensure that the sum of each row is equal to 1.0. Non-permitted transitions shown with grey shading
CKD - chronic kidney disease; RRT - renal replacement therapy; SoC – standard of care

Overall survival

The company's model assumes that mortality risk in each cycle is dependent on treatment group and current CKD stage. Mortality risks for states CKD1 to CKD5 (pre-RRT) were based on parametric survival models fitted to data from DAPA-CKD[19] which were subsequently adjusted to reflect the characteristics of patients in the CPRD dataset.[15] Mortality risks for the dialysis and transplant states were based on external data (Sugrue *et al*.[38]).

Overall survival - states CKD1-5 (pre-RRT)

The company's survival analysis for CKD states 1-5 involved four main steps: (i) a set of covariables was selected for inclusion in the parametric models; (ii) parametric survival models were fitted to the OS data from DAPA-CKD, including covariables;[19] (iii) the goodness-of-fit of candidate parametric survival distributions was assessed and (iv) the selected survival distribution was adjusted to reflect the population values from the CPRD dataset.[15]

An initial set of covariables was identified based on pre-specified subgroups in DAPA-CKD.[19] These covariables were then tested in univariate analyses to identify those which were likely to be predictive of mortality in the DAPA-CKD trial population. The company then undertook multivariable analysis to determine which covariables were still influential after multivariable adjustment, their effect size, and the clinical face validity of the direction of the effect on the outcome (further details on these judgements are provided in the company's clarification response,[16] question B12). Covariables which did not improve model fit were removed using backwards stepwise elimination based on the Akaike Information Criterion (AIC) and *p*-values.

The company then fitted seven standard parametric survival models to the available OS data from DAPA-CKD.[19] These included: the exponential; Weibull; Gompertz; log-normal; log-logistic; gamma and generalised gamma distributions. The models were jointly fitted to the data for both trial arms, including a covariate for treatment group which provides an estimate of treatment effect (an HR for PH models or an acceleration factor [AF] for acceleration failure time [AFT] models) in addition to the covariables selected from step (i).

The company then assessed the statistical goodness-of-fit of the multivariable models using the AIC and the Bayesian Information Criterion (BIC). The long-term plausibility of the extrapolated models was assessed by comparison against published life expectancy tables for patients with CKD reported from a large population-based registry in Canada.[48] Additionally, a clinical expert elicitation exercise was carried out in collaboration with six clinical experts (see clarification response,[16] questions B4 and B12).

The final multivariable survival models included the survival model parameters (e.g. scale and shape), the treatment effect indicating covariate and covariables for age, sex, race, BMI, eGFR category, haemoglobin, glomerulonephritis, SBP, potassium, and history of HF, MI and stroke. Goodness-of-fit statistics for the candidate models are shown in Table 21. Comparisons of the observed Kaplan-Meier plots for OS and the fitted multivariable models (excluding the additional impact of transitions between health states) were not provided in the CS[1] or the company's clarification response.[16] The company's survival analysis indicated that log-logistic model provided the best fit according to the AIC, whilst the exponential model provided the best fit according to the BIC. However, the CS[1] states that with the exception of the gamma distribution which had noticeably higher AIC and BIC values, goodness-of-fit was comparable between the models. The company selected the Gompertz model for the base case analysis on the grounds of long-term plausibility through reference to the Canadian registry analysis[48] and the clinical expert elicitation exercise.[16]

Table 21: Goodness-of-fit statistics, OS, DAPA-CKD overall population

Model	AIC	BIC
Exponential	5061.10	**5236.01**
Weibull	5057.33	5241.96
Gompertz	5061.78	5246.42
Log-normal	5066.77	5251.40
Log-logistic	**5056.32**	5240.96
Gamma	5495.05	5679.69
Generalised gamma	5144.07	5338.42

Best fitting model shown in bold
AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion

The company then adjusted the Gompertz survival model to reflect the mortality risk in the CPRD population by multiplying each covariable by its respective population value in the CPRD dataset.[15] Predicted survival for each individual CKD state was then estimated by applying a value of 1.0 to the relevant eGFR category for that health state, whilst holding all other population values at their mean for the overall population. These two steps are used to estimate the log HR for each CKD-specific OS model in each treatment group. The fitted survival model coefficients and the population values from the CPRD dataset are shown in Table 22.

Table 22: Survival model parameters and CPRD population values

Characteristic	Gompertz survival model coefficient [SE]	CPRD population value
Shape	0.00026 [0.00]	N/a
Rate	0.00069 [0.00]	N/a
Dapagliflozin	-0.36597 [0.13]	N/a
Age (years)	0.03436 [0.01]	[redacted]
Female	-0.36049 [0.14]	[redacted]
BMI (kg/m2)	-0.02235 [0.01]	[redacted]

Characteristic	Gompertz survival model coefficient [SE]	CPRD population value
Race: White	0.81962 [0.20]	[redacted]
Race: Black or African American	0.63375 [0.34]	[redacted]
Race: Other	0.84351 [0.25]	[redacted]
Smoker	Not included	[redacted]
eGFR <15 ml/min/1.73 m^2 [CKD5]	1.47894 [0.37]	Value of 1.0 applied to relevant CKD state in model
eGFR 15–30 ml/min/1.73 m^2 [CKD4]	0.53771 [0.30]	
eGFR 30–60 ml/min/1.73 m^2 [CKD3]	0.28160 [0.28]	
Dialysis	Not included	[redacted]
Transplant	Not included	[redacted]
uACR: 30-300 mg/g	Not included	[redacted]
uACR: >=300 mg/g	Not included	[redacted]
Type 2 diabetes	Not included	[redacted]
Glomerulonephritis	-0.45994 [0.29]	[redacted]
ACE inhibitor	Not included	[redacted]
ARB	Not included	[redacted]
MRA	Not included	[redacted]
Diuretic	Not included	[redacted]
Potassium (mmol/L)	-0.16838 [0.11]	[redacted]
Systolic blood pressure (mmHg)	-0.00930 [0.00]	[redacted]
Haemoglobin (g/dL)	-0.22982 [0.04]	[redacted]
Prior HF	0.81752 [0.16]	[redacted]
Prior MI	0.37557 [0.17]	[redacted]
Prior Stroke	0.47429 [0.20]	[redacted]

CPRD - Clinical Practice Research Datalink; eGFR - estimated glomerular filtration rate; BMI - body mass index; uACR - urine albumin-to-creatinine ratio; ACE - angiotensin-converting enzyme; ARB - angiotensin II receptor blocker; MRA - mineralocorticoid receptor antagonist; HF - heart failure; MI - myocardial infarction; SE - standard error

Overall survival – dialysis and transplant states

The company's approach to modelling mortality risk in patients who are receiving dialysis or who have undergone kidney transplant is not described in the CS.[1] The model assumes that the hazard of death is constant; hence, survival for these patients follows an exponential distribution. Annotations contained in the VBA code in the company's model indicated that annual probabilities of death for these states were obtained from Sugrue *et al*,[38] which were then converted to monthly probabilities. These risks are not adjusted to the CPRD population[15] and are assumed to be the same across all subgroups. The model assumes a relative treatment effect on the risk of death in the dialysis state, which involves applying the treatment effect covariate (the HR for dapagliflozin) from the DAPA-CKD multivariable survival analysis to the exponential model for dialysis from Sugrue *et al*.[38]

The adjusted survival models by health state for dapagliflozin and SoC are shown in Figure 8 and Figure 9, respectively. The modelled OS estimates for dapagliflozin and SoC, including the impact of transitions between health states, are shown in Figure 10.

Figure 8: Modelled survival by model health state, adjusted to CPRD population, dapagliflozin group

CKD - chronic kidney disease; RRT - renal replacement therapy

Figure 9: Modelled survival by model health state, adjusted to CPRD population, SoC group

CKD - chronic kidney disease; RRT - renal replacement therapy

Figure 10: Modelled OS from company's economic model, including CPRD adjustment and impact of transitions between health states over time

OS - overall survival; SoC - standard of care

Monthly probabilities of hHF and AKI

The company's economic model includes two transient events, hHF and AKI, which are assumed to lead to QALY losses and additional costs. As with OS, the company's model assumes that the risk of these events is conditional on treatment group and current CKD stage. The company estimated the risks of these events using data from DAPA-CKD[19] and subsequently adjusted these to the CPRD population.[15]

The company fitted separate generalised estimating equations (GEE) models to IPD on hHF and AKI from DAPA-CKD[19] using a multivariable approach with covariables identified based on pre-specified subgroups in DAPA-CKD.[19] For each of the AKI and hHF models, covariables were tested in univariate analyses to identify those factors which were likely to be predictive of these events in the DAPA-CKD trial population. Multivariable analysis was then used to determine which covariables were still influential after multivariable adjustment, their effect size, and the face validity of the direction of the effect on the event risk. Covariables which did not improve model fit were removed from the model using backwards stepwise elimination based on the Quasi-Information Criterion (QIC) and *p*-values.

The final model for hHF included an intercept term as well as covariables for treatment group, age, T2DM, BMI, race, smoking status, eGFR category, uACR, potassium, haemoglobin and history of HF. The final model for AKI included an intercept term as well as covariables for treatment group, race, eGFR category, glomerulonephritis, potassium, haemoglobin, history of HF and history of MI. The GEE model coefficients and the CPRD population values are summarised in Table 23. The adjusted model estimates the log odds of hHF/AKI by summing the product of model coefficients and the CPRD population values plus the intercept term, which is then converted to a probability. The resulting adjusted monthly probabilities by CKD stage and treatment group are summarised in Table 24.

Table 23: Summary of company's multivariable survival, hHF and AKI risk models and CPRD population values

Characteristic	hHF GEE model	AKI GEE model	CPRD population value
Intercept	-11.41542	-6.81785	N/a
Dapagliflozin	-0.64716	-0.30783	N/a
Age (years)	0.04654	Not included	[redacted]
Female	Not included	Not included	[redacted]
BMI (kg/m2)	0.05873	Not included	[redacted]
Race: White	0.65848	0.54789	[redacted]
Race: Black or African American	0.41411	0.55403	[redacted]
Race: Other	-0.35959	0.32357	[redacted]
Smoker	0.48239	Not included	[redacted]
eGFR <15 ml/min/1.73 m^2 [CKD5]	0.87720	2.12615	Value of 1.0 applied to relevant CKD state in model
eGFR 15–30 ml/min/1.73 m^2 [CKD4]	0.85811	0.61858	
eGFR 30–60 ml/min/1.73 m^2 [CKD3]	0.33567	0.01084	
Dialysis	Not included	Not included	[redacted]
Transplant	Not included	Not included	[redacted]
UACR: 30-300 mg/g	1.32207	Not included	[redacted]
UACR: >=300 mg/g	1.63788	Not included	[redacted]
T2DM	0.81195	Not included	[redacted]
Glomerulonephritis	Not included	-0.59022	[redacted]
ACE inhibitor	Not included	Not included	[redacted]
ARB	Not included	Not included	[redacted]
MRA	Not included	Not included	[redacted]
Diuretic	Not included	Not included	[redacted]
Potassium (mmol/L)	-0.43026	0.25111	[redacted]
SBP (mmHg)	Not included	Not included	[redacted]
Haemoglobin (g/dL)	-0.15531	-0.14558	[redacted]
Prior HF	1.75096	0.76177	[redacted]
Prior MI	Not included	0.32089	[redacted]
Prior stroke	Not included	Not included	[redacted]

CPRD - Clinical Practice Research Datalink; T2DM - type 2 diabetes mellitus; uACR - urine albumin-to-creatinine ratio; BMI - body mass index; ACE - angiotensin-converting enzyme; ARB - angiotensin II receptor blocker; MRA - mineralocorticoid receptor antagonist; SBP - systolic blood pressure; HF - heart failure; MI - myocardial infarction

Table 24: Estimated monthly risks of hHF and AKI for dapagliflozin and SoC from GEE models, adjusted to CPRD population

Option	CKD1	CKD2	CKD3a	CKD3b	CKD4	CKD5 (pre-RRT)	Dialysis	Transplant
hHF – monthly probability								
Dapagliflozin	0.0001	0.0001	0.0001	0.0001	0.0002	0.0002	0.0002	0.0004
SoC	0.0002	0.0002	0.0002	0.0002	0.0004	0.0004	0.0004	0.0004
AKI – monthly probability								
Dapagliflozin	0.0007	0.0007	0.0007	0.0007	0.0012	0.0055	0.0055	0.0075
SoC	0.0009	0.0009	0.0009	0.0009	0.0017	0.0075	0.0075	0.0075

CKD - chronic kidney disease; SoC - standard of care; hHF - hospitalisation for heart failure; AKI - acute kidney injury; RRT - renal replacement therapy; GEE - generalised estimating equations

AE frequency

The model assumes that AEs result in QALY losses and additional costs. The frequency of AEs relating to volume depletion, major hypoglycaemic events, bone fractures, DKA and amputation were based on a *post hoc* analysis of data from DAPA-CKD[19] which took patient exposure into account. Whilst dapagliflozin is known to be associated with increases in genital infection and urinary tract infections (UTIs), these AEs were not routinely collected in DAPA-CKD; hence, the frequencies of these AEs were instead taken from DECLARE-TIMI 58[21] for the proportion of patients with comorbid T2DM at baseline. The AE frequencies applied in each monthly model cycle are shown in Table 25.

Table 25: Monthly AE frequencies

AE	Dapagliflozin	SoC	Source
Volume depletion	[redacted]	[redacted]	DAPA-CKD[19]
Major hypoglycaemic events	[redacted]	[redacted]	
Bone fractures	[redacted]	[redacted]	
DKA	[redacted]	[redacted]	
Amputation	[redacted]	[redacted]	
Genital infections	[redacted]	[redacted]	DECLARE-TIMI 58[21]
UTI	[redacted]	[redacted]	

AE - adverse event; SoC - standard of care; DKA - diabetic ketoacidosis; UTI - urinary tract infection

Health-related quality of life

The company's model includes utility values associated with each health state and disutilities associated with transient events and AEs. These values were estimated from analyses of IPD from DAPA-CKD[19] or were taken from published literature.[20, 39, 40] The utility and disutility values used in the company's model are summarised in Table 26.

Utility values obtained from DAPA-CKD (CKD1 to CKD5 (pre-RRT), hHF, AKI and selected AEs)

Health utility values for states CKD1-5 (pre-RRT) were based on data collected within DAPA-CKD.[19] DAPA-CKD included data collection using the EQ-5D-5L questionnaire at randomisation, day 120,

day 240, day 360 and every 12 months thereafter, as well as at the study closure visit or at the premature treatment discontinuation visit.[1] The company mapped the available EQ-5D-5L data to the 3L version using the algorithm reported by Van Hout *et al.*[49] The company fitted a mixed effects model to the data to account for repeated measures and within-patient correlation with adjustments for age, sex, T2DM status, CKD stage, uACR category, hospitalisation for HF, hyperkalaemia, AKI, volume depletion, hypoglycaemia, fracture, amputation, genital infection and UTI.[1] Further details of the mixed effect model, including the estimated model coefficients, are available from Section B.3.4.1 of the CS.[1]

Other utility values sourced from the literature (dialysis, transplant and alternative AE estimates)
Utility values for the dialysis and transplant health states were obtained from a study which reported EQ-5D estimates for 1,251 patients with kidney failure who had received renal transplants compared to those receiving haemodialysis, peritoneal dialysis or were waiting to start dialysis (Lee *et al*.[39]). The utility value for the dialysis state was calculated as a weighted average of EQ-5D values for haemodialysis (utility = 0.44, proportion = 0.76) and peritoneal dialysis (utility = 0.53, proportion = 0.24). The utility value for the transplant state was taken directly from the Lee *et al*. publication.

Whilst the company's mixed effects model included all AEs included in the economic model, the CS[1] highlights that the direction of effect was not clinically plausible for volume depletion and major hypoglycaemic events, as the model suggests these AEs are associated with improved HRQoL. Instead, disutility values for these events were taken from alternative sources (DAPA-HF[20] and Currie *et al*.[40])

Table 26: HRQoL parameters included in the company's model

Health state utility values		
Health state	**Mean utility**	**Source**
CKD 1	[redacted]	DAPA-CKD[19]
CKD 2		
CKD 3a		
CKD 3b		
CKD 4		
CKD 5 (pre-RRT)		
Dialysis	0.46	Lee *et al*.[39]
Transplant	0.71	
Disutilities applied to transient events		
hHF	[redacted]	DAPA-CKD[19]
AKI		
Disutilities applied to AEs		
Volume depletion	0.05	DAPA-HF[20]
Major hypoglycaemic events	0.01	Currie *et al*.[40]
Fractures	[redacted]	DAPA-CKD[19]
DKA	0.00	Assumption
Amputation	[redacted]	DAPA-CKD[19]
Genital infections		
UTI		

CKD - chronic kidney disease; RRT - renal replacement therapy; hHF - hospitalisation for heart failure; AKI - acute kidney injury; AE - adverse event; diabetic ketoacidosis; UTI - urinary tract infection

Resource use and costs

The model includes costs associated with: (i) drug acquisition; (ii) disease management (health state costs for CKD1-5); (iii) dialysis (iv) transplantation; (v) the management of hHF and AKI, and (vi) the management of AEs (see Table 27).

Table 27: Summary of costs applied in the company's model

Cost parameter	Dapagliflozin (plus SoC)*	SoC
Drug acquisition cost per month	£41.02†	£1.27
Disease management - CKD1-3b (per month)	£100.95	£100.95
Disease management – CKD4 (per month)	£353.47	£353.47
Disease management – CKD5 (per month)	£1,239.35	£1,239.35
Disease management – dialysis (per month)	£2,696.70	£2,696.70
Disease management – transplant (initial cost, once-only)	£27,032.64	£27,032.64
Disease management – transplant (maintenance cost, per month)	£495.75	£495.75
Cost per hHF event	£2,005.28	£2,005.28
Cost per AKI event	£1,875.63	£1,875.63
AEs (per cycle)	[redacted]	[redacted]

SoC - standard of care; CKD - chronic kidney disease; hHF - hospitalisation for heart failure; AKI - acute kidney injury; AE - adverse event

** Includes drug costs for SoC (cost of dapagliflozin excluding SoC is £39.75)*

† The company's indirect comparison of dapagliflozin and canagliflozin assumes equivalent costs between the two options

CKD - chronic kidney disease; SoC - standard of care; hHF - hospitalisation for heart failure; AKI - acute kidney injury; AE - adverse event

(i) Drug acquisition costs

The drug treatments included in the model, the proportion of patients assumed to be receiving each drug and their estimated costs are summarised in Table 28. The model does not include any adjustments for relative dose intensity (RDI) or drug wastage.

Table 28: Dosing and drug costs (annual and per monthly cycle) for treatments included in the company's model (adapted from CS, Tables 32 and 33)

Treatment group	Drug	Dosage schedule (daily)	% treatment allocation	Drug costs (unit costs, annual)	Drug costs (weighted, annual)	Drug costs (weighted, monthly)
Dapagliflozin*	Dapagliflozin	10mg	100.00%	£476.98	£476.98	£39.75
SoC	Ramipril	10mg	[redacted]	£4.30	[redacted]	[redacted]
	Losartan	100mg	[redacted]	£9.39	[redacted]	[redacted]
	Irbesartan	300mg	[redacted]	£34.54	[redacted]	[redacted]
	Atorvastatin	80mg	[redacted]	£14.86	[redacted]	[redacted]
	Aspirin	150mg	[redacted]	£3.43	[redacted]	[redacted]
	Total	**-**	**-**	**£66.52**	**£15.28**	**£1.27**

** Excludes cost of SoC drug treatments*

The list price for dapagliflozin is £36.59 per pack of 10mg tablets (28 tablets).[22] In line with the draft SmPC,[33] dapagliflozin is assumed to be given at a fixed dose of 10mg once daily. Discontinuation of dapagliflozin is assumed at a constant rate, based on an estimated annual probability of [redacted] in DAPA-

CKD,[1] or whilst patients are in the transplant health state. The model assumes that patients receiving dapagliflozin will not require any additional tests or follow-up appointments.

SoC is assumed to include: ramipril (an ACE inhibitor), losartan or irbesartan (ARBs), atorvastatin (a statin) and aspirin (an antiplatelet). The daily dosage for each drug is based on their respective SmPCs,[50-54] whilst the proportion of patients receiving each drug type is based on the CPRD dataset.[15] Unit costs for each drug were taken from the Commercial Medicines Unit (CMU) Electronic Market Information Tool (eMIT).[41] The same SoC drug costs are applied in both treatment groups and patients are assumed to receive these treatments indefinitely.

Canagliflozin is included as a comparator in one of the company's scenario analyses in people with CKD and comorbid T2DM. Canagliflozin has a list price of £39.20 per pack of 100mg tablets (30 tablets).[22] The maximum daily dose for canagliflozin is not reported in the CS;[1] the ERG believes that in line with its SmPC, a fixed dose of 100mg once daily has been assumed in the model. The ERG notes that the cost of canagliflozin is identical to that for dapagliflozin.

(ii) Disease management costs

Health care resource use related to the management of CKD includes costs associated with: (i) hospital care for health states CKD1-5 (pre-RRT); (ii) dialysis; (iii) kidney transplantation and (iv) hospitalisation for the management of hHF and AKI. These costs are summarised in Table 29.

Table 29: Costs associated with CKD health states, dialysis, transplantation and transient events

Health State/Event	Annual cost	Monthly cost	Cost per event
CKD1	£1,211.41	£100.95	-
CKD2	£1,211.41	£100.95	-
CKD3a	£1,211.41	£100.95	-
CKD3b	£1,211.41	£100.95	-
CKD4	£4,241.65	£353.47	-
CKD5 (pre-RRT)	£14,872.17	£1,239.35	-
Dialysis	£32,360.41	£2,696.70	-
Transplant (initial cost)	-	-	£27,032.64
Transplant (maintenance cost)	£5,948.98	£495.75	-
hHF	-	-	£2,005.28
AKI	-	-	£1,875.63

CKD - chronic kidney disease; RRT - renal replacement therapy; hHF - hospitalisation for heart failure; AKI - acute kidney injury

Monthly costs of disease management for CKD1-5 (pre-RRT) are based on annual costs reported by Kent *et al*. 2015,[11] which includes only hospital care (inpatient admissions, day cases or outpatient attendances). Costs associated with dialysis are based on annual costs reported in NICE Guideline 107[43]

and include costs associated with the dialysis procedure, transport to the dialysis centre and other costs, such as access procedures, outpatient appointments and the management of complications. Costs were uplifted to 2019/2020 prices using inflation indices published by the Personal Social Services Research Unit (PSSRU).[44]

(iii) Costs associated with transplant surgery and management

Costs associated with kidney transplantation include: (i) the initial costs of the transplant procedure, which are applied once-only to patients entering the transplant health state, and (ii) ongoing maintenance costs, which are applied in all cycles to patients in the transplant state (see Table 29). The former were obtained from NHS Reference Costs 2018/2019,[42] including codes related to kidney transplant which includes the surgery, and pre and post-transplant examinations (currency codes LA01A, LA02A, LA03A, LA12A, LA13A, LA11Z, LA14Z from Total Healthcare Resource Group [HRGs] estimates). The latter were taken from a fact sheet published by NHS Blood and Transplant.[55]

(iv) Transient acute events management costs

The costs of hHF and AKI events were derived from a group of procedures related to HF (codes EB03A to EB03E, non-elective long and short stays) and AKI (codes LA07H to LA07P, LE01A and B and LE02A and B, from Total HRGs) from NHS Reference Costs 2018/2019.[42] Each hHF and AKI event is estimated to cost £2,005.28 and £1,875.63, respectively.

(iv) AE management costs

Costs related to the management of treatment-specific AEs are included in each model cycle (see Table 30). Monthly AE frequencies were based on data from DAPA-CKD[19] and DECLARE-TIMI 58.[21] Unit costs were taken from NHS Reference Costs 2018/2019,[42] Curtis *et al.*,[44] published literature[45-47] and assumptions. Monthly costs of managing AEs were estimated to be £14.47 for the dapagliflozin group and £15.20 for the SoC group.

Table 30: Monthly frequencies, unit costs and total monthly costs for AEs used in the model

AE	Frequency of AEs (monthly)		Unit cost	Total costs (weighted, monthly)	
	Dapagliflozin	SoC		Dapagliflozin	SoC
Volume depletion	[redacted]	[redacted]	£40.10	[redacted]	[redacted]
Major hypoglycaemic events	[redacted]	[redacted]	£450.67	[redacted]	[redacted]
Bone fractures	[redacted]	[redacted]	£2,362.87	[redacted]	[redacted]
DKA	[redacted]	[redacted]	£2,237.47	[redacted]	[redacted]
Amputation	[redacted]	[redacted]	£13,540.96	[redacted]	[redacted]
Genital infections	[redacted]	[redacted]	£40.10	[redacted]	[redacted]
UTI	[redacted]	[redacted]	£40.10	[redacted]	[redacted]
Total	-	-	-	**£14.47**	**£15.20**

AE - adverse event; SoC - standard of care; DKA - diabetic ketoacidosis; UTI - urinary tract infection

Model evaluation methods

The CS[1] presents ICERs for dapagliflozin versus SoC for the overall CPRD population based on both the deterministic and probabilistic versions of the model. The results of the probabilistic sensitivity analysis (PSA) are presented as cost-effectiveness planes and cost-effectiveness acceptability curves (CEACs), based on 1,000 Monte Carlo simulations. The results of the deterministic sensitivity analyses (DSAs) are also presented graphically. The CS also reports on a number of subgroup and scenario analyses which estimate the ICER for dapagliflozin in various CPRD and DAPA-CKD subgroups[15, 19] (see Table 18) and which explore the impact of alternative assumptions regarding: OS, discontinuing treatment in patients upon initiation of dialysis, patients leaving the model at RRT, and using alternative disutilities for AEs. The scenario analyses also include an indirect comparison of dapagliflozin versus canagliflozin in the DAPA-CKD comorbid T2DM population, [redacted].

5.2.5 Company's original model results

This section describes the results of the company's original submitted model. Following the clarification round, the company submitted an updated version of the model which addresses several concerns raised by the ERG.[16] The results of the company's updated base case model and additional scenario analyses presented in the company's clarification response are briefly summarised in Section 5.3.5.

Central estimates of cost-effectiveness

Table 31 presents the central estimates of cost-effectiveness for the overall CPRD population generated using the company's original model. A breakdown of health outcomes and costs is presented in Table 32. The probabilistic version of the model suggests that dapagliflozin is expected to generate an additional 0.76 QALYs at an additional cost of £5,134 per patient; the corresponding ICER is expected to be £6,717 per QALY gained. The deterministic version of the model leads to a slightly lower ICER of £6,655 per QALY gained.

Table 31: Central estimates of cost-effectiveness, overall CPRD population, dapagliflozin versus SoC

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER
Probabilistic model							
Dapagliflozin	11.82	6.83	£56,839	1.47	0.76	£5,134	**£6,717**
SoC	10.35	6.07	£51,706	-	-	-	-
Deterministic model							
Dapagliflozin	11.67	6.80	£56,526	1.47	0.77	£5,118	**£6,655**
SoC	10.19	6.03	£51,408	-	-	-	-

CKD - chronic kidney disease; LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio

** Undiscounted*

Table 32: Breakdown of QALY gains and costs, overall CPRD population, dapagliflozin versus SoC

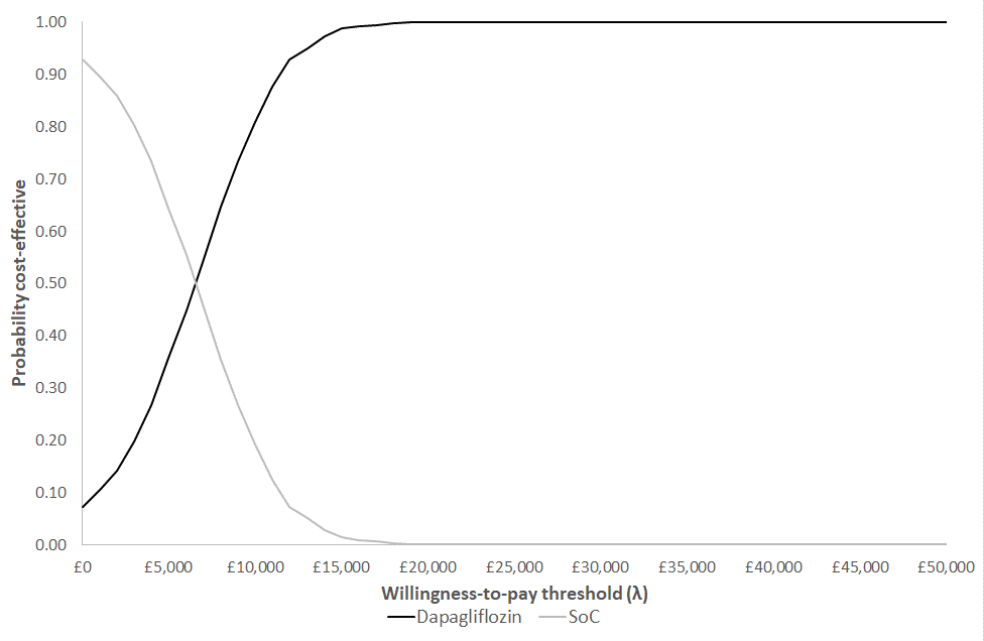
Model estimate	Dapagliflozin	SoC	Incremental
LYGs*	11.67	10.19	1.47
QALYs CKD stages 1-5 (pre-RRT)	6.15	5.39	0.76
QALYs dialysis	0.41	0.40	0.01
QALYs transplant	0.25	0.25	0.00
QALY losses AEs and transient events	-0.01	-0.01	0.00
Total QALYs	6.80	6.03	0.77
Drug costs	£3,212	£126	£3,086
CKD management costs (excluding RRT)	£19,926	£18,498	£1,428
Dialysis costs	£28,395	£27,858	£537
Transplant costs	£2,932	£2,939	-£7
AEs and transient event costs	£2,060	£1,987	£73
Total costs	£56,526	£51,408	£5,118

SoC - standard of care; LYG - life year gained; QALY - quality-adjusted life year; CKD - chronic kidney disease; RRT - renal replacement therapy; AE - adverse event
** Undiscounted*

Company's PSA results

Figure 11 presents CEACs for dapagliflozin versus SoC within the overall CPRD population. Assuming a willingness-to-pay (WTP) threshold of £20,000 per QALY gained, the company's model estimates that the probability that dapagliflozin generates more net benefit than SoC is approximately 1.0.

Figure 11: CEACs, overall CPRD population, dapagliflozin versus SoC (re-drawn by the ERG)

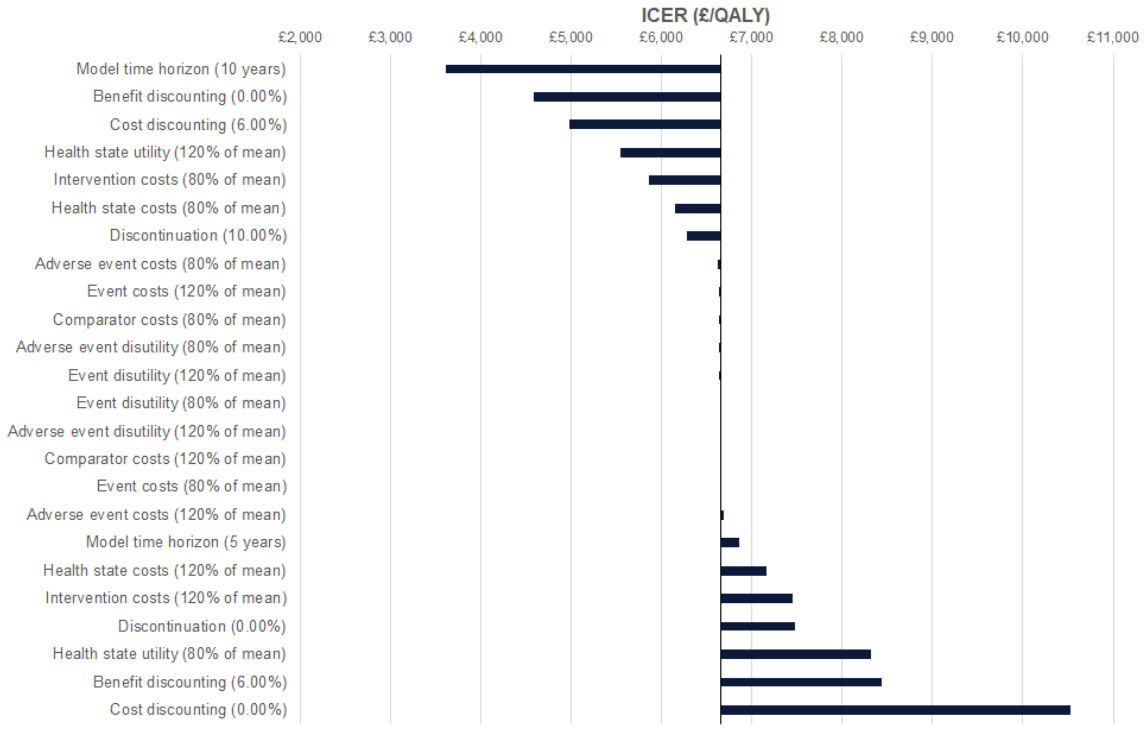


SoC - standard of care

Company's DSA results

Figure 12 presents the results of the company's DSAs for the overall CPRD population. The ICERs generated from the DSAs range from £3,616 per QALY gained (model time horizon = 10 years) to £10,527 per QALY gained (discount rate for costs = 0%).

Figure 12: Deterministic sensitivity analysis results, overall CPRD population, dapagliflozin versus SoC (generated by the ERG using the company's model)



Company's subgroup and scenario analysis results

Table 33 presents the results of the company's subgroup and scenario analyses. The alternative analyses across subgroups of patients in the CPRD dataset and the DAPA-CKD trial[15, 19] consistently indicate that the ICER for dapagliflozin versus SoC is below £7,000 per QALY gained. [redacted]. The use of alternative parametric survival models for OS results in comparatively more favourable ICERs, with all models except for the exponential distribution leading to a situation in which dapagliflozin dominates SoC. Whilst the CS does not present a scenario in which OS is modelled using the 2-parameter gamma distribution, an additional analysis undertaken by the ERG suggests that dapagliflozin is also dominant using this model. The scenarios in which patients discontinue dapagliflozin upon initiating dialysis or exit the model at dialysis or transplant (SA17 and SA18) lead to lower ICERs relative to the base case.

The use of alternative disutilities for major hypoglycaemic events, DKA and amputation have virtually no impact on the ICER.

Table 33: Company's scenario analysis results (generated by the ERG using the company's model)

Scenario analysis no.	Scenario	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER
-	Company's base case	1.47	0.77	£5,118	**£6,655**
SA1	DAPA-CKD overall population	1.78	0.84	£4,563	£5,457
SA2	CPRD subgroup – with comorbid T2DM	1.45	0.77	£5,110	£6,671
SA3	CPRD subgroup – without comorbid T2DM	1.48	0.77	£5,096	£6,619
SA4	CPRD subgroup – with uACR <200mg/g	1.46	0.76	£5,054	£6,608
SA5	CPRD subgroup – with uACR ≥200mg/g	1.50	0.78	£5,137	£6,558
SA6	DAPA-CKD subgroup – with comorbid T2DM (vs. SoC)	1.72	0.83	£4,675	£5,648
SA7	DAPA-CKD subgroup – with comorbid T2DM (vs. canagliflozin)	[redacted]	[redacted]	[redacted]	[redacted]
SA8	DAPA-CKD subgroup – without comorbid T2DM	1.92	0.85	£4,357	£5,098
SA9	DAPA-CKD subgroup – with comorbid CVD	1.64	0.82	£4,891	£5,971
SA10	DAPA-CKD subgroup – without comorbid CVD	1.87	0.85	£4,405	£5,213
SA11	DAPA-CKD subgroup – without comorbid T2DM and without comorbid CVD	1.99	0.86	£4,287	£4,979
SA12	OS - exponential	1.86	0.91	£5,864	£6,447
SA13	OS – Weibull	1.42	0.76	-£519	Dominating
SA14	OS – log-normal	1.23	0.67	-£3,087	Dominating
SA15	OS – log-logistic	1.31	0.72	-£1,540	Dominating
SA16	OS – generalised gamma	1.29	0.71	-£3,675	Dominating
SA17	Patients discontinue upon initiating dialysis	1.29	0.71	£1,672	£2,361
SA18	Patients exit model at RRT	1.41	0.76	£4,398	£5,756
SA19	Alternative disutilities for major hypoglycaemic events, DKA and amputation	1.47	0.77	£5,118	£6,655

SA - scenario analysis; LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; CPRD - Clinical Practice Research Datalink; uACR - urine albumin-to-creatinine ratio; T2DM - type 2 diabetes mellitus; SoC - standard of care; CVD - cardiovascular disease; OS - overall survival; RRT - renal replacement therapy; DKA - diabetic acidosis
** Undiscounted*

5.3 Critical appraisal of the company's model

The ERG adopted a number of approaches to explore, interrogate and critically appraise the company's economic analysis and the underlying model upon which this is based. These included:

- Consideration of key items contained within published economic evaluation and health economic modelling checklists.[35, 56]
- Scrutiny of the company's model by health economic modellers and discussion of issues identified amongst the members of the ERG.
- Double-programming the deterministic version of the company's model using Excel formulae to fully assess the logic of the model structure, to draw out any unwritten assumptions and to identify any apparent errors in the company's implementation of the model.
- Examination of the correspondence between the company's executable model and its description in the CS.[1]
- Replication of the results of the company's base case analysis, PSA, DSAs and scenario analyses reported in the CS.
- Where possible, checking key parameter values used in the company's model against their original data sources.
- The use of expert clinical input to judge the credibility of the company's economic analyses and the assumptions underpinning the model.

5.3.1 Model verification by the ERG

Table 34 presents a comparison of the results of the deterministic version of the company's base case model and the ERG's double-programmed model. As shown in the table, the ERG's results are very similar to those generated using the company's model. The ERG was also able to generate similar results for each of the company's scenario and subgroup analyses using the double-programmed model. The ERG's double-programming exercise revealed some minor implementation errors and conceptual issues in the company's model. These are discussed in detail in Section 5.3.4 and are addressed as part of the ERG's exploratory analyses in Section 5.4.

Table 34: Comparison of results generated using the company's model and the ERG's double-programmed model

	LYGs*	QALYs	Cost	ICER
Company's model				
Dapagliflozin	11.67	6.80	£56,526	-
SoC	10.19	6.03	£51,408	-
Incremental	1.47	0.77	£5,118	**£6,655**
ERG's double-programmed model				
Dapagliflozin	11.67	6.80	£57,561	-
SoC	10.19	6.03	£52,411	-
Incremental	1.48	0.77	£5,150	**£6,672**

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; SoC - standard of care
** Undiscounted*

5.3.2 Correspondence of the model inputs and the original sources of parameter values

Where possible, the ERG checked the model input values against their original sources, although many of these were based on analyses of IPD data from DAPA-CKD,[19] which were not available to the ERG. As such, the ERG was unable to check the accuracy of the data used to inform most of the transition probabilities, or the statistical models used to estimate risks of mortality, AKI, hHF, or health utility.

The ERG identified several potential discrepancies between the following model input values[1] and their original sources:

- The ERG was unable to exactly replicate the estimated costs for hHF and AKI based on the NHS Reference Costs codes reported in the CS.[1]
- With respect to the analysis of the DAPA-CKD overall population (company scenario analysis 1), some of the patients' baseline characteristics used in the model do not match the values reported in the study CSR,[19] including the use of ACE inhibitors, ARBs, mineralocorticoid receptor antagonists (MRAs), diuretics, and prior incidence of stroke. The ERG is unclear why the values used in the model do not reflect the FAS.
- Some of baseline characteristics in DAPA-CKD (e.g. uACR) are expressed using different thresholds compared with those reported in the CSR and could not be checked by the ERG.

The other model parameters appear to be consistent with their original sources.

5.3.3 Adherence of the company's model to the NICE Reference Case

The extent to which the company's economic analyses adhere to the NICE Reference Case[57] is summarised in Table 35.

Table 35: Adherence of the company's economic analysis to the NICE Reference Case

Element	Reference case	ERG comments
Defining the decision problem	The scope developed by NICE	The company's economic analysis is generally in line with the final NICE scope.[17] The final scope defines the intervention as *"dapagliflozin in combination with optimised standard care (including treatment with an ACE inhibitor or ARB)"* and the comparator as *"established clinical management without dapagliflozin."* The company's economic analysis includes SoC as a single comparator within the base case analysis. SoC is assumed to include a mix of ramipril, irbesartan, losartan, atorvastatin and aspirin. However, based on the CPRD dataset, [redacted] of the modelled population in both modelled treatment groups is assumed to neither receive an ACE inhibitor nor an ARB. As such, the model assumes that [redacted] of the target population is not currently receiving any treatment which directly targets CKD progression. The ERG believes there is uncertainty surrounding whether the CPRD population used in the model is fully consistent with the target CKD population in whom dapagliflozin would be used. The company's scenario analyses include an indirect comparison of dapagliflozin versus canagliflozin in patients with CKD and comorbid T2DM. [redacted] This comparator is not explicitly listed in the NICE scope.
Comparator(s)	As listed in the scope developed by NICE	
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	The economic analysis adopts a direct health perspective, including health effects on patients with CKD with/without comorbid conditions.
Perspective on costs	NHS and PSS	Costs include those borne by the NHS and PSS, although some relevant cost components appear to be missing from the model (see Section 5.3.4, critical appraisal point [10]).
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	The company's model adopts a cost-utility approach. Results are presented in terms of the incremental cost per QALY gained.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The model adopts a [redacted] year (lifetime) horizon. At the end of the time horizon, some patients are predicted to still be alive (see Section 5.3.4, critical appraisal point [7]).

Element	Reference case	ERG comments
Synthesis of evidence on health effects	Based on systematic review	Transition probabilities between health states, OS and risks of transient events (hHF and AKI) for patients with CKD stages 1-5 (pre-RRT) were derived from DAPA-CKD, the pivotal trial of dapagliflozin versus SoC for CKD.[19] An external study (Sugrue *et al*.[38]) was used to inform transitions and mortality risks in people who have undergone RRT (dialysis and/or transplant); based on the information provided in the CS, it is unclear whether an alternative source might be more suitable. OS and transient event risks are generalised to the UK population using data from the CPRD.[15]
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults.	Health utility values for states relating to CKD stages 1-5 (pre-RRT) are based on a linear mixed effects model fitted to EQ-5D data collected in DAPA-CKD.[19] Utility decrements associated with AKI and hHF and most AEs are also based on this model. Utility values for dialysis, transplant and some AEs are based on EQ-5D estimates from the literature.[39]
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	No additional equity weighting is applied to estimated QALY gains.
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	The model includes relevant NHS and PSS costs, uplifted to current values where applicable.
Discount rate	The same annual rate for both costs and health effects (currently 3.5%)	Costs and health outcomes are discounted at a rate of 3.5% per annum.

ERG - Evidence Review Group; NICE - National Institute for Health and Care Excellence; ACE - angiotensin-converting enzyme; ARB - angiotensin II receptor blocker; SoC - standard of care; CPRD - Clinical Practice Research Datalink; CKD - chronic kidney disease; T2DM - type 2 diabetes mellitus; ICER - incremental cost-effectiveness ratio; QALY - quality-adjusted life year; NHS - National Health Service; PSS - Personal Social Services; hHF - hospitalisation for heart failure; AKI - acute kidney injury; RRT - renal replacement therapy; OS - overall survival; EQ-5D - Euroqol 5-Dimensions; AE - adverse event

5.3.4 Key issues identified from the ERG's critical appraisal

This section presents a discussion of the issues identified from the ERG's critical appraisal of the company's original economic analysis. The main issues identified by the ERG are summarised in Box 1. A detailed discussion of these issues is presented in the subsequent sections. Following the clarification round, the company submitted an updated base case model which addresses some of these issues; this model is briefly discussed in Section 5.3.5.

Box 1: Main issues identified from ERG's critical appraisal

1. Model errors
2. Uncertainty surrounding the effectiveness of dapagliflozin in certain subgroups
3. Issues relating to the company's model structure
4. Concerns regarding the application of state-specific survival models and relative treatment effects on OS
5. Concerns regarding CPRD adjustment
6. Concerns regarding plausibility of estimated transition probabilities
7. Issues relating to survival modelling
8. Uncertainty surrounding discontinuation assumptions
9. Issues relating to HRQoL
10. Issues relating to costs
11. Concerns regarding company's model predictions

(1) Model errors

The ERG's double-programming exercise revealed four minor errors in the implemented model:

(i) The model applies the subsequent period matrix one cycle too early in both treatment groups (from Month 4 rather than Month 5)

(ii) Whilst the CS[1] (page 79) states that the model includes a half-cycle correction, this is not included in the implemented model

(iii) The company's model applies a discontinuation probability of zero in the first model cycle; patients cannot discontinue dapagliflozin until the second model cycle

(iv) Drug cost calculations assume that there are 365 days per year, rather than 365.25 days.

The company's clarification response[16] (questions B25 and B28) confirms that items (i) and (ii) above represent errors in the original model and CS, respectively. The company's response (question B27) also acknowledges item (iii) and comments that this relates to the order in which events are applied in the model calculations. Amongst other changes, the company's updated base case model was amended to address items (i) and (iii) (see Section 5.3.5). The updated model does not include half-cycle

correction, although the ERG agrees with the company that this is unlikely to have a material impact on the model results. The issue relating to drug costs (item [iv]) was identified by the ERG after the clarification round; this will have a negligible impact on the ICER and can be disregarded.

(2) Uncertainty surrounding the effectiveness of dapagliflozin in certain subgroups

The anticipated wording of the marketing authorisation for the CKD indication is expected to relate to use of dapagliflozin for [redacted][33] The ERG's clinical advisors noted that there are some patient populations for whom evidence of efficacy for dapagliflozin is weak or absent. In particular, the inclusion criteria for DAPA-CKD[19] required patients to have a uACR of at least 200mg/g (≥22.6mg/mmol) at study entry. The ERG's clinical advisors noted that DAPA-CKD is the only study of an antidiabetic medication in a non-diabetic population; hence, the only evidence for dapagliflozin in a non-diabetic CKD population is in those with proteinuria. The inclusion criteria in DAPA-CKD also required patients to have an eGFR of ≥25ml/min/1.73m;[2] hence, the trial excluded very high-risk patients with CKD stage 5, and very few patients with CKD stage 4 were recruited. The eligibility criteria also excluded patients who had previously undergone organ transplantation and those with T1DM. [redacted] The ERG's clinical advisors commented that dapagliflozin would be an important drug for the management of people with CKD, but they would not use it in populations for whom evidence is lacking or absent. The CS[1] presents further evidence from DAPA-HF[20] and DECLARE-TIMI 58[21] which is intended to support the use of dapagliflozin regardless of uACR or CKD category. However, the ERG notes that the company's economic model is based on effectiveness evidence drawn exclusively from DAPA-CKD, whilst DAPA-HF and DECLARE-TIMI 58 are used only to inform the impacts of selected AEs.

The ERG also notes that whilst the company's economic analysis is intended to reflect the UK population through the use of patient characteristics from the CPRD dataset (people with CKD stages 1-4),[15] this raises some questions regarding the definition of the target population for dapagliflozin and how the drug would be used in clinical practice. The CS[1] states that dapagliflozin is expected to be used *"in addition to optimised SoC, which may include ACE inhibitors and ARBs."* In DAPA-CKD,[19] 97% of patients were receiving an ACE inhibitor or ARB at baseline. However, in the CPRD dataset, [redacted] of people were not receiving either of these therapies. In response to a request for clarification from the ERG[16] (question B1), the company commented that: (i) some people with CKD in the CPRD dataset might not be eligible for ACE inhibitor/ARB therapy under current NICE CKD guidelines; (ii) some people may have started but discontinued ACE inhibitors/ARBs due to AEs; (iii) some people will not be able to tolerate ACE inhibitors/ARBs and (iv) the mechanism of action for dapagliflozin is both

complementary to and distinct from ACE inhibitors/ARBs and the benefits of dapagliflozin have been seen in people not receiving these therapies (i.e. in subgroup analyses of DECLARE-TIMI 58[21] and DAPA-HF[20]). The company's clarification response also claims that *"the treatment effect with dapagliflozin is expected to be consistent regardless of background therapy."* The ERG's clinical advisors agreed that many patients with CKD do not receive ACE inhibitor/ARB therapy in practice for a variety of reasons, but commented that the strongest evidence for the effectiveness of dapagliflozin in treating CKD is from DAPA-CKD, in which almost all patients were receiving ACEi/ARBs as background therapy. They considered it possible that the benefits of SGLT2 inhibitors might be similar in people with CKD and proteinuria who are not treated with ACE inhibitors/ARBs, but commented that the evidence is much less certain in these groups and that the use of dapagliflozin in this context would be going beyond the available trial data from DAPA-CKD. The clinical experts further commented that the supporting subgroup analyses from DECLARE-TIMI 58 and DAPA-HF are limited. In particular, subgroup analyses for the renal outcome in DECLARE-TIMI 58 appear to suggest lower treatment effects for patients not treated with ACE inhibitors/ARBs at baseline compared to those receiving these therapies (HR = 0.77, 95% CI 0.44 -1.37 versus HR = 0.50, 95% CI 0.39-0.63),[58] which at least allows the hypothesis that SGLT inhibitors may provide less benefit for patients with T2DM who, for whatever reason, are not treated with ACE inhibitors/ARBs. In addition, the experts highlighted that in DAPA-HF, 94% of patients were receiving ACE inhibitors, ARBs or sacubitril-valsartan (assuming that no patients received combinations of these therapies); hence, this trial does not provide much information regarding the effectiveness of dapagliflozin in patients not receiving these therapies.

(3) Issues relating to the company's model structure

Overall, the ERG and its clinical advisors consider the company's overall model structure to be reasonable. eGFR is routinely measured in clinical practice and CKD stage categories represent an appropriate metric through which to characterise progression of the disease. In addition, the ERG's clinical advisors commented that it is appropriate to assume that mortality risk will increase and HRQoL will decrease with advancing CKD stage. The clinical advisors also considered the inclusion of AKI and hHF to be relevant as these events are associated with increases in acute care costs and decreases in HRQoL. The advisors further commented that the structural assumption that relative treatment effects will be lost upon discontinuation of dapagliflozin is reasonable for this class of drug.

The ERG notes two minor issues relating to the company's general model structure:

- The ERG's clinical advisors commented that being hospitalised for HF is associated with an increased risk of death. However, the company's model does not include a causal link between transient events and mortality. It is however possible that these deaths are implicitly captured in the overall mortality risks estimated within each health state.

- The model applies the relative treatment effect on OS from the multivariable survival analysis and the relative treatment effect on hHF/AKI from the GEE models, both of which are fitted to data from DAPA-CKD,[19] to patients who are in the dialysis health state. The CS[1] does not provide any evidence to support the assumption that patients on dialysis who are still receiving dapagliflozin have lower event risks compared to those who are receiving SoC alone. The company's clarification response includes an additional scenario analysis in which the treatment effect on OS was removed from the dialysis state; this resulted in a lower ICER for dapagliflozin (see Section 5.3.5).

(4) Concerns regarding the application of state-specific survival models and relative treatment effects on OS

Whilst the ERG considers the company's economic model structure to be reasonable, the ERG has some concerns regarding how the model uses evidence to estimate OS in the SoC group and relative survival benefits in the dapagliflozin group. As described in Section 5.2.4, the company's model applies state-specific mortality risks estimated from the multivariable survival model fitted to OS data from DAPA-CKD,[19] and models transitions through the health states using matrix multiplication based on DAPA-CKD and external data. Relative treatment effects for dapagliflozin versus SoC on survival are thus modelled in two ways: (a) directly - through lower risks of mortality within each CKD state based on the application of a treatment-related HR derived from the multivariable survival model, and (b) indirectly - through the use of transition matrices which reflect slower disease progression for dapagliflozin than SoC. The ERG's concerns on this aspect of the model are as follows:

(i) The appropriateness of the company's approach to modelling progression and death rests on the ability of the multivariable survival model to do two things: (a) to characterise the cumulative risk of death over time for patients with a given baseline CKD stage, which fully accounts for the impact of disease progression observed in the trial follow-up, independent of treatment received (estimated as HRs for CKD stages), and (b) to isolate the additional relative treatment effect of dapagliflozin versus SoC over and above any OS impacts mediated through changes in CKD stage (estimated as the treatment-related HR which is applied across all CKD stages). Within the company's clarification response[16] (question B31) and the factual accuracy check,[37] the company clarified that CKD stage was included as a time-updated covariate in the multivariable survival model. Including post-randomisation covariates in an analysis is unconventional. No information was provided in the CS or the clarification response on how this was done, and the fully specified survival model and the code used to fit the model were not provided. As a general point, the ERG notes that the inclusion of post-randomisation covariates in survival models can lead to problems in determining causality. In particular, if part of the causal effect of treatment is through CKD stage, this approach will block that effect, and the resulting model coefficients may not be meaningful.

(ii) State-specific mortality risks are estimated in the model by applying a value of 1.0 to the relevant eGFR category for each CKD state, whilst holding all other covariables at their mean values. The ERG believes that this is an incorrect interpretation of the multivariable model output, and that it reflects a "mean of covariates" approach, which has been shown to lead to bias when estimating survival functions.[59] The ERG believes that predicted OS from the multivariable model should instead be estimated using the "corrected group prognosis" method, whereby survival models are estimated for each level of categorical covariable, which are then weighted according to their incidence. As part of their factual accuracy check,[37] the company stated that such an approach would be prohibitively complex and that it would be unlikely to have a material impact on the model results. The ERG notes that the extent of bias on the model predictions and the impact on the ICER is not known.

(iii) As discussed later in critical appraisal point [11], the company's unadjusted economic model (which reflects characteristics of the DAPA-CKD trial population), over-predicts OS in both treatment groups. As the ERG has not seen the company's statistical code or the data used for model-fitting, the precise source of the problem is not fully clear. However, it appears that the risks of progression and death may have been mis-specified and this may be a consequence of issues (i) and/or (ii) described above.

The ERG believes that given the data available from DAPA-CKD[19] and the company's general model structure, it may have been more appropriate to use an alternative approach to estimate health state transitions and survival together (e.g. a time-homogeneous Markov model[60]). This could have been implemented as a piece-wise model (split by pre- and post-Month 5 intervals) and may also have allowed for the inclusion of covariates to enable adjustment to the CPRD population. It is likely that this approach would have avoided any potential risks of double-counting treatment effects on OS; however, it may impose more restrictive assumptions regarding the hazard of death over time.

(5) Concerns regarding CPRD adjustment

The company's base case model and subgroup analyses include the adjustment of risks of mortality, AKI and hHF to reflect the overall CPRD population.[15] Transition probabilities are based on unadjusted values observed in DAPA-CKD.[19] These same transition probabilities are applied across all subgroup analyses, irrespective of baseline uACR or the presence or absence of comorbidity. The ERG notes the following observations regarding the company's adjustment approach:

- As a general principle, it may be reasonable to adjust the model population to better reflect the target population. However, as discussed under critical appraisal point [2], the ERG is unsure whether the CPRD population reflects the target population of CKD patients in whom dapagliflozin would be used in practice, as many of these patients were not receiving an ACE inhibitor or ARB therapy.

- The company's decision to apply these adjustments increases the complexity of the statistical models required to predict risks of mortality, AKI and hHF. As discussed in critical appraisal point [4], the ERG believes that the implementation of the outputs of the multivariable survival model in the economic model is problematic.
- The ERG considers it inconsistent to adjust some model parameters to the target population, whilst leaving others unadjusted. Specifically, the ERG and their clinical advisors did not consider it plausible that the transition probabilities estimated for the overall DAPA-CKD population would be identical in the overall CPRD population, or that they would remain the same across all subgroups of patients with or without comorbidity or with different uACR levels. As such, the ERG has concerns regarding the reliability of the results of the subgroup analyses presented in the CS.[1]

The company's clarification response[16] (question B9) comments that the company is unaware of methods for adjusting transition probabilities which are equivalent to those used to adjust the survival equations and that the only feasible approach would be to sub-divide the patient count data from DAPA-CKD[19] according to the specific subgroups of interest. The company highlights that this would reduce sample size for each analysis and that DAPA-CKD is considered to be representative of UK clinical practice. The company's response provides additional economic subgroup analyses based on this subgrouping approach (see Section 5.3.5). The ERG acknowledges that these additional analyses provide some exploration of the impact of estimating subgroup-specific transition probabilities, albeit only within the DAPA-CKD trial population, rather than the CPRD population.[15]

(6) Concerns regarding plausibility of estimated transition probabilities

The ERG notes that some of the estimated transition probabilities applied in the company's model do not appear to be clinically plausible. For example, patients in CKD1 have a higher probability of undergoing dialysis or transplant compared with patients in CKD2-4, and patients can transition from CKD5 to CKD1 in a single 1-month cycle (see Table 19 and Table 20). In response to a request for clarification from the ERG (question B3),[16] the company stated that these unexpected probabilities were a consequence of applying non-informative priors of 1.0 to all transitions and that this skewed some of the estimated transition probabilities where observed data were lacking. The company's response states that they attempted resolve this problem through the use of alternative priors, but found that this caused further problems in estimating probabilities for other transitions. Instead, the company presented an additional scenario analysis in which the priors for these transitions were set equal to zero (see Section 5.3.5). The company's additional scenario analysis suggests that the impact on the ICER is negligible.

(7) Issues relating to survival modelling

(a) Absence of a general population mortality constraint

The company's economic model applies a Gompertz survival model in states CKD1-5 (pre-RRT) and exponential models for the dialysis and transplant health states. Within the company's original economic model, these survival distributions are not constrained by mortality risks in the general population (e.g. from life tables). Figure 13 presents a comparison of monthly mortality risk for the modelled dapagliflozin and SoC groups compared with age- and sex-matched general population risks. The figure shows that, for older patients, the model-predicted mortality risk is lower than that for the general population for both modelled treatment groups; this implies that it is better to have CKD than not. The company's updated model includes a general population mortality constraint based on ONS life tables for the UK (see Section 5.3.5).

Figure 13: Comparison of monthly risk of death for modelled treatment groups versus general population life tables

SoC - standard of care

(b) Concerns regarding company's multivariable survival modelling

The CS[1] provides limited detail regarding survival modelling, particularly with respect to how judgements were made regarding selection of covariables and how the preferred model was selected. Covariables were selected for inclusion in the multivariable models using a backwards stepwise elimination procedure and clinical judgment; however, the CS[1] does not specify the form of multivariable survival model that was used during this process. Ideally, covariate selection should have

been conducted individually for each parametric model type thereby ensuring consistency (rather than selecting covariates using a Cox model and then fitting parametric models). However, no details were provided on this aspect of the company's analysis.

The survival models fitted were limited to standard parametric models: more flexible models were not considered. In their clarification response[16] (question B4a), the company refers to TSD 14 (Latimer *et al.*[61]) and states that it would be "*inconsistent with the provided guidance to continue investigating more flexible methods*". The ERG disagrees with this interpretation. More flexible models may not be appropriate given the immaturity of the data; however, this was not well justified by the company.

The CS[1] states that the company's survival analysis followed best practice guidelines, including TSD 14.[61] This recommends a five-step model selection procedure:

(i) Consideration of whether there is a proportional treatment effect over time or whether treatment arms should be modelled separately, using log cumulative hazard plots and quantile-quantile plots.
(ii) Consideration of which parametric models are appropriate given the shape of the hazard functions and survival curves
(iii) Consideration of internal validity using visual inspection and statistical tests of goodness-of-fit
(iv) Consideration of external validity including the plausibility of the extrapolated long-term treatment effect
(v) Choice of the most appropriate model and sensitivity analysis using alternative plausible models.

These steps are discussed in turn below.

Step (i) Consideration of proportional treatment effect over time

The models considered by the company all assume a proportional treatment effect over time (an HR for PH models or an AF for AFT models); however, no evidence is presented in the CS[1] to support this assumption. In their clarification response[16] (question B4d), the company presented validation of the PH assumption using scaled Schoenfeld residuals and a statistical test for proportionality. However, the fitted Cox PH model did not include all of the covariables selected for inclusion in the final model and statistical tests are often of limited value when data are immature. Log cumulative hazard plots were not presented.

Step (ii) Consideration of appropriateness of candidate survival models

In their response to clarification question B4b,[16] the company stated that models such as the exponential, log-logistic and log-normal were considered to have "*poor clinical face validity*" whereas the Gompertz

model was considered to have "*good marginal properties.*" However, the empirical hazard function for the OS data from the DAPA-CKD trial[19] was not shown to verify these claims.

Step (iii) Consideration of goodness-of-fit

Goodness-of-fit based on all AIC and BIC was presented in the CS[1] for all parametric models and a comparison of the final fitted models to the observed Kaplan-Meier survival estimates was not provided by the company within the CS or the company's clarification response.[16] The CS states that with the exception of the gamma distribution, goodness-of-fit was comparable between the models. Differences in AIC/BIC of up to 5 are generally considered negligible; however, the chosen Gompertz model had an AIC and BIC that was 5.46 and 10.41 higher than the best fitting model according to each metric.

Step (iv) Consideration of external validity and plausibility

The CS[1] states that external plausibility was considered based on clinical judgement and external data from a Canadian registry.[48] Further details of the process were provided in the company's clarification response[16] (question B4c). Six clinical experts were provided with a data book and asked 10 calibration questions which were used to weight the contribution of each expert based on the quality of each participant's response. These weights were applied to generate averaged group estimates for OS for the population enrolled in DAPA-CKD[19] at 10 and 20 years. These values are shown alongside the parametric model predictions in Figure 14.

Figure 14: Fitted overall survival models for patients in the DAPA-CKD placebo arm (reproduced from company's clarification response, Figure 2)

SMR - standardised mortality ratio

Step (v) Choice of most appropriate model and sensitivity analysis

The Gompertz model was selected as it was considered to provide the most plausible estimates of long-term OS. However, with the exception of the gamma model, all parametric models provided extrapolations which were within the range of expert elicited values (see Figure 14). The ERG notes that these plots do not appear to include general population mortality constraints; had such constraints been included, the differences between the predicted OS probabilities at later ages would have been

reduced, which in principle could have influenced judgements about their plausibility. Each of these models were considered by the company in their scenario analyses (see Table 33); except for the scenario in which the exponential distribution was applied, these alternative models suggested that dapagliflozin dominates SoC.

Overall, the ERG considers that the assumption of a proportional treatment effect over time was not well justified and other key details were not clearly presented in the CS or clarification responses.[1, 16] However, assuming that a proportional treatment effect is appropriate, the choice of the Gompertz model and inclusion of other parametric models in scenario analyses is considered reasonable.

(c) Concerns regarding survival models applied for dialysis and transplant health states

The survival models for the dialysis and transplant states are not described in the CS.[1] These are based on probabilities reported in Sugrue *et al.*,[38] which are assumed to be constant over time in the model. The CS does not clearly state how this study was identified, whether other potentially more appropriate alternative studies exist, or whether it is reasonable to assume that the hazard of death in the dialysis and transplant states is constant.

The company's clarification response[16] (question B5) states that Sugrue *et al.*[38] was identified through the company's SLR of modelling approaches during the model conceptualisation and development process. The response also highlights that the values reported in this study reflect the mean estimates of transition probabilities from several separate economic models. The company's response does not provide any further information to support the robustness of this approach and no justification is given to support the assumption that the risk of death in these states is constant over time.

(8) Uncertainty surrounding discontinuation assumptions

The company's model applies a time-invariant probability of discontinuing dapagliflozin of [redacted] per year, which is converted to a monthly probability. The CS[1] does not provide any details regarding: how this discontinuation probability was derived; whether it was based on a parametric survival analysis; whether it is adjusted for competing risks (CKD progression and death) or whether it is reasonable to assume that the risk is constant over time.

As part of their clarification response[16] (questions B16 and B17), the company presented additional scenario analyses which apply alternative assumptions regarding discontinuation, including an analysis in which probability of discontinuation is assumed to decrease linearly to zero after four years, and a further analysis in which discontinuation was based on a gamma distribution fitted to data from DAPA-CKD[19] (see Section 5.3.5). The results of these analyses indicate that the model results are not sensitive

to assumptions regarding discontinuation; this is likely to be a consequence of the assumption that the treatment effect for dapagliflozin is lost at the point of discontinuation.

(9) Issues relating to HRQoL

Overall, the ERG believes that the HRQoL values applied in the company's model are generally appropriate. Whilst there are no previous NICE appraisals of treatments for slowing disease progression in people with CKD against which to compare the health state utility values, the company's clarification response[16] (question B19, Table 18) provides a number of estimates from the literature which indicate that the utility values estimated from DAPA-CKD are broadly similar to values estimated from other datasets. The ERG notes that the company's HRQoL assumptions are subject to some minor issues; these are described briefly below.

(a) Lack of adjustment of utility values for increasing age

The company's original model assumed that health utilities remain constant over time. Figure 15 presents a comparison of utility values applied to each health state versus general population utility based on the characteristics of patients in the CPRD dataset.[15] As shown in the figure, the utility values applied in states CKD1-4 are higher than the general population estimate at all timepoints, and by around age 82 years, estimated general population utility is lower than that for all health states except dialysis. The ERG believes that this is logically inconsistent, since it implies that it is better to have CKD than not. The company's updated base case model includes age-adjusted utilities (see Section 5.3.5).

Figure 15: Comparison of modelled health state utility versus general population utility

CKD - chronic kidney disease

(b) Use of linear model to predict EQ-5D

The majority of utility values applied in the company's model have been derived from a linear mixed effects model fitted to EQ-5D data collected in DAPA-CKD.[19] The ERG notes that the problems of fitting linear models to EQ-5D response data have been discussed in the literature (for example, Hernandez *et al.*[47]). The ERG considers that a mixture model, rather than a linear model, would have been better able to reflect the underlying distribution of the EQ-5D data. However, the ERG considers this to be minor issue.

(c) Face validity problems with modelled utility estimates

As noted in the CS,[1] the coefficients of the linear model for volume depletion and major hypoglycaemic events indicate that these AEs are associated with improvements in HRQoL – this lacks face validity. In order to address this issue, the company applied other disutility values obtained from other sources (DAPA-HF[20] and Currie *et al.*[40]). This casts some doubt on the reliability of the estimates obtained from the linear mixed effects model. The ERG notes that the company's decision to replace these values with estimates from external sources is reasonable and that the AE disutility values have a negligible impact on the ICER for dapagliflozin.

(10) Issues relating to costs

Overall, the ERG considers that the cost estimates used in the company's model are reasonable and well justified in the CS.[1] However, the ERG notes that:

(i) Drug acquisition costs are not adjusted for observed RDI in DAPA-CKD and wastage is not included (for example, if a patient dies before completing a pack of treatment). The model also excludes costs associated with prescribing or dispensing. The impact of these issues on the ICER for dapagliflozin is unclear, but is unlikely to be substantial.

(ii) Drug costs included in the model for SoC treatments do not include any costs for antidiabetic drugs (such as insulin, hypoglycaemic agents and/or GLP-1 receptor agonists), even though data from the CPRD dataset reported in the CS suggests that [redacted] of patients have T2DM.[15] The company's clarification response[16] (question B21) argues that these are unrelated costs, but also presents an additional scenario analysis whereby an estimated annual cost of managing diabetes of £335.02 was included for those patients with comorbid T2DM (this estimate includes costs of insulin, testing strips and drugs for control of blood sugar levels). The company also presented a further scenario analysis which also included an estimated cost of £51.17 relating to drugs used to manage CKD complications (including vitamin D, EPOs/ESAs, and phosphate binders). The impact on the ICER for dapagliflozin is minor.

(iii) Health state costs for CKD stages 1-5 (pre-RRT) are based on annual costs reported by Kent *et al*,[11] which include only hospital care (inpatient admissions, day cases and some outpatient attendances). As these estimates exclude costs associated with primary care (where most

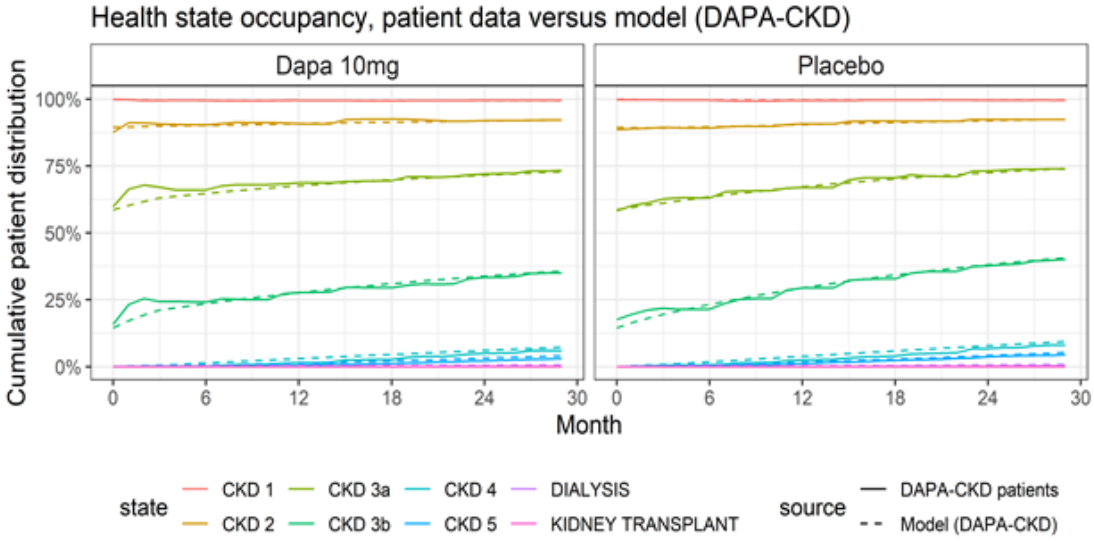
treatment of early CKD takes place), prescribing and some outpatient costs, the CKD-specific health state costs used in the model are likely underestimated. As dapagliflozin is predicted to extend OS, this suggests that the ICER would increase if these missing costs were included. In their clarification response (question B20),[16] the company presents a scenario analysis which applies alternative cost estimates based on data from the CPRD cohort of the DISCOVER CKD study.[62] These estimates include GP, outpatient and clinical care visits and ambulance use, but exclude any costs associated with inpatient hospitalisation and drug treatments. The company justified this through the intention to *"avoid double-counting with the HF hospitalisation and AKI hospitalisation events in the model"*, and *"as drug costs are captured as part of background therapy costs"*. The ERG considers that both sources (Kent *et al* and the DISCOVER CKD study) are likely to represent underestimates.

(iv) The NHS Blood and Transplant fact-sheet[55] which was used as the source for the maintenance costs following transplant does not provide any detail on how these costs were derived. As such, it is unclear whether this cost estimate is reasonable.

(11) Concerns regarding company's model predictions

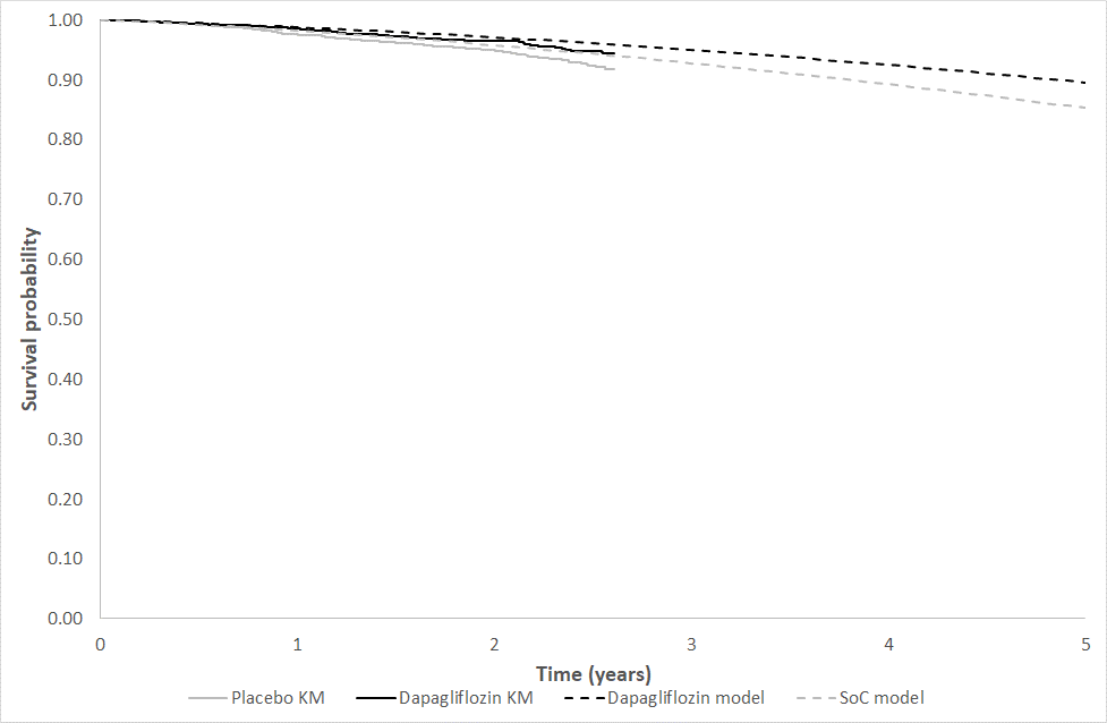
The CS[1] provides limited evidence to demonstrate the extent to which the economic model can predict the CKD stage and OS outcomes observed in DAPA-CKD.[19] The company's clarification response[16] (question B30) presents a plot showing the observed CKD stage over time from DAPA-CKD versus the equivalent predictions from the economic model; this comparison is reproduced in Figure 16. The ERG agrees with the company that this indicates that the model appears to provides a good representation of the observed CKD stage data from the trial.

Figure 16: Observed versus predicted CKD stage, unadjusted DAPA-CKD population (reproduced from company's clarification response, question B30)



The company's clarification response[16] (question B31) also presents a comparison of observed versus predicted OS based on DAPA-CKD.[19] However, the plot shown is based on a new simpler Gompertz model which only includes CKD stage as a covariable; all other covariables included in the OS multivariable model used in the economic model are excluded. The ERG does not consider this plot to be meaningful as it is not the same parametric survival model used the economic model. Subsequently, the ERG digitised the Kaplan-Meier OS data from DAPA-CKD and superimposed predicted OS from the company's unadjusted model for the overall DAPA-CKD population (see Figure 17). An equivalent plot was also provided in the company's updated response to clarification question B31. These plots indicate that the company's economic model overestimates OS in both treatment groups. This raises further concern regarding the company's overall approach for modelling health state transitions and CKD stage-specific mortality risks. The ERG believes that this poor prediction indicates that event risks may have been mis-specified and is likely to be a consequence of the approach used to model OS conditional on CKD stage, as described in critical appraisal point [4].

Figure 17: Observed versus predicted OS – unadjusted DAPA-CKD population (generated using the company's model)



KM - Kaplan-Meier; SoC - standard of care

5.3.5 Company's updated model provided following the clarification round

As part of their clarification response,[16] the company submitted an updated base case model and presented the results of a number of additional scenario analyses using this revised model.[16] The company's updated base case model includes the following amendments:

(a) A general population mortality constraint is included

(b) Utilities are adjusted for age using the regression equation reported by Ara and Brazier[63]
(c) Both initial and maintenance costs are applied in the year of the transplant
(d) The subsequent period matrices are applied from Month 5 rather than Month 4
(e) Discontinuation is applied from the first model cycle
(f) The time horizon is truncated to a maximum patient age of 100 years (previously [redacted] years).

The company's additional scenario analyses provided post-clarification include: modifying the priors applied to transition probabilities; removing the treatment effect for OS applied to the dialysis state; assuming no relative treatment effect on OS beyond the follow-up period in DAPA-CKD;[19] applying alternative discontinuation assumptions; using alternative utility values for CKD states; exploring alternative cost assumptions; applying a simpler unadjusted model for OS and applying subgroup-specific transition matrices within the DAPA-CKD population.

The results of the company's updated base case analyses are presented in Table 36. The results of the company's additional scenario analyses are summarised in Table 37.

The probabilistic version of the company's updated model suggests that the ICER for dapagliflozin versus SoC is expected to be £5,827 per QALY gained. This is slightly lower than the company's original estimate (probabilistic ICER=£6,717 per QALY gained). The highest ICER generated from the additional scenario analyses presented in the company's clarification response[16] is estimated to be £9,706 per QALY gained (ASA11c - subgroup-specific transition probabilities, DAPA-CKD without comorbid T2DM and without comorbid CVD). As shown in Table 36, there is a noticeable difference between the absolute LYGs estimated using the probabilistic and deterministic versions of the updated model; this is partially a consequence of the inclusion of the general population mortality constraint.

Table 36: Central estimates of cost-effectiveness, company's updated base case model

Option	LYGs*	QALYs	Costs	Inc. LYGs	Inc. QALYs	Inc. costs	ICER
Probabilistic model							
Dapagliflozin	10.45	6.03	£51,339	0.90	0.47	£2,759	**£5,827**
SoC	9.55	5.56	£48,641	-	-	-	-
Deterministic model							
Dapagliflozin	10.87	6.21	£53,366	0.97	0.50	£3,095	**£6,158**
SoC	9.90	5.71	£50,271	-	-	-	-

LYG - life year gained; QALY - quality-adjusted life year; Inc. - incremental; ICER; SoC - standard of care
** Undiscounted*

Table 37: Additional scenario analysis results presented in the company's clarification response

Additional scenario analysis	Incremental - dapagliflozin vs SoC		
	QALYs	Costs	ICER
Company's updated base case	0.50	£3,095	**£6,158**
ASA1: Problematic priors removed from transition matrices	0.50	£3,015	**£5,974**
ASA2: Relative effect on OS removed from dialysis state	0.46	£295	**£645**
ASA3: Relative effect on OS removed after 2.4 years	0.26	-£1,945	**Dominating**
ASA4: Discontinuation probability tapers to zero after 4 years	0.62	£4,217	**£6,841**
ASA5: Discontinuation modelled using gamma distribution	0.54	£3,439	**£6,414**
ASA6: TA599 utility values	0.52	£3,095	**£5,941**
ASA7: Costs based on CPRD cohort of DISCOVER CKD[62]	0.50	£3,830	**£7,621**
ASA8: Include drug costs for managing CKD complications	0.50	£3,131	**£6,229**
ASA9: Include drug costs for managing CKD complications and T2DM	0.50	£3,195	**£6,357**
ASA10a: Gompertz model applied to DAPA-CKD overall population	0.77	£4,489	**£5,841**
ASA10b: Simple Gompertz model applied to DAPA-CKD overall population	0.82	£5,317	**£6,493**
ASA11a: Subgroup-specific transition probabilities - DAPA-CKD with comorbid T2DM	0.76	£4,532	**£5,929**
ASA11b: Subgroup-specific transition probabilities - DAPA-CKD with comorbid CVD	0.78	£3,567	**£4,560**
ASA11c: Subgroup-specific transition probabilities - DAPA-CKD without comorbid T2DM and without comorbid CVD	0.65	£6,275	**£9,706**

ASA - additional scenario analysis; SoC - standard of care; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; CPRD - Clinical Practice Research Datalink; CKD - chronic kidney disease; T2DM - type 2 diabetes mellitus; CVD - cardiovascular disease

5.4 Exploratory analyses undertaken by the ERG

5.4.1 Exploratory analysis – methods

The ERG considers all of the amendments applied in the company's updated base case model to be appropriate. The ERG was able to generate similar results to those for almost all additional scenario analyses presented in the company's clarification response (see Table 37) using the ERG double-programmed model. The ERG believes that, taken together, the range of scenario and subgroup analyses presented in the original CS[1] and the additional scenario analyses contained within the company's clarification response[16] address many, but not all, of the important areas of uncertainty around the cost-effectiveness of dapagliflozin for treating CKD. Owing to the issues related to the definition of the target population and the poor fit to OS in the unadjusted model, the ERG does not have a preferred base case scenario.

In order to explore other remaining uncertainties, the ERG undertook three sets of additional exploratory analyses, which included:

(a) Re-implementing each of the company's original scenario and subgroup analyses from the original CS within the updated base case model.

(b) Exploring additional scenarios with the purpose of "stress-testing" the company's updated model. These are briefly outlined in Table 38.

(c) Quantification of the consequences of decision uncertainty, based on the approaches described by Hettle *et al.*[64] and Grimm *et al*.[65]

Table 38: Summary of additional exploratory analyses undertaken by the ERG

Scenario	Description of analysis	Justification
EA1	HR for OS set equal to 1.0, treatment-specific matrices retained	Stress test to explore maximum impact of any potential overestimation of relative OS benefits
EA2	Treatment-specific matrices removed (both set equal to SoC group transitions), HR for OS retained	Stress test to explore maximum impact of any potential overestimation of relative OS benefits
EA3	Discontinuation based on Weibull model	Second-best fitting model according to AIC and BIC
EA4	Utility value for dialysis set equal to 0.70	Higher utility values have been reported in the literature (e.g. the systematic review reported by Wyld *et al.*[66])
EA5	CKD1-5 costs doubled	Stress test due to some relevant cost components excluded from Kent *et al*
EA6	Costs and disutilities for hHF and AKI set equal to zero	To demonstrate limited impact of these events on the ICER
EA7*	HR of 1.4 applied to CKD-specific survival models to force economic model for DAPA-CKD to fit observed OS data in DAPA-CKD trial[19]	This exploratory analysis attempts to address the poor fit of the unadjusted model to the OS data from DAPA-CKD. The ERG notes that this analysis is not ideal and its results should be interpreted with caution.

EA - exploratory analysis; HR - hazard ratio; OS - overall survival; hHF - hospitalisation for heart failure; CKD - chronic kidney disease; AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion; ICER - incremental cost-effectiveness ratio; ERG - Evidence Review Group

** This exploratory analysis was undertaken using the ERG's double-programmed model*

5.4.2 Exploratory analysis – results

(a) Replication of company's original scenario and subgroup analyses using updated model

The results of the company's original scenario analyses from the CS[1] using the updated model are shown in Table 41 in Appendix 1. The updated ICERs for most scenarios are similar to those generated using the company's original model. The highest ICER generated from these scenario and subgroup analyses is £6,916 per QALY gained (SA18 - patients leave the model at RRT).

(b) Additional exploratory analyses undertaken by the ERG

The results of the ERG's additional exploratory analyses are shown in Table 39. The ICERs for all but one of these scenarios are below £10,000 per QALY gained. The one exception relates to the scenario in which transition probabilities for both groups are set equal to those for the SoC group (ICER = £28,862 per QALY gained). Whilst this exploratory analysis highlights that the treatment-specific transition probabilities (and their impacts on mortality risks) are a key driver of the ICER for dapagliflozin, the ERG does not consider this scenario to be plausible given the eGFR outcomes observed in DAPA-CKD.[19] The ERG also notes that in analysis EA7, whereby CKD-specific mortality

risks are increased to force the model to better fit the observed OS in DAPA-CKD, the ICER remains below £7,000 per QALY gained. This analysis is however not ideal.

Table 39: Results of ERG's additional exploratory analyses

Option	LYGs*	QALYs	Costs	Inc. LYGs	Inc. QALYs	Inc. costs	ICER
Company's updated base case							
Dapagliflozin	10.87	6.21	£53,366	0.97	0.50	£3,095	**£6,158**
SoC	9.90	5.71	£50,271	-	-	-	-
EA1: HR for OS removed, treatment-specific matrices retained							
Dapagliflozin	10.11	5.86	£47,161	0.21	0.15	-£3,110	**Dominating**
SoC	9.90	5.71	£50,271	-	-	-	-
EA2: Treatment-specific matrices removed, HR for OS retained							
Dapagliflozin	10.71	6.07	£60,717	0.82	0.36	£10,447	**£28,862**
SoC	9.90	5.71	£50,271	-	-	-	-
EA3: Discontinuation based on Weibull model							
Dapagliflozin	10.95	6.25	£53,746	1.06	0.54	£3,475	**£6,442**
SoC	9.90	5.71	£50,271	-	-	-	-
EA4: Utility value for dialysis set equal to 0.70							
Dapagliflozin	10.87	6.39	£53,366	0.97	0.50	£3,095	**£6,215**
SoC	9.90	5.89	£50,271	-	-	-	-
EA5: CKD1-5 costs doubled							
Dapagliflozin	10.87	6.21	£72,624	0.97	0.50	£3,914	**£7,788**
SoC	9.90	5.71	£68,710	-	-	-	-
EA6: Costs and disutilities for hHF and AKI set equal to zero							
Dapagliflozin	10.87	6.21	£52,977	0.97	0.50	£3,164	**£6,300**
SoC	9.90	5.71	£49,813	-	-	-	-
EA7: Mortality risks down-weighted by HR of 1.4 to force model fit (DAPA-CKD population)							
Dapagliflozin	13.95	7.41	£72,198	1.67	0.76	£4,806	**£6,344**
SoC	12.28	6.65	£67,392	-	-	-	-

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; Inc. - incremental; SoC - standard of care; HR - hazard ratio; OS - overall survival; hHF - hospitalisation for heart failure; AKI - acute kidney injury

(c) Quantification of consequences of decision uncertainty

This section briefly summarises the estimated consequences of decision uncertainty. As discussed in Section 5.3.4, there is uncertainty regarding the definition of the target population of people with CKD in whom dapagliflozin would be used. The analysis assumes a notional effective population size of 200,000 people with CKD over the lifetime of the decision, assuming no requirement for phased roll-out. Results are presented in terms of net health effects and the global Expected Value of Perfect Information (EVPI), both valued in terms of QALYs (see Table 40 and Figure 18).

The results of the analysis of consequences of decision uncertainty can be summarised as follows.

- The ICER for dapagliflozin is low relative to usual NICE thresholds[57]
- The probability that dapagliflozin is cost-effective at a WTP threshold of £20,000 per QALY gained is close to 1.0.

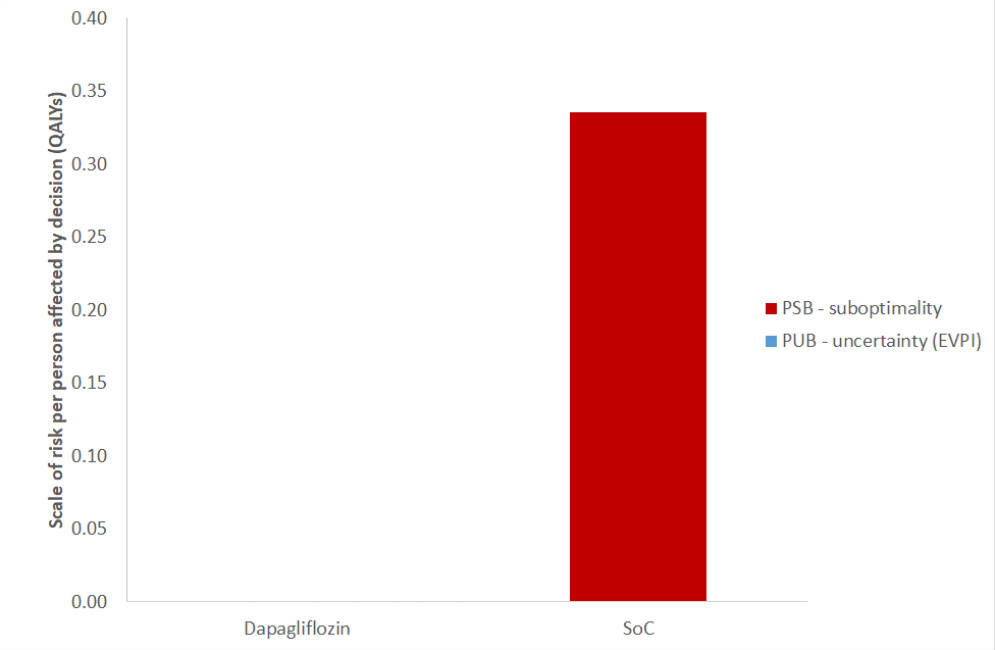
- Irrespective of the assumed WTP threshold, almost all of the payer burden of uncertainty is associated with selecting the sub-optimal treatment, which in this case is expected to be SoC. In other words, the NHS stands to lose more health by adopting a sub-optimal treatment given current information (SoC) than it stands to gain by delaying the decision in order to collect more information to reduce existing decision uncertainty.

Table 40: Consequences of decision uncertainty

WTP threshold	ICER	Probability cost-effective at WTP threshold	Incremental net health benefit (scaled up to population, in QALYs)	Consequences of decision uncertainty (population EVPI, in QALYs)
£20,000/QALY gained	£5,827	0.99	67,095	79
£30,000/QALY gained		1.00	76,291	18

WTP - willingness-to-pay; ICER - incremental cost-effectiveness ratio; QALY - quality-adjusted life year; EVPI - expected value of perfect information

Figure 18: Consequences of decision uncertainty in terms of Payer Uncertainty Burden and Payer Sub-optimality Burden, λ=£20,000/QALY (QALYs per patient)



PSB - payer sub-optimality burden; PUB - payer uncertainty burden; EVPI - expected value of perfect information

5.5 Discussion

The company's economic analysis is generally in line with the scope for the appraisal. The results of the economic analyses presented by the company and the ERG are summarised as follows:

- The company's updated probabilistic base case ICER is expected to be £5,827 per QALY gained. The deterministic ICER from the updated base case model is slightly higher (ICER = £6,158 per QALY gained).

- Based on the company's updated model, the highest ICER from the scenario analyses presented in the CS[1] is £6,916 per QALY gained. The highest ICER estimated within the additional scenario analyses provided in the company's clarification response[16] is £9,706 per QALY gained.
- All but one of the ERG's additional exploratory analyses result in ICERs which are lower than £10,000 per QALY gained. The one scenario which generated a higher ICER shows the importance of the transition probabilities, but is not plausible given the eGFR data observed in DAPA-CKD.[19]
- The analysis of the consequences of decision uncertainty suggests high net health effects from adopting dapagliflozin and comparatively lower EVPI.

The ERG considers that the results of the analyses presented by the company and the ERG should be interpreted with some caution for two reasons:

(i) It is unclear whether the CPRD dataset[15] reflects the target population in whom dapagliflozin would be used in clinical practice, particularly with respect to the use of ACE inhibitor/ARB therapy.

(ii) The company's unadjusted model over-predicts OS for both groups in the DAPA-CKD population.

The impact of these resolving issues on the ICER for dapagliflozin is not fully clear.

6 END OF LIFE

The CS does not make a case that dapagliflozin meets NICE's End-of-Life criteria.

7 OVERALL CONCLUSIONS

The key evidence for the clinical effectiveness and safety of dapagliflozin in treating CKD is the DAPA-CKD trial. This was an event-driven, multicentre, international double-blind RCT which included adult patients with CKD with or without comorbid T2DM. Dapagliflozin was associated with a statistically significant risk reduction of 39% (HR 0.61; 95% CI: 0.51, 0.72; $p<0.001$) in the primary endpoint (i.e. composite endpoint of sustained decline in eGFR ≥50%, ESKD or death from renal or CV causes) compared with placebo. Statistically significant benefits for dapagliflozin were observed for most of the individual components of the primary outcome (where assessed) as well as for secondary outcomes. Dapagliflozin provided treatment benefit in all pre-specified analyses of relevant subgroups, although a *p*-value for interaction of <0.05 was observed for SBP. [redacted]. Safety outcomes in DAPA-CKD were generally consistent with available safety data for dapagliflozin in other indications (diabetes and HF). The ERG considers DAPA-CKD to be at low risk of bias. The ERG notes that whilst DAPA-CKD included many of the types of patients who might be treated with dapagliflozin in clinical practice, several groups of patients were excluded from the trial, including patients with urine albumin excretion <22.6mg/mmol, those with prior organ transplant, and those with T1DM. Also, whilst almost all patients in the trial were receiving ACE inhibitor or ARB therapy, many patients with CKD do not receive these therapies in clinical practice.

The company's updated base case model suggests that the ICER for dapagliflozin versus SoC is expected to be £5,827 per QALY gained. The highest ICER generated from the company's deterministic scenario and subgroup analyses is estimated to be £9,706 per QALY gained. The ICERs estimated from additional exploratory analyses undertaken by the ERG are all below £10,000 per QALY gained, with the exception of one extreme scenario whereby the transition probabilities for SoC are applied in both treatment groups; whilst this highlights that transition probabilities are a key driver of the ICER, this does not reflect a plausible scenario given the outcomes observed in DAPA-CKD. The analysis of the consequences of decision uncertainty indicates that net health effects are high, whilst EVPI is low. This suggests that the NHS stands to lose more health by adopting a sub-optimal treatment given current information (which is expected to be SoC) than it stands to gain by delaying the decision in order to collect more information to reduce existing decision uncertainty. However, the ERG notes that the company's economic model for the DAPA-CKD population (without adjustment to CPRD characteristics) overestimates OS in both treatment groups. Consequently, the model results presented by the company and the ERG should be interpreted with some degree of caution.

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9 APPENDICES

Appendix 1: CS scenario analysis results generated using the company's original and updated models

Table 41: Company's original scenario analysis results using company's original and updated models

Scenario no.	Scenario description	Company's original model described in CS[1]			Company's updated model (post-clarification)[16]		
		Inc. QALYs	Inc. costs	ICER	Inc. QALYs	Inc. costs	ICER
-	**Company's base case**	0.77	£5,118	**£6,655**	0.50	£3,095	**£6,158**
SA1	DAPA-CKD overall population	0.84	£4,563	**£5,457**	0.77	£4,489	**£5,841**
SA2	CPRD subgroup – with comorbid T2DM	0.77	£5,110	**£6,671**	0.47	£2,821	**£5,982**
SA3	CPRD subgroup – without comorbid T2DM	0.77	£5,096	**£6,619**	0.50	£3,085	**£6,126**
SA4	CPRD subgroup – with uACR <200mg/g	0.76	£5,054	**£6,608**	0.41	£2,190	**£5,396**
SA5	CPRD subgroup – with uACR ≥200mg/g	0.78	£5,137	**£6,558**	0.67	£4,412	**£6,613**
SA6	DAPA-CKD subgroup – with comorbid T2DM (vs. SoC)	0.83	£4,675	**£5,648**	0.76	£4,564	**£6,006**
SA7	DAPA-CKD subgroup – with comorbid T2DM (vs. canagliflozin)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SA8	DAPA-CKD subgroup – without comorbid T2DM	0.85	£4,357	**£5,098**	0.79	£4,327	**£5,505**
SA9	DAPA-CKD subgroup – with comorbid CVD	0.82	£4,891	**£5,971**	0.76	£4,779	**£6,317**
SA10	DAPA-CKD subgroup – without comorbid CVD	0.85	£4,405	**£5,213**	0.77	£4,344	**£5,607**
SA11	DAPA-CKD subgroup – without comorbid T2DM and without comorbid CVD	0.86	£4,287	**£4,979**	0.79	£4,270	**£5,390**
SA12	OS - exponential	0.91	£5,864	**£6,447**	0.37	£1,403	**£3,829**
SA13	OS – Weibull	0.76	-£519	**Dominating**	0.35	-£3,139	**Dominating**
SA14	OS – log-normal	0.67	-£3,087	**Dominating**	0.23	-£5,319	**Dominating**
SA15	OS – log-logistic	0.72	-£1,540	**Dominating**	0.30	-£4,001	**Dominating**
SA16	OS – generalised gamma	0.71	-£3,675	**Dominating**	0.15	-£6,698	**Dominating**
SA17	Patients discontinue upon initiating dialysis	0.71	£1,672	**£2,361**	0.46	£148	**£323**
SA18	Patients exit model at RRT	0.76	£4,398	**£5,756**	0.52	£3,600	**£6,916**
SA19	Alternative disutilities for major hypoglycaemic events, DKA and amputation	0.77	£5,118	**£6,655**	0.50	£3,095	**£6,158**

SA - scenario analysis; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; CPRD - Clinical Practice Research Datalink; uACR - urine albumin-to-creatinine ratio; T2DM - type 2 diabetes mellitus; SoC - standard of care; CVD - cardiovascular disease; OS - overall survival; RRT - renal replacement therapy; DKA - diabetic acidosis

Appendix 2: Methods for implementing the ERG's exploratory analyses

This appendix details how to implement the ERG's exploratory analyses. Note that all exploratory analyses presented in the report are based on the updated version of the company's model, with exception of the Exploratory Analysis 7, which has been implemented in the ERG's double-programmed model.

Exploratory Analysis 1

In spreadsheet 'Adjusted Equation Library', replace the value in cell D15 with "0."

Exploratory Analysis 2

In worksheet "Data Library", replace the values:

- in cells E165:E228 with the values from cells E229:E292; and
- in cells E293:E356 with the values from cells E357:E420.

Exploratory Analysis 3

Go to worksheet "ERG Scenarios" drop-down box in cell G36 and select "Yes". Go to worksheet "Model interface" and select "Weibull" in the drop-down box in cell E37.

Exploratory Analyses 4

In worksheet "Data Library", replace the value in cell E121 with "0.70".

Exploratory Analysis 5

Go to worksheet "Data Library" and multiply the values in cells E56:E61 by 2.

Exploratory Analyses 6

In worksheet "Data Library", set value in cells E65, E66, E123 and E124 to zero.

Exploratory Analysis 7

This exploratory analysis was undertaken using the ERG's rebuilt model. This was done by applying the DAPA-CKD overall population characteristics and raising all CKD-specific mortality models for states CKD1-5 to the power of HR=1.4.

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Dapagliflozin for treating chronic kidney disease [ID3866]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG 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 Friday 9 July 2021** 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 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Issue 1 Target population

Description of problem	Description of proposed amendment (change in red)	Justification for amendment	ERG response
Page: 12 These include: people with urine albumin excretion <22.6mg/mmol; people with ESKD; people with prior organ transplantation, and people with T1DM. Whilst the CS presents further evidence from DAPA-HF and DECLARE-TIMI 58 which is intended to support the use of dapagliflozin regardless of uACR or eGFR, the company's economic model is based on effectiveness evidence drawn exclusively from DAPA-CKD.	Page: 12 These include: people with urine albumin excretion <22.6mg/mmol; people with ESKD; people with prior organ transplantation, and people with T1DM. Whilst the CS presents further evidence from DAPA-HF and DECLARE-TIMI 58 which is intended to ~~support the use of~~ demonstrate the generalisability of dapagliflozins treatment effect regardless of uACR or eGFR, the company's economic model is based on effectiveness evidence drawn exclusively from DAPA-CKD.	The data from DECLARE-TIMI 58 and DAPA-HF are presented to illustrate that the treatment effect with dapagliflozin is consistent across a broader range of uACR and eGFR categories than were included in the DAPA-CKD trial; demonstrating that the effectiveness evidence from DAPA-CKD can reasonably be applied to the broader CKD patient population represented by the CPRD dataset.	The text has been amended in line with the company's request.
Page 13: They considered it possible that the benefits of sodium-glucose cotransporter-2 (SGLT2) inhibitors might be similar in people with CKD and proteinuria who are not treated with ACE inhibitors/ARBs, but commented that the evidence is much less certain in these groups, and that the use of dapagliflozin in this context would be going beyond the available trial data	Page 13: They considered it possible that the benefits of sodium-glucose cotransporter-2 (SGLT2) inhibitors might be similar in people with CKD and proteinuria who are not treated with ACE inhibitors/ARBs, but commented that the evidence is ~~much~~ less certain in these groups~~, and that the use of dapagliflozin in this context would be going beyond the available trial data~~	There is trial evidence from both DECLARE-TIMI 58 and DAPA-HF which shows the treatment effect of dapagliflozin does not significantly differ between patients receiving and not receiving background ACEi/ARB therapy (see section 2.13.2 of document B for data). The statement that the evidence is less certain is fair given that this analysis is not possible in the DAPA-CKD trial because so few patients were not taking ACEi/ARB background therapy at baseline,	This is not factually inaccurate – the text reflects the views of the ERG's clinical advisors. For the sake of clarity, we have included additional information obtained from our advisors. In the executive summary, the text on page 13 has been amended to read *"…going beyond the available trial data from DAPA-CKD. They also commented that the*

		but it is inaccurate to say that use in this instance would be going against available trial data.	*supporting evidence for people not treated with ACE inhibitors/ARBs from DECLARE-TIMI 58 and DAPA-HF is uncertain."* Additionally, in Section 5.3.4 (critical appraisal point [2]), a more detailed summary of the clinical advisors' views has been provided: *"They considered it possible that the benefits of SGLT2 inhibitors might be similar in people with CKD and proteinuria who are not treated with ACE inhibitors/ARBs, but commented that the evidence is much less certain in these groups and that the use of dapagliflozin in this context would be going beyond the available trial data from DAPA-CKD. The clinical experts further commented that the supporting subgroup analyses from DECLARE-TIMI 58 and DAPA-HF are limited. In particular, subgroup analyses for the renal outcome in DECLARE-TIMI 58 appear to suggest lower treatment effects for patients*

			not treated with ACE inhibitors/ARBs at baseline compared to those receiving these therapies (HR = 0.77, 95% CI 0.44 -1.37 versus HR = 0.50, 95% CI 0.39-0.63),[57] which at least allows the hypothesis that SGLT inhibitors may provide less benefit for patients with T2DM who, for whatever reason, are not treated with ACE inhibitors/ARBs. In addition, the experts highlighted that in DAPA-HF, 94% of patients were receiving ACE inhibitors, ARBs or sacubitril-valsartan (assuming that no patients received combinations of these therapies); hence, this trial does not provide much information regarding the effectiveness of dapagliflozin in patients not receiving these therapies."
Page 13: The advisors further commented that of those patients in the CPRD dataset who were receiving ACE inhibitors/ARBs, many may not have met the inclusion criteria for the trial. The ERG notes that these issues raise questions regarding the suitability of the adjustment of	Page 13: The advisors further commented that of those patients in the CPRD dataset who were receiving ACE inhibitors/ARBs, many may not have met the inclusion criteria for the trial. ~~The ERG notes that these issues raise questions regarding the suitability of the adjustment of baseline characteristics and event risks to the CPRD population.~~	A limited number of the patients in the CPRD dataset who were receiving ACEi/ARB therapy may fall outside of the inclusion criteria for DAPA-CKD with respect to their uACR or eGFR measurements. However, as shown in the evidence from DECLARE-TIMI 58 and DAPA-HF presented in section	This is not a factual inaccuracy. As described above, the ERG believes that there is uncertainty regarding the treatment benefits of dapagliflozin in CKD patients who are not receiving ACE inhibitors/ARBs due to limited evidence. If the target

baseline characteristics and event risks to the CPRD population. Page 26: The ERG also notes that it is unclear how many patients in the CPRD dataset would have been eligible for recruitment into the DAPA-CKD trial. The ERG therefore believes there is uncertainty regarding the company's intended target population and the relevance of the company's adjustment to the CPRD population. This issue is discussed further in Section 5.3.4.	Page 26: The ERG also notes that it is unclear how many patients in the CPRD dataset would have been eligible for recruitment into the DAPA-CKD trial. ~~The ERG therefore believes there is uncertainty regarding the company's intended target population and the relevance of the company's adjustment to the CPRD population. This issue is discussed further in Section 5.3.4.~~	2.13.2 of document B, the treatment effect of dapagliflozin is consistent in patients with uACR <200 (lower than DAPA-CKD trial) and ≥200 (DAPA-CKD like population) and across eGFR ranges lower than those included in the DAPA-CKD trial. The CPRD population will include some additional patients that wouldn't have met the trial inclusion criteria (e.g. those with type 1 diabetes), but the proportion is expected to be very small and unlikely to have a large impact. We therefore believe that this data sufficiently addresses the data limitations and therefore the degree of uncertainty is low. We respectfully request that the ERG rephrase to qualify the likely degree of residual uncertainty.	population is restricted to the DAPA-CKD population, rather than all patients with CKD in the CPRD dataset, then adjustments using the full CPRD dataset would not be fully reflective of the target population. The company's suggested amendment has not been made.

Issue 2 Background

Description of problem	Description of proposed amendment (change in red)	Justification for amendment	ERG response
Page 18: An overview of the treatment pathway is presented in Section B.1.3.3 of the CS.[1] This refers to NICE Clinical Guideline 182 (Chronic kidney disease in adults:	Page 18: An overview of the treatment pathway is presented in Section B.1.3.3 of the CS.[1] This refers to NICE Clinical Guideline 182 (Chronic kidney disease in adults: assessment and management)[3] and the	Publication timelines delayed to 25th August 2021	The text has been amended in line with the company's request.

assessment and management)[3] and the revised guideline draft for consultation, which is expected to be published in June 2021.	revised guideline draft for consultation, which is expected to be published in ~~June~~ August 2021.		

Issue 3 Critique of Company's Definition of the Decision Problem

Description of problem	Description of proposed amendment (change in red)	Justification for amendment	ERG response
Page 22, Table 4: Intervention / comparator ERGs comments: Generally in line with scope. However, the economic analysis reflects a population in whom only [redacted] of patients are receiving ACE inhibitor/ARB therapy. In DAPA-CKD, 97% of patients were receiving ACE inhibitors/ARBs. It is unclear how many patients in the CPRD dataset would have been eligible for the trial.	Page 22, Table 4: Intervention / comparator ERGs comments: Generally in line with scope. However, the economic analysis reflects a population in whom only [redacted] of patients are receiving ACE inhibitor/ARB therapy. In DAPA-CKD, 97% of patients were receiving ACE inhibitors/ARBs. Analyses are presented in the clinical effectiveness section showing generalisability of treatment effect with dapagliflozin regardless of ACE inhibitor / ARB therapy. It is unclear how many patients in the CPRD dataset would have been eligible for the trial.	As it stands this section does not accurately summarise all of the data presented in the company submission on the issue of background therapy and its impact on dapagliflozin's treatment effect. The suggested addition is required to accurately reflect the evidence.	This is not factually inaccurate. The table briefly highlights headline comments from the ERG and is not intended to summarise the full range of evidence presented in the CS. The supporting evidence from DECLARE-TIMI 58 and DAPA-HF, and issues relating to the use of background therapies, the target population, and the model are discussed in the executive summary and in Section 5.3.4 of the main report.

Page 25: It should be noted that except for assumptions around certain adverse events (AEs) associated with dapagliflozin, DAPA-HF and DECLARE-TIMI 58 are not used to inform the company's economic model	Page 25: It should be noted that data from DAPA-HF and DECLARE-TIMI 58 are not used directly to inform the company's economic model [moved text] except for assumptions around certain adverse events (AEs) associated with dapagliflozin, but they are used to inform the modelling approach and assumption of generalizability of DAPA-CKD trial data to the broader target population.	The analyses from DECLARE-TIMI 58 and DAPA-HF presented in section 2.13.2 of document B inform the modelling approach and assumptions; the subgroup analyses validate the assumption that the DAPA-CKD data is generalisable to the broader CKD patient population.	This is not a factual inaccuracy. However, the text has been amended to state explicitly that data from DAPA-HF and DECLARE-TIMI 58 are not used to inform the model. The subsequent text amendment has not been made as the economic model is driven by treatment effects estimated using DAPA-CKD, not the other dapagliflozin trials.
Page 25: Dapagliflozin does not currently have a marketing authorisation in the UK for the treatment of adult patients with CKD.	Page 25: Dapagliflozin does not currently have a marketing authorisation in the UK for the treatment of adult patients with CKD but this is expected in [redacted]	Please include the expected licence date.	The text has been updated as requested.

Issue 4 Multivariable survival model

Description of problem	Description of proposed amendment (change in red)	Justification for amendment	ERG response
Page 13: The multivariable survival model predicts mortality risk according to CKD stage at baseline,	Page 13: The multivariable survival model predicts mortality risk according to time-updated CKD stage ~~at baseline, irrespective of whether patients in the trial changed~~	The eGFR range / CKD stage covariable in the all-cause mortality survival model was time-updated. In the cost-effectiveness model, the all-cause mortality is	The use of time-varying covariates was not described in the CS. Whilst the ERG agrees that it is appropriate to

irrespective of whether patients in the trial changed CKD state, or received dialysis or a transplant. Page 88: The multivariable survival model fitted to the OS data from DAPA-CKD includes baseline eGFR categories as covariables. The impact of transitions between CKD states which occurred within the observed period of the trial on mortality risk may already be reflected in the underlying survival data used to inform the multivariable survival model. For example, the estimated mortality risk in the CKD1 state of the multivariable survival model reflects the risk of death in people who had stage CKD1 at trial entry, irrespective of whether they remained in that state or progressed to more severe CKD stages, underwent dialysis or received a kidney transplant during the trial follow-up. However, this state-specific survival model is applied in the economic model as the risk for a patient who has stage CKD1 at each time *t*. The same issue applies to each of states CKD1-5	~~CKD state, or received dialysis or a transplant~~. Page 88: The multivariable survival model fitted to the OS data from DAPA-CKD includes time-updated ~~baseline~~ eGFR categories as covariables. This means that the impact of CKD stage on mortality hazard is accurately reflected in the model, even when the proportion of early vs late stage CKD patients changes in the modelled population over time. For example, at model initiation, a large proportion of patients reside within CKD stage 3a, with the remaining patients distributed across CKD stages 1, 2, 3b and 4. Over time, patients with more severe stages of CKD are more likely to die compared patients with less severe stages of CKD. Consequently, the composition of patients and therefore the mortality hazards in the overall population shift in two opposing ways: as more severe CKD patients die, the overall hazard shifts towards the hazard associated with the less severe CKD stages (main effect); and as patient experience CKD progression, the overall hazard shifts towards the hazard associated with more severe CKD stages (smaller effect). These changes in mortality hazard are captured in the survival model through the time-updated CKD stage covariable. ~~The impact of transitions between CKD states which occurred within the observed period of the trial on mortality risk may already be reflected in the underlying survival data used to inform the multivariable survival model. For example, the estimated mortality risk in the CKD1 state of the multivariable survival model reflects the risk of death in people who had stage CKD1 at trial entry, irrespective of whether they remained in that state or progressed to more severe CKD stages, underwent dialysis or~~	calculated based on the patient health state distributions in any given cycle (in addition to other covariables). Given the eGFR range / CKD stage covariable in the survival model is time-updated, we believe the ERG's concerns should be considered as resolved, as the mortality hazard applied in the economic model have been correctly implemented and are consistent with the predictions of the multivariable survival model derived from DAPA-CKD. We acknowledge that this point was not clear in the company submission, but it was explained in response to ERG clarification questions, (see references below): Response to B9: *The change in CKD stage distribution over time in the modelled population, through the application of transition probabilities, impacts the survival, hHF and AKI risk profiles of the population. These outcomes are modelled through adjusted survival and risk equations which include time-varying CKD stage distribution as one of the covariables.*	update the ERG report to reflect the approach adopted by the company, the ERG has different reservations regarding this general modelling approach. The key point here is that the economic model based on the multivariable survival model, including the impact of transitions between CKD states, does not provide a good representation of the OS data from DAPA-CKD. This can be seen in Figure 17 of the ERG report and in Figure 1 of the company's updated response to clarification question B31. The poor fit of the model indicates that there is likely to be a problem in how event risks for progression and death are specified within the statistical models. The precise cause of this problem is unclear. The first bullet of critical appraisal point [4] has

and means that the economic model is applying mortality risks which are not consistent with the predictions of the multivariable survival model.	~~received a kidney transplant during the trial follow-up. However, this state-specific survival model is applied in the economic model as the risk for a patient who has stage CKD1 at each time *t*. The same issue applies to each of states CKD1-5 and means that the economic model is applying mortality risks which are not consistent with the predictions of the multivariable survival model.~~	Response to B11: *Importantly, the multivariable survival equation was derived in the context of the observed delay in CKD progression associated with dapagliflozin over time, where CKD stages were covariables in the survival equation.* Original response to B31: *The "adjusted"/"controlled" overall survival model is the parametric survival model applied in the company base case, which adjusts for time-updated CKD stage as well as baseline patient characteristics.* Updated response to B31: *Because of the strong association between CKD stage (disease severity) and mortality hazard,1, 2 it is particularly important that time-varying CKD stage is taken into account when modelling all-cause mortality (see "uncontrolled" survival model provided in original response to B31). [subsequent 3 paragraphs in response to B31 provided further explanation]*	been replaced with the following text: *"The appropriateness of the company's approach to modelling progression and death rests on the ability of the multivariable survival model to do two things: (a) to characterise the cumulative risk of death over time for patients with a given baseline CKD stage, which fully accounts for the impact of disease progression observed in the trial follow-up, independent of treatment received (estimated as HRs for CKD stages), and (b) to isolate the additional relative treatment effect of dapagliflozin over SoC over and above any OS impacts mediated through changes in CKD stage (estimated as the treatment-related HR which is applied across all CKD stages). Within the company's clarification response[16] (question B31) and factual accuracy check,[37] the company*

			clarified that CKD stage was included as a time-updated covariate in the multivariable survival model. Including post-randomisation covariates in an analysis is unconventional. No information was provided in the CS or the clarification response on how this was done, and the fully specified survival model and the code used to fit the model were not provided. As a general point, the ERG notes that the inclusion of post-randomisation covariates in survival models can lead to problems in determining causality. In particular, if part of the causal effect of treatment is through CKD stage, this approach will block that effect, and the resulting model coefficients may not be meaningful." A brief summary of this issue has also been added to the executive

			summary to reflect this issue. Minor text changes have been applied to other sections of the report to ensure that the issue is consistently described.
Page 13: The company's economic model estimates state-specific mortality risks using a "mean of covariates" approach. The ERG considers that this reflects a misinterpretation of the outputs of the multivariable survival model, which has been shown to lead to bias when estimating survival distributions. Page 88: State-specific mortality risks are estimated in the model by applying a value of 1.0 to the relevant eGFR category for each CKD state, whilst holding all other covariables at their mean values. The ERG believes that this is an incorrect interpretation of the multivariable model output, and that it reflects a	Page 13: The company's economic model estimates state-specific mortality risks using a "mean of covariates" approach. The ERG considers that this reflects a misinterpretation of the outputs of the multivariable survival model, which has been shown to lead to bias when estimating survival distributions. However, determination of time-updated covariate by CKD stage is prohibitively complex and unlikely to have a material impact on the model results. The current approach is consistent with other appraisals (e.g. TA679) and therefore considered appropriate given the complexity and limited impact of the alternative. Page 88: State-specific mortality risks are estimated in the model by applying a value of 1.0 to the relevant eGFR category for each CKD state, whilst holding all other covariables at their mean values. The ERG believes that this is an incorrect interpretation of the multivariable model output, and that it reflects a "mean of covariates" approach, which has been shown to lead to bias when estimating survival functions.[57] The ERG believes that predicted OS from the multivariable model	Determination of time-updated covariable by CKD stage is prohibitively complex and unlikely to have a material impact on the model results. One alternative modelling approach could be to apply the "simple Gompertz" model, which only includes time-updated CKD stage, treatment, age and sex as covariables. This modelling approach would model the mortality hazard *associated* with each CKD stage, rather than merely reflecting the differences in hazard associated with the time-updated CKD stage variable itself. A scenario analysis with this reduced survival model ("simple Gompertz") was provided in our original response to B31, which demonstrated that this alternative modelling approach only has a minor impact on the ICER	This is not a factual inaccuracy. The ERG has reservations in relation to the appropriateness of the company's chosen approach. The complexity of the alternative is not necessarily a corroboration of the current approach being correct. The following text has been added for clarity: *"As part of their factual accuracy check,[58] the company highlighted that such an approach would be prohibitively complex and that it would be unlikely to have a material impact on the model results.*

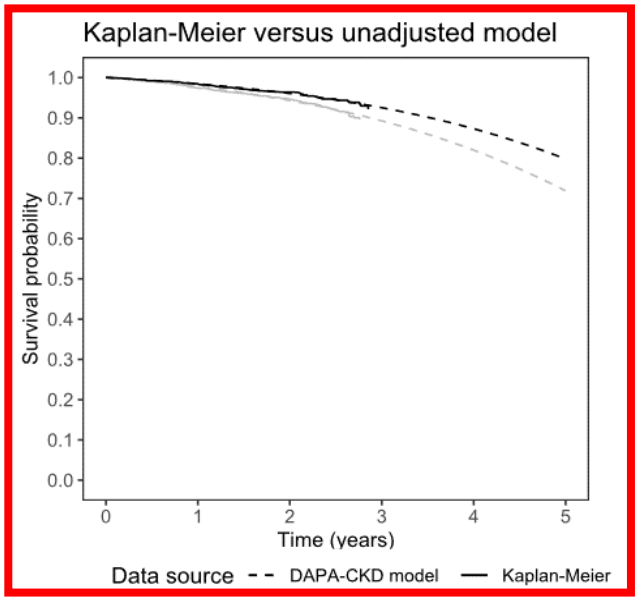
"mean of covariates" approach, which has been shown to lead to bias when estimating survival functions. The ERG believes that predicted OS from the multivariable model should instead be estimated using the "corrected group prognosis" method, whereby survival models are estimated for each level of categorical covariable, which are then weighted according to their incidence.	should instead be estimated using the "corrected group prognosis" method, whereby survival models are estimated for each level of categorical covariable, which are then weighted according to their incidence. However, determination of time-updated covariate by CKD stage is prohibitively complex and unlikely to have a material impact on the model results. The current approach is consistent with other appraisals (e.g. TA679) and therefore considered appropriate given the complexity and limited impact of the alternative.	(change from £5,457/QALY gained to £6,072/QALY gained).	*The ERG notes that the extent of bias on the model predictions and the ICER is not known."*
Page 13–14: Applying relative treatment effects on OS both via the survival distributions and delayed disease progression may be double-counting the relative benefits of dapagliflozin. Page 89: The ERG believes that the company's interpretation of the multivariable survival model is incorrect as the eGFR covariables reflect baseline values only, and that whilst removing either mechanism of survival benefit may underestimate the relative treatment effect of dapagliflozin, including both mechanisms simultaneously may	Page 13–14: Applying relative treatment effects on OS both via the survival distributions and delayed disease progression may be double-counting the relative benefits of dapagliflozin. The company maintains that there is no double-counting, because the multivariable survival model was derived in the context of the observed delay in CKD progression associated with dapagliflozin over time, where time-updated CKD stages were covariables in the survival equation. As such, a proportion of the treatment effect of dapagliflozin on all-cause mortality is mediated through the delay in CKD progression and a proportion of the benefits is mediated directly through the dapagliflozin coefficient of the all-cause mortality survival model. Page 89: As discussed in critical appraisal point [4], the ERG believes that the implementation of the outputs of the multivariable survival model in the economic model is problematic. The company maintains that this approach	As explained in response to clarification questions B11, the multivariable survival model was derived in the context of the observed delay in CKD progression associated with dapagliflozin over time. This approach intrinsically avoids double-counting, and is akin to the suggestion by the ERG to estimate health state transitions and survival together. A benefit of this approach compared to that proposed by the ERG, is that this approach is able to accommodate changes to the mortality hazard over time, and avoids the restrictive assumption of constant mortality hazard over time. This approach to jointly derive the transition probabilities and the	As described above, the ERG has amended the text around concerns regarding the overall modelling approach & OS estimation. The point regarding double-counting might still be an issue, but this is now included only as part of the exploratory analyses and is not specifically discussed in the critical appraisal. The company's second suggested amendment does not appear to be accurate as the transition probabilities and survival models do

overestimate it. This could have been implemented as a piece-wise model (split by pre- and post-Month 5 intervals) and may also have allowed for the inclusion of covariates to enable adjustment to the CPRD population. It is likely that this approach would have avoided the risk of double-counting treatment effects on OS; however, it may impose more restrictive assumptions regarding the hazard of death over time. Page 89: As discussed in critical appraisal point [4], the ERG believes that the implementation of the outputs of the multivariable survival model in the economic model is problematic.	is appropriate and statistically sound, as the transition probabilities and the survival model were jointly derived.	multivariable survival model was also supported by the clinical experts consulted during model conceptualisation and development. This approach is also aligned with the feedback from the ERG's clinical advisors who commented "that it is appropriate to assume that mortality risk will increase and HRQoL will decrease with advancing CKD stage" (ERG report, page 87).	not appear to have been jointly derived – they are based on separate analyses (although CKD stage is included as a covariate in the survival model).
Page 66: The long-term plausibility of the extrapolated models was assessed by comparison against published life expectancy tables for patients with CKD reported from a large population-based registry in Canada. Page 67:	Page 66: The long-term plausibility of the extrapolated models was assessed by comparison against published life expectancy tables for patients with CKD reported from a large population-based registry in Canada. Additionally, a clinical expert elicitation exercise was carried out in collaboration with 6 clinical experts (see response to B4c and B12). This elicitation study confirmed that the Gompertz survival equation for all-cause mortality selected for the cost-effectiveness model has clinical validity.	As outlined in the company submission and further clarified in response to ERG clarification questions, the choice of the Gompertz distribution for the all-cause survival model was based on clinical expert input (through an elicitation exercise), in addition to comparison against the data from CKD patients in Canada.	Page 66: The following text has been added: *"Additionally, a clinical expert elicitation exercise was carried out in collaboration with six clinical experts (see clarification response,[16] questions B4 and B12)."* The choice of Gompertz

The company selected the Gompertz model for the base case analysis on the grounds of long-term plausibility through reference to the Canadian registry analysis.	Page 67: The company selected the Gompertz model for the base case analysis on the grounds of long-term plausibility through reference to the Canadian registry analysis and based on the output from a clinical expert elicitation exercise carried out in collaboration with 6 clinical experts (see response to B4c and B12).		model is detailed on the subsequent page and does not need to be mentioned here as well. Page 67 The following text has been added: *"The company selected the Gompertz model for the base case analysis on the grounds of long-term plausibility through reference to the Canadian registry analysis[47] and the clinical expert elicitation exercise.[16]"*
Page 67: Comparisons of the observed Kaplan-Meier plots for OS and the fitted multivariable models (excluding the additional impact of transitions between health states) were not provided in the CS[1] or the company's clarification response. Page 93: Goodness-of-fit based on all AIC and BIC was presented in the CS for all parametric models and	Page 67: Comparisons of the observed Kaplan-Meier plots for OS and the fitted multivariable models (excluding the additional impact of transitions between health states) were not provided in the CS, but provided in the updated response to B31 for the Gompertz distribution as requested by the ERG ~~or the company's clarification response~~. Page 93: Goodness-of-fit based on all AIC and BIC was presented in the CS for all parametric models and a comparison of the final fitted models to the observed Kaplan-Meier survival estimates was not provided by	A comparison of the observed data from DAPA-CKD (Kaplan-Meier plots) and the survival model based on the Gompertz distribution was provided in the updated response to B31, in line with the ERG's request.	The ERG does not believe the company's suggested amendments are accurate. The ERG wanted to see a plot of the fitted multivariable model (excluding the impact of transitions between CKD states) against the observed Kaplan-Meier function in order to assess the internal validity of this

a comparison of the final fitted models to the observed Kaplan-Meier survival estimates was not provided by the company within the CS or the company's clarification response.	the company within the CS, however a comparison of the Kaplan-Meier survival estimates and the survival estimates based on the Gompertz distribution was provided in the updated response to B31, in line with the ERG request ~~or the company's clarification response~~.		model. This has not been provided. The additional models referred to in the company's updated response to clarification question B31 relate to (i) a univariate Gompertz model and (ii) the economic model OS projections based on the multivariable survival model. The univariate model is not relevant to this point as it is not the final survival model used in the base case economic analysis or subgroup analyses. The footnotes to Figure 1 of the updated response to question B31 state that the multivariable model predictions are *"economic model output and are dependent upon the time-varying CKD state occupation, including non-Gompertz mortality hazard in transplant and dialysis states."*

			The text has not been amended.
Page 14: The company's unadjusted economic model, which does not include adjustment to the CPRD population, overestimates OS for dapagliflozin and SoC observed in DAPA-CKD. This is likely to be a consequence of issues (i) to (iii) listed above. This raises some doubts regarding the confidence that should be placed on the model results. Page 98: Subsequently, the ERG digitised the Kaplan-Meier OS data from DAPA-CKD and superimposed predicted OS from the company's unadjusted model for the overall DAPA-CKD population (see **Error! Reference source not found.**). An equivalent plot was also provided in the company's updated response to clarification question B31. These plots indicate that the company's economic model overestimates OS in both treatment groups. This raises further concern regarding the company's overall approach for modelling health	Page 14: ~~The company's unadjusted economic model, which does not include adjustment to the CPRD population, overestimates OS for dapagliflozin and SoC observed in DAPA-CKD. This is likely to be a consequence of issues (i) to (iii) listed above. This raises some doubts regarding the confidence that should be placed on the model results.~~ Page 98: The company's clarification response (question B31) also presents a comparison of observed versus predicted OS based on DAPA-CKD. However, the plot shown is based on a new simpler Gompertz model which only includes CKD stage as a covariable; all other covariables included in the OS multivariable model used in the economic model are excluded. Following further clarification, the company provided an updated response to B31 with the univariate unadjusted survival model (where treatment is the only covariable). ~~The ERG does not consider this plot to be meaningful as it is not the same parametric survival model used the economic model.~~ Subsequently, the ERG digitised the Kaplan-Meier OS data from DAPA-CKD and superimposed predicted OS from the company's unadjusted model for the overall DAPA-CKD population (see **Error! Reference source not found.**). An equivalent plot was also provided in the company's updated response to clarification question B31. These plots indicate that the unadjusted univariate survival model has a good fit to the Kaplan-Meier plot from DAPA-CKD ~~company's economic model overestimates~~	Figure 17 in the ERG report is factually inaccurate and does not appear to show the unadjusted univariate survival model. Instead, the plot in figure 17 appears to represent the multivariable fully-adjusted survival model used in the company base case. Following further clarifications from the ERG, we provided an updated response to B31, which included a figure of the univariate unadjusted survival model, which has a good fit to the Kaplan-Meier plot from DAPA-CKD. A zoomed-in version of this plot has been provided in the column to the right, which can be used to correct Figure 17 in the ERG report. As explained in the factually accuracy corrections above and in the updated response to B31, transition probabilities and survival equations were jointly derived based on data from DAPA-CKD, which allows the survival model to take time-updated CKD stage into account and therefore more accurately model the survival hazard over time when the CKD stage composition of the population	This is not a factual inaccuracy. The plot shown in Figure 17 of the ERG report compares the OS predictions of the company's base case economic model, which uses the multivariable Gompertz OS model, versus the observed Kaplan-Meier OS function (digitised by the ERG). This plot indicates that the model overestimates OS in both treatment groups. The univariate model is not presented in Figure 17 because it is not the final model used in the company's economic base case. Because the plot already shown in Figure 17 relates to the model used in the company's base case, the report has not been amended. The ERG notes that the ICERs using the simpler

state transitions and CKD stage-specific mortality risks. The ERG believes that this poor prediction is likely to be a consequence of the approach used to model OS conditional on CKD stage, as described in critical appraisal point [4].	~~OS in both treatment groups. This raises further concern regarding the company's overall approach for modelling health state transitions and CKD stage-specific mortality risks. The ERG believes that this poor prediction is likely to be a consequence of the approach used to model OS conditional on CKD stage, as described in critical appraisal point [4].~~ Page 98, Figure 17:  Page 104: ~~The company's approach to modelling may potentially over-estimate the relative benefit of dapagliflozin on OS.~~	diverges from the initial trial distribution. Furthermore, when comparing the unadjusted univariate survival model with the multivariate fully-adjusted survival model at 2.4 years (median follow-up of DAPA-CKD), the survival difference between the treatment arm and placebo arm were ~2.4% versus ~1.8%, suggesting that the use of the univariate unadjusted survival would result in a greater treatment effect (less conservative with respect to dapagliflozin). This observation is in line with the scenario analyses provided in our updated response to B31, which shows that the ICER for scenario #2 (DAPA-CKD overall population) decreases from £5,457/QALY gained to £4,759/QALY gained when using the univariate unadjusted survival model instead of the multivariate fully-adjusted survival model. We believe that the additional clarifications and justifications for correction provided above are sufficient to alleviate the ERG's concern on this point throughout the ERG report.	Gompertz models remain <£10,000 per QALY gained and that, ultimately, the ERG's concerns regarding overestimation of OS in both groups may not have a large impact on the cost-effectiveness of dapagliflozin. This same point is also already apparent from the ERG's exploratory analyses.

Page 104: The company's unadjusted model over-predicts OS for both groups in the DAPA-CKD population. Page 106: However, the ERG notes that the company's economic model for the DAPA-CKD population (without adjustment to CPRD characteristics) overestimates OS in both treatment groups. Consequently, the model results presented by the company and the ERG should be interpreted with some degree of caution.	~~The company's unadjusted model over-predicts OS for both groups in the DAPA-CKD population.~~ Page 106: ~~However, the ERG notes that the company's economic model for the DAPA-CKD population (without adjustment to CPRD characteristics) overestimates OS in both treatment groups. Consequently, the model results presented by the company and the ERG should be interpreted with some degree of caution.~~		

Issue 5 Descriptions of the model

Description of problem	Description of proposed amendment (change in red)	Justification for amendment	ERG response
Page 56: The model was developed prior to the release of the results of the DAPA-CKD trial.	Page 56: The model abstract was published ~~was developed~~ prior to the release of the results of the DAPA-CKD trial and the model poster presentation was subsequently updated using results from the DAPA-CKD trial.	The model development started prior to the results from the DAPA-CKD trial were available, but the poster presentation was updated following the read-out of DAPA-CKD.	The text has been amended in line with the company's request.
Page 59: Health utility is not adjusted for increasing age.	Page 59: Health utility is not adjusted for increasing age in the original company base case, but the company amended the model to adjust health utility by age in the revised base case, following ERG clarification questions.	Clarification that the revised company base case now include age-adjusted health utility.	Section 5.2 of the ERG report states *"This section describes the company's original submitted model, as described in the CS.[1] Following the clarification round, the company submitted an updated base case model. The revised model and its results are summarised separately in Section 5.3.5."* We believe that it is already be clear that this section is about the original model, not the updated model. However, for the sake of clarity, the text has been updated to read *"Health utility is not adjusted for increasing age (note – this was amended in the company's updated model)."*

Issue 6 Costs

Description of problem	Description of proposed amendment (change in red)	Justification for amendment	ERG response
Page 75: Monthly costs of disease management for CKD1-5 (pre-RRT) are based on annual costs reported by Kent *et al*. 2015, which includes only hospital care (inpatient admissions, day cases or outpatient attendances).	Page 75: Monthly costs of disease management for CKD1-5 (pre-RRT) are based on annual costs reported by Kent *et al*. 2015, which includes only hospital care (inpatient admissions, day cases or outpatient attendances). Alternative CKD management costs from DISCOVER CKD were also provided in response to ERG clarification questions and incorporated as a sensitivity analysis. These alternative costs captured the costs of GP visits, outpatient visits, critical care visits and ambulance use.	In response to B20, alternative CKD health state management costs were provided and incorporated in the economic analysis as a scenario analysis.	This description relates to the analyses presented in the CS. The additional sensitivity analyses using costs from DISCOVER CKD are already mentioned in the critical appraisal section (page 97) and the results are already presented as part of the additional sensitivity analyses (page 100). No further amendment is necessary.
Page 76: With the exception of values taken from NHS Reference Costs 2018/2019, costs were uplifted to 2019/2020 prices using inflation indices published by the Personal Social Services Research Unit (PSSRU).	Page 76: ~~With the exception of values taken from NHS Reference Costs 2018/2019,~~ Costs were uplifted to 2019/2020 prices using inflation indices published by the Personal Social Services Research Unit (PSSRU).	All costs, including those from NHS Reference Costs 2018/2019 were uplifted to 2019/2020 prices.	The text has been amended as suggested.
Page 82: The ERG was unable to exactly replicate the estimated costs for hHF and AKI based on the NHS Reference Costs codes reported in the CS.	Page 82: The ERG was unable to exactly replicate the estimated costs for hHF and AKI based on the NHS Reference Costs codes reported in the CS, likely due to the uplifting of NHS Reference Costs 2018/2019 in the	Most likely the discrepancy in NHS reference costs identified is because NHS Reference Costs 2018/2019 were uplifted to 2019/2020 in the company submission.	The ERG was unable to replicate the exact values for hHF and AKI costs, solely based on the NHS Reference Costs codes reported in the CS, even when uplifting the NHS Reference Costs

	company submission to a cost year of 2019/2020.		2018/2019 to 2019/2020 prices. Therefore, the text suggested by the company has not been included.

Issue 7 Minor inaccuracies

Description of problem	Description of proposed amendment (change in red)	Justification for amendment	ERG response
Page 10: Dapagliflozin is assumed to affect costs by: • Increasing total costs as a consequence of the acquisition cost of dapagliflozin • Increasing lifetime costs of CKD management (pre-RRT) due to extended OS • Increasing the lifetime costs of dialysis • Increasing the total costs of managing transient events and other AEs.	Dapagliflozin is assumed to affect costs by: • Increasing total costs as a consequence of the acquisition cost of dapagliflozin • Increasing lifetime background therapy costs of CKD management (pre-RRT) due to extended OS • Increasing the lifetime costs of dialysis, due to patients spending longer in earlier stages of CKD • Increasing the total costs of managing transient events and other AEs.	These results require further contextualisation to avoid misinterpretation.	Both points are already accurate in the ERG report. Health state costs in states CKD1-5 (excluding SoC drug costs) are higher in the dapagliflozin arm, which can be seen in the breakdown of costs presented in Table 32 of the ERG report. The undiscounted dialysis costs are higher in the dapagliflozin group because patients in the dapagliflozin group spend slightly longer in this state than BSC-treated

			patients. Therefore, the company's suggestions have not been included in the ERG report.
Page 11: Benefits of dapagliflozin were observed for most of the individual components of the primary outcome as well as for secondary outcomes. Page 54: A positive treatment benefit for dapagliflozin was demonstrated for the primary endpoint of the trial (a composite outcome of sustained decline in eGFR ≥50%, ESKD or death from renal or CV causes), most individual components of the primary composite endpoint and secondary outcomes in the overall population and relevant subgroups. Page 106: Benefits of dapagliflozin were observed for most of the individual components of the primary outcome as well as for secondary outcomes.	Page 11: Statistically significant benefits of dapagliflozin were observed for most of the individual components of the primary outcome as well as for secondary outcomes. Page 54: A statistically significant positive treatment benefit for dapagliflozin was demonstrated for the primary endpoint of the trial (a composite outcome of sustained decline in eGFR ≥50%, ESKD or death from renal or CV causes), most individual components of the primary composite endpoint and secondary outcomes in the overall population and relevant subgroups. Page 106: Statistically significant benefits of dapagliflozin were observed for most of the individual components of the primary outcome as well as for secondary outcomes.	A numerical benefit of treatment with dapagliflozin was observed for **all** components of the primary endpoint. These sentences could therefore be considered misleading.	The text has been amended throughout to improve accuracy throughout.
Page 11: Dapagliflozin demonstrated a consistent treatment benefit in all pre-specified analyses of relevant subgroups, except for systolic blood pressure (SBP).	Dapagliflozin demonstrated a consistent treatment benefit in all pre-specified analyses of relevant subgroups, ~~except for~~ , although a p-value for interaction <0.05 was observed for	These sentences could be considered misleading. Dapagliflozin did demonstrate a consistent treatment benefit	The text has been amended.

Page 106: Dapagliflozin provided treatment benefit in all pre-specified analyses of relevant subgroups, except for SBP.	systolic blood pressure (SBP; ≤130 mmHg versus >130 mmHg). Dapagliflozin provided treatment benefit in all pre-specified analyses of relevant subgroups, although a p-value for interaction <0.05 was observed for ~~except for~~ SBP.	across all subgroups, although a difference was observed between systolic BP subgroups (≤130 mmHg versus >130 mmHg; [redacted]), with patients with systolic BP of ≤130 mmHg at baseline experiencing a greater treatment benefit.	
Page 39: Baseline median [IQR] uACR was 109.05mg/mmol [53.34–1,345.04] (965mg/g [472–11,903 mg/g]); approximately half of the patients in each treatment group presented with severely increased albuminuria (uACR >1,000mg/g [113mg/mmol]).	Baseline median ~~[IQR]~~ uACR was 107.39.05mg/mmol ~~[53.34–1,345.04]~~ (96549mg/g ~~[472–11,903 mg/g]~~); approximately half of the patients in each treatment group presented with severely increased albuminuria (uACR >1,000mg/g [113mg/mmol]).	The data presented in the ERG report are incorrect, as they refer to the dapagliflozin arm of DAPA-CKD specifically rather than the whole trial population.	The text has been amended.
Page 44: Table 10: Primary composite outcome, individual components of the primary outcome and death from any cause: DAPA-CKD (reproduced from CS, Table 15)	Primary composite outcome, individual components of the primary outcome and death from any cause: DAPA-CKD (reproduced from CS, Tables 15 and 16)	The data presented in Table 10 of the ERG report are derived from both Tables 15 and 16 of the CS.	The table title has been amended.
Page 44: Table 10 is missing explanatory footnotes.	Please add the following footnotes to the table: Footnotes: [a]Not calculated for this endpoint due to an insufficient number of events, [b]N/A denotes not applicable because p values for efficacy outcomes are reported only for outcomes that were included in the hierarchical testing strategy. [c] Deaths adjudicated as "cause undetermined" with regard to CV death or non-CV death were	These footnotes are needed for interpretation of the trial results.	The table has been amended and footnotes have been added.

<table>
<tr><td></td><td>included in as CV deaths in the analysis of the primary endpoint. Undetermined cause of death refers to a death not attributable to a CV or non-CV cause due to the lack of information or insufficient supporting information to assign the cause of death.</td><td></td><td></td></tr>
<tr><td>Page 45:

Within Table 11, the p-value for the composite of death from cardiovascular causes or hospitalisation for heart failure is listed as 0.009</td><td>Please report this p-value to 4 decimal places to align with the preceding text (0.0089).</td><td>Citing p-values rounded to different numbers of decimal places in the text versus the table may lead to confusion.</td><td>The text has been amended as suggested.</td></tr>
<tr><td>Page 45:

The CS1 (Section 2.6.3.) also describes additional outcomes relating to the positive treatment effect of dapagliflozin versus placebo on AKI ([redacted]), n=[redacted]% versus [redacted]% of patients, respectively) and [redacted].</td><td>The CS1 (Section 2.6.3.) also describes additional outcomes relating to the positive treatment effect of dapagliflozin versus placebo on AKI ([redacted] n=[redacted]% versus [redacted]% of patients, respectively) and change in uACR from baseline.</td><td>AKI was measured as doubling as serum creatinine from baseline in the DAPA-CKD study.</td><td>The text has been amended as suggested.</td></tr>
<tr><td>Page 49:

Although this is accurate, the ERG considers additional reporting of the rates would have been more appropriate, especially for AEs leading to discontinuation of the active treatment (dapagliflozin versus placebo: (n=[redacted]) versus n=[redacted])).</td><td>Although this is accurate, the ERG considers additional reporting of the rates would have been more appropriate, especially for AEs leading to discontinuation of the active treatment (dapagliflozin versus placebo: n=[redacted]%) versus n=[redacted])) (~~n=[redacted] versus [redacted]~~ [redacted]).</td><td>Data reported are those for any adverse event related to study drug, and should be corrected. It is also unclear exactly what the ERG felt should be included here further to that already provided.</td><td>The text has been amended as suggested.</td></tr>
<tr><td>Page 102, Table 39
<table><tr><th>Option</th><th>LYGs*</th><th>QALYs</th><th>Costs</th><th>Inc. LYGs</th><th>Inc. QALYs</th><th>Inc. costs</th><th>ICER</th></tr></table></td><td>The LYG in the ERG report does not aligned with the most recent version of the</td><td>This is not a factual inaccuracy. The LYGs presented in</td></tr>
</table>

Company's updated base case							
Dapagliflozin	8.79	6.21	£53,366	0.69	0.50	£3,095	**£6,158**
SoC	8.10	5.71	£50,271	-	-	-	-
EA1: HR for OS removed, treatment-specific matrices retained							
Dapagliflozin	8.24	5.86	£47,161	0.15	0.16	-£3,110	**Dominating**
SoC	8.10	5.71	£50,271	-	-	-	-
EA2: Treatment-specific matrices removed, HR for OS retained							
Dapagliflozin	8.68	6.07	£60,717	0.58	0.36	£10,447	**£28,862**
SoC	8.10	5.71	£50,271	-	-	-	-
EA3: Discontinuation based on Weibull model							
Dapagliflozin	8.84	6.25	£53,746	0.74	0.54	£3,475	**£6,442**
SoC	8.10	5.71	£50,271	-	-	-	-
EA4: Utility value for dialysis set equal to 0.70							
Dapagliflozin	8.79	6.39	£53,366	0.69	0.50	£3,095	**£6,215**
SoC	8.10	5.89	£50,271	-	-	-	-
EA5: CKD1-5 costs doubled							
Dapagliflozin	8.79	6.21	£72,624	0.69	0.50	£3,914	**£7,788**
SoC	8.10	5.71	£68,710	-	-	-	-
EA6: Costs and disutilities for hHF and AKI set equal to zero							
Dapagliflozin	8.79	6.21	£52,977	0.69	0.50	£3,164	**£6,300**
SoC	8.10	5.71	£49,813	-	-	-	-
EA7: Mortality risks down-weighted by HR of 1.4 to force model fit (DAPA-CKD population)							
Dapagliflozin	13.95	7.41	£72,198	1.67	0.76	£4,806	**£6,344**
SoC	12.28	6.65	£67,392	-	-	-	-

model from ERG clarification questions response. The LYGs have been updated in red in the column to the left.

all of the results tables in the ERG report are undiscounted. No amendments have been made to the table.

The incremental QALY value highlighted in red (0.16) by the company is incorrectly reported in the company's fact check response and has not been amended in the ERG report.

			ERG response
Page 61, Table 17: The source for AE frequency is listed as DAPA-CKD only. Page 72: Whilst dapagliflozin is known to be associated with increases in genital infection and urinary tract infections (UTIs), these AEs were not routinely collected in DAPA-CKD; hence, the frequencies of these AEs were instead taken from DECLARE-TIMI 58.	Page 61, Table 17: Please add DECLARE-TIMI to the list of sources for AE frequency. Page 72: Whilst dapagliflozin is known to be associated with increases in genital infection and urinary tract infections (UTIs), these AEs were not routinely collected in DAPA-CKD; hence, the frequencies of these AEs were instead taken from DECLARE-TIMI 58 for the proportion of patients with comorbid T2DM at baseline.	Genital infection and UTI frequency data were derived from DECLARE-TIMI and applied to only the proportion of patients with T2DM. This is currently unclear in the ERG report.	The text has been amended as requested.
Page 81, Table 34: The results of the ERG's double-programmed model are inaccurate	Results from the version of the ERG model shared with ERG clarification questions: Dapa costs: £57,584 SoC costs: £52,432 Incr. costs: £5,152 ICER: £6,671	These values appears to differ from the ERG model shared with the ERG clarification questions.	After submitting the double-programmed version of the model, the ERG identified some minor errors in the version sent to the company. As this model was later used to verify the company's scenario and subgroup analyses, these errors were subsequently corrected; the results presented in Table 34 of the ERG report include these corrections. The ERG report has not been amended.
Page 82:	Page 82:	The AE frequencies used in the model were from a post-hoc analysis to derive annual incidence	This discrepancy has been removed from the list and the

The frequencies of AEs used in the model do not match the values reported in the CSR.	The frequencies of AEs used in the model do not match the values reported in the CSR. The company clarified that the AE rates applied in the cost-effectiveness model were derived as an annual incidence rate (events per patient year) from DAPA-CKD.	rates (events per patient year), which took patient exposure into account. This results in slightly different numbers to the data reported in the CSR (number [%] of subjects with AE).	description of the source of AE frequencies has been updated.
Page 112: In spreadsheet 'Adjusted Equation Library', replace the value in cell D15 with "1."	In spreadsheet 'Adjusted Equation Library', replace the value in cell D15 with "0".	The value in cell D15 should be replaced with "0" to give a HR of 1.	The text has been amended.

Issue 8 Typographical errors

Description of problem	Description of proposed amendment (change in red)	Justification for amendment	ERG response
Page 19: Sodium-glucose cotransporter (SGLT2) inhibitors, such as dapagliflozin and canagliflozin, may also be recommended for patients with T2DM and uACR ≥30mg/mmol	Sodium-glucose cotransporter (SGLT2) inhibitors, such as dapagliflozin and canagliflozin, may also be recommended for patients with T2DM and uACR >30mg/mmol	Typographical error	The text has been amended.
Page 24: Approximately, 50% of patients randomised to each treatment arm in DAKA-CKD had severe albuminuria	Page 24: Approximately, 50% of patients randomised to each treatment arm in DA~~K~~PA-CKD had severe albuminuria	Typographical error	The text has been amended.

Page 35: The CS states that recruitment aimed to "ensure a minimum of 30% of patients were recruitment to either the diabetic or non-diabetic subpopulation"	The CS states that recruitment aimed to "ensure a minimum of 30% of patients were recruited to either the diabetic or non-diabetic subpopulation"	Typographical error	The text has been amended.
Page 53: Table 15: Results of MAIC, HR (95% CI) Outcome: CREDENCE renal composite Primary: [redacted]	Table 15: Results of MAIC, HR (95% CI) Outcome: CREDENCE renal composite Primary: [redacted]*	Typographical error	The text has been amended.
Page 55: The searches covered: MEDLINE and Embase (separately, using appropriate index terms in each); CRD databases (the archives of DARE and NHS EED).	The searches covered: MEDLINE and Embase (separately, using appropriate index terms in each); CRD databases (the archives of the HTA database and NHS EED).	Typographical error	The text has been amended.
Page 59: A treatment-related HR is applied to the per-cycle conditional probability of survival in all health states except for the transplant state	Page 59: A treatment-related log HR is applied to the per-cycle conditional probability of survival in all health states except for the transplant state	Typographical error	The text has been amended.
Page 65: Table 20: Monthly transition probabilities From\To: CKD5 (pre-RRT) CKD4: 0.174	Table 20: Monthly transition probabilities From\To: CKD5 (pre-RRT) CKD4: 0.175	Typographical error	The text has been amended.

Page 76: The costs of hHF and AKI events were derived from a group of procedures related to HF (currency codes LA07H to LA07P, LE01A and B and LE02A and B, from Total HRGs) and AKI (codes EB03A to EB03E, non-elective long and short stays) from NHS Reference Costs 2018/2019.	The costs of hHF and AKI events were derived from a group of procedures related to HF (codes EB03A to EB03E, non-elective long and short stays) and AKI (currency codes LA07H to LA07P, LE01A and B and LE02A and B, from Total HRGs) from NHS Reference Costs 2018/2019.	Typographical error	The text has been amended..
Page 86: The CS presents further evidence from DAPA-HF and DECLARE-TIMI 58 which is intended to support the use of dapagliflozin regardless of uCAR or CKD category.	Page 86: The CS presents further evidence from DAPA-HF and DECLARE-TIMI 58 which is intended to support the use of dapagliflozin regardless of uACR or CKD category.	Typographical error	The text has been amended.

Issue 9 AIC/CIC highlighting

Location of incorrect marking	Description of incorrect marking	Amended marking	ERG report
Page 20	Confidentiality highlighting is missing here. This information is commercially sensitive and therefore should be marked as confidential.	Please amend as follows: According to the CS, dapagliflozin will be positioned as an additional treatment option for [redacted]	Marking has been updated as requested
Page 25	Confidentiality highlighting is missing here. This information is commercially sensitive	Please amend as follows:	Marking has been updated as requested

	and therefore should be marked as confidential.	Dapagliflozin does not currently have a marketing authorisation in the UK for the treatment of [redacted]	
Page 47 Figure 5: Forest plots of primary efficacy outcome according to pre-specified subgroups for DAPA-CKD T2DM at BL: [redacted]	This academic in confidence highlighting can now be removed, as a recently published paper has reported these data.	Please amend as follows: T2DM at BL: 0.24 This figure is now reported in Heerspink et al. 2021, which has been published since the submission was shared with NICE.	Marking has been updated as requested
Page 53	Academic in confidence highlighting is missing here. This information could be used to determine the results of the MAIC which is unpublished and therefore this should be marked as confidential.	Please amend as follows: [redacted]	Marking has been updated as requested. Note that additional marking has been added elsewhere in the report to ensure that the results of the MAIC remain confidential.
Page 57	Academic in confidence highlighting is missing here. This information is unpublished and therefore should be marked as confidential.	Please amend as follows: [redacted]	Marking has been updated as requested
Page 57	Academic in confidence highlighting is missing here. This information could be used to determine the results of the MAIC which is	Please amend as follows: [redacted]	Marking has been updated as requested

	unpublished and therefore this should be marked as confidential.	[redacted]	
Page 62	Academic in confidence highlighting is missing here. This information is unpublished and therefore should be marked as confidential.	Please amend as follows: [redacted]	Marking has been updated as requested
Page 77	Academic in confidence highlighting is missing here. This information could be used to determine the results of the MAIC which is unpublished and therefore this should be marked as confidential.	Please amend as follows: [redacted]	Marking has been updated as requested

Page 79	Academic in confidence highlighting is missing here. This information could be used to determine the results of the MAIC which is unpublished and therefore this should be marked as confidential.	Please amend as follows: 	Marking has been updated as requested
Page 83 Table 35	Academic in confidence highlighting is missing here. This information could be used to determine the results of the MAIC which is unpublished and therefore this should be marked as confidential.	Please amend as follows: 	Marking has been updated as requested.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Dapagliflozin for treating chronic kidney disease [ID3866]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments by **5pm** on **Friday 27 August 2021**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**AstraZeneca**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Uncertainty surrounding the target population and the effectiveness of dapagliflozin in patients excluded from DAPA-CKD	YES	**Uncertainty of the relative treatment effect of dapagliflozin in patients with CKD who are not receiving concomitant ACE inhibitor/ARB therapy** In the ERG report, several concerns were raised around the generalisability of the treatment effect with dapagliflozin depending on background angiotensin-converting enzyme (ACE) inhibitor/ angiotensin receptor blocker (ARB) therapy and the data that had been presented to support this. In the DAPA-CKD trial, 97% of patients were on ACE inhibitor/ARB therapy, and 94% of the DAPA-HF trial were on some form of ACE inhibitor/ARB/ angiotensin receptor neprilysin inhibitor (ARNI) therapy. Whilst subgroup analyses from the DECLARE-TMI 58 trial indicate that the relative treatment effect of dapagliflozin versus placebo is maintained regardless of background ACE inhibitor/ARB therapy in patients with type 2 diabetes mellitus (T2DM), the clinical advisors consulted by the ERG commented that the evidence is uncertain. AstraZeneca acknowledges the limitations of the evidence and the target population of this appraisal has therefore been amended to those with background ACE inhibitor/ARB, unless not tolerated. The Clinical Practice Research Datalink (CPRD) analysis which has been used to derive the patient characteristics and adjust event risks in the cost-effectiveness model has been revised to reflect this change in target population (please see Appendix 1). Furthermore, patients with type 1 diabetes mellitus (T1DM), polycystic kidney disease (PKD), New York Heart Association (NYHA) class IV heart failure (HF) and organ transplant were also excluded from the new analysis as per DAPA-CKD trial exclusion criteria. AstraZeneca believe that a recommendation from NICE for use of dapagliflozin in patients already treated

		with an ACE inhibitor/ARB for their chronic kidney disease (CKD) if tolerated, reflects a patient population that's broadly similar to the DAPA-CKD trial population. **Uncertainty of the relative treatment effect of dapagliflozin in patients with CKD and a uACR <200 mg/g** The ERG and NICE have also raised concerns about uncertainties surrounding the strength or absence of evidence for other patient populations not included in the DAPA-CKD trial, particularly highlighting the lack of direct or indirect evidence in patients without T2DM and with urinary albumin creatinine ratio (uACR) <200 mg/g. Whilst AstraZeneca recognises there is some uncertainty in the evidence, the MHRA, EMA and FDA have all granted a marketing authorisation for the use of dapagliflozin to treat adults with CKD, without any restrictions based on uACR, irrespective of diabetes status. This broad label allowing initiation of dapagliflozin in all eligible patients with CKD stages 1 to 4 was granted based on the results from the DAPA-CKD study, as well as the strength of supporting clinical evidence from DECLARE-TIMI 58 and DAPA-HF trials and the strong mechanistic rationale for the similarity of renal efficacy in patients with T2DM and without T2DM. The MHRA (and independently, the EMA) determined this evidence was sufficient to robustly demonstrate the renal efficacy of dapagliflozin in patients outside of the DAPA-CKD trial, including in patients without T2DM and with low uACR. During the clinical assessment conducted by the regulators, the MHRA clinical assessor stated the following: [redacted] As a result of the regulators assessment, we believe that sufficient clinical evidence has been presented to support a recommendation in patients with CKD, irrespective of diabetes status and uACR levels. We do, however, recognise, that currently an assessment of the likely cost-effectiveness in patients without T2DM and a uACR <200 mg/g has not explicitly been presented. Therefore, to address the ERG's concerns regarding the uncertainty of the clinical and cost effectiveness of dapagliflozin in patients with uACR and estimated glomerular filtration rate (eGFR) outside of the DAPA-CKD trial range, the following additional analyses have been undertaken which are discussed below and presented in more detail: 1) Analysis to estimate outcomes in patients with low uACR 2) Broad population cost-effectiveness model

		1) Analysis to estimate treatment outcomes in patients with low uACR Overview During the scrutiny phase to determine the appraisal routing the ERG and NICE highlighted the lack of direct evidence available on the renal efficacy of dapagliflozin in patients with CKD without T2DM and with uACR <200 mg/g. To address this, a simulated treatment outcomes analysis was performed which uses DAPA-CKD data to estimate the relative treatment effect of dapagliflozin vs. placebo in patients with CKD and uACR <200 mg/g.[1] The overall approach used a Poisson model to fit the estimated annual event rate (offset log[time], dependent only on uACR as continuous variable). The uACR range was then extended to 30-5,000 mg/g and the rate ratio between the dapagliflozin arm and the placebo arm at each uACR level was determined. Separate analyses were performed for patients with T2DM and without T2DM, with annual event rates estimated as a function of uACR (Appendix 3). Rate ratios were calculated stratified by T2DM status at baseline for the following outcomes: composite primary endpoint of DAPA-CKD (sustained eGFR decline ≥50%, end-stage kidney disease [ESKD], cardiovascular [CV] death and renal death), sustained eGFR decline ≥50% and ESKD. Results Estimated event rates suggest that in the overall DAPA-CKD population (i.e. patients with and without T2DM), the treatment effect of dapagliflozin versus placebo [redacted] For ESKD the treatment effect [redacted] (Figure 1 and Table 1).

Figure 1: Ratio of annual event rates per 100 patients with dapagliflozin versus placebo, for the primary endpoint, sustained eGFR decline ≥50% and ESKD

Footnotes: Values <1.0 indicate a lower rate of events. Gold bands represent 95% confidence intervals. Note logarithmic vertical axis scale for comparison of ratios. The primary endpoint was ≥50% sustained decline in eGFR, ESKD, CV death or renal death.
Abbreviations: eGFR: estimated glomerular filtration rate; ESRD, end-stage renal disease; uACR: urinary albumin creatinine ratio.
Source: AstraZeneca Data on File 2021d: Simulated treatment outcomes analysis summary.[1]

Table 1: Estimate of dapagliflozin efficacy by event rate ratio

Endpoint	uACR (mg/g)	Event rate ratio
Primary endpoint	30	[redacted]
	300	[redacted]
	1,000	[redacted]
Sustained eGFR decline >50%	30	[redacted]
	300	[redacted]
	1,000	[redacted]

ESKD	30	[redacted]
	300	[redacted]
	1,000	[redacted]

Abbreviations: eGFR: estimated glomerular filtration rate; ESKD: end-stage kidney disease; T2DM: type 2 diabetes mellitus; uACR: urinary albumin creatinine ratio.
Source: AstraZeneca Data on File 2021d: Simulated treatment outcomes analysis summary.[1]

An analysis was also conducted to explore the treatment effect of dapagliflozin versus placebo in patients with low uACR, stratified by T2DM status. Given the lower number of patients without T2DM in the DAPA-CKD trial, this analysis was associated with some uncertainty. Nonetheless, the analysis found that the dapagliflozin treatment effect versus placebo [redacted]

For ESKD the treatment effect was [redacted] (Figure 2, Table 2). In the cost-effectiveness model, it was conservatively assumed that the relative treatment effect of dapagliflozin in non-T2DM patients to be the same as in T2DM patients. [redacted]

Figure 2: Ratio of annual event rates per 100 patients with dapagliflozin versus placebo, for the primary endpoint, sustained eGFR decline ≥50% and ESKD, stratified by T2DM status

[redacted]

Footnotes: Values <1.0 indicate a lower rate of events. Gold and blue bands represent 95% confidence intervals for patients with T2DM and without T2DM, respectively. Note logarithmic vertical axis scale for comparison of ratios. The primary endpoint was ≥50% sustained decline in eGFR, ESKD, CV death or renal death. Patient numbers: T2DM: 1455 dapagliflozin, 1451 placebo; non-T2DM: 697 dapagliflozin, 701 placebo.
Abbreviations: eGFR: estimated glomerular filtration rate; ESRD: end-stage renal disease; T2DM: type 2 diabetes mellitus; uACR: urinary albumin creatinine ratio.
Source: AstraZeneca Data on File 2021d: Simulated treatment outcomes analysis summary.[1]

Table 2: Estimate of dapagliflozin efficacy by event rate ratio by uACR and stratified by T2DM status at baseline

Endpoint	Baseline status	uACR (mg/g)	Event rate ratio
Primary endpoint	Non-T2DM	30	[redacted]
		300	[redacted]
		1000	[redacted]
	T2DM	30	[redacted]
		300	[redacted]
		1000	[redacted]
Sustained eGFR decline >50%	Non-T2DM	30	[redacted]
		300	[redacted]
		1000	[redacted]
	T2DM	30	[redacted]
		300	[redacted]
		1000	[redacted]
ESKD	Non-T2DM	30	[redacted]
		300	[redacted]
		1000	[redacted]
	T2DM	30	[redacted]
		300	[redacted]

		1000	[redacted]

Footnotes: Patient numbers: T2DM- N: 1455 dapagliflozin, 1451 placebo; non-T2DM: 697 dapagliflozin, 701 placebo.
Abbreviations: eGFR: estimated glomerular filtration rate; ESKD: end-stage kidney disease; T2DM: type 2 diabetes mellitus; uACR: urinary albumin creatinine ratio.
Source: AstraZeneca Data on File 2021d: Simulated treatment outcomes analysis summary.[1]

Based on these additional analyses, it can be concluded that the treatment effect of dapagliflozin to reduce primary and renal decline endpoints compared to placebo [redacted] Whilst the lower number of non-T2DM patients in the trial is associated with some uncertainty in Poisson model prediction of event rates, this analysis shows [redacted] These results further justify the modelling of treatment benefit with dapagliflozin as add on to ACE inhibitor/ARB therapy across a broader population than was included in the DAPA-CKD trial.

2) Broad population cost-effectiveness model

Overview

Within the ERG report, it was noted that the original company model was based on effectiveness evidence drawn exclusively from DAPA-CKD, without the use of data from DECLARE TIMI 58 and DAPA-HF to support the effectiveness of dapagliflozin in subgroups across the broad CKD population (Section 5.3.4, point 2). To address this point, a new modelling approach was developed with clinical expert input from [redacted] which directly uses treatment effect data from the CKD subgroup of DECLARE TIMI 58. A "$DECLARE_{CKD}$" dataset was derived from DECLARE TIMI 58 by excluding patients with eGFR>60 and uACR<30. This dataset was used in the new broad population modelling approach to support the treatment effect of dapagliflozin in CKD patients with low uACR, by informing transition probabilities, all-cause mortality and HF hospitalisation. AKI was not modelled for CKD patients with low uACR, because this endpoint was not captured in the DECLARE TIMI 58 trial.

The overall approach for the broad population model was to split the cost-effectiveness analysis into three sub-analyses. The cost-effectiveness of the overall population, was derived by calculating weighted average costs and QALYs from the three sub-analyses, with weights based on CPRD prevalence data. The three sub-analyses were:

- Sub-analysis 1, patients with uACR≥200 mg/g
- Sub-analysis 2, patients with uACR<200 mg/g with T2DM

- Sub-analysis 3, patients with uACR<200 mg/g without T2DM

Non-T2DM correction factor

The event rate in non-T2DM patients was observed to be lower for patients with uACR≥200 mg/g in the DAPA-CKD trial, and it was expected that this trend would also extend to CKD patients with uACR<200 mg/g. This assumption is supported by an extensive study by the CKD Prognosis Consortium, which concluded that despite the higher risk of events in CKD patients with diabetes, the relative event risks by uACR remain the same irrespective of the presence or absence of diabetes.[2] The results from this study infer that the impact of diabetes on event rates is constant across uACR levels, and that therefore the non-T2DM correction factor from DAPA-CKD is generalisable to sub-analysis 3.

The event rates and non-T2DM correction factor derived from DAPA-CKD are shown in Table 3.

Table 3: Derivation of adjustment factor from DAPA-CKD for event rates in non-T2DM versus T2DM patients

Outcome	T2DM status	Patients	Events	Patient-years	Rate per 100 patient-years	Ratio, non-T2DM correction factor
All-cause mortality	non-T2DM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	T2DM	[redacted]	[redacted]	[redacted]	[redacted]	
Hospitalisation for HF	non-T2DM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	T2DM	[redacted]	[redacted]	[redacted]	[redacted]	
End-stage kidney disease	non-T2DM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	T2DM	[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations: HF: heart failure; T2DM: type 2 diabetes mellitus.

Survival modelling using DECLARE$_{CKD}$ – unified dataset approach

Initially, the survival data from DAPA-CKD and DECLARE$_{CKD}$ were analysed separately, to derive a DAPA-CKD survival model and a DECLARE$_{CKD}$ survival model. However, the survival predicted by DECLARE$_{CKD}$ was shorter than the survival predicted by DAPA-CKD. [redacted]

[redacted]

[redacted] (Figure 3).

Figure 3: KMs and adjusted survival curves for dapagliflozin and placebo arms from DECLARE$_{CKD}$, DAPA-CKD and DAPA-CKD with T2DM.

Footnotes: Points and error bars represent 50th centile and 10-90th centile range, respectively, of expected survival of a CKD patient with albuminuria under standard of care in the expert elicitation exercise (see response to clarification questions for full details).
Abbreviations: KM: Kaplan-Meier.

		Because of the counterintuitive survival predictions from analysing the DAPA-CKD and $DECLARE_{CKD}$ datasets separately, a range of alternative modelling approaches were explored as options for survival modelling to generate more clinically-valid predictions across in the broad CKD population. As a first step, the DAPA-CKD and $DECLARE_{CKD}$ datasets were combined into a unified dataset, with a fully adjusted survival model fitted to this data, with uACR as a categorical variable (A1: <30 mg/g, A2: 30-300 mg/g, A3: >300 mg/g). Covariables for the survival model were derived from those identified during the analysis of DAPA-CKD, with the exception of glomerulonephritis since these data were unknown for patients in $DECLARE_{CKD}$. The coefficients of the final model are summarised in Appendix 2. Figure 4 shows the placebo survival curve for a broad population where 11.5% of patients have uACR ≥200 mg/g and 88.5% of patients have uACR <200 mg/g. The weighting of patients by uACR (11.5% high and 88.5% low) is based on results from the updated CPRD analysis (see Appendix 1). The Gompertz distribution severely underestimated the survival of a broad CKD population, whereas all other distributions provide survival estimates at the upper confidence interval of the expected survival elicited from clinical experts. Because the clinical experts were asked to estimate the survival in a CKD patient with albuminuria (more severe patients), it is expected that an average CKD patient from the broad CKD population would have a longer survival than what was elicited from the clinical experts. The survival predictions for the dapagliflozin arm are shown in Figure 5. Given the comparatively similar AIC and BIC among the best fitting distributions that converged (scores within 5 points of the minimum, Table 4), and based on the long-term plausibility of the survival estimates, the Weibull distribution was used in the broad population model analysis, alongside transition probabilities derived from DAPA-CKD (applied to sub-analyses 1, 2 and 3) and $DECLARE_{CKD}$ (applied to sub-analysis 2 and 3). The transition probability matrices were derived using the same method as in the original company model and shown in Appendix 4. This broad population cost-effectiveness analysis is referred to in the results below as unified broad population analysis 1 (UBP1).

		Figure 4: KMs and adjusted survival curves for placebo – unified broad population analysis 1 (weighted by [redacted]% uACR ≥200 and [redacted]% uACR <200, based on updated CPRD analysis)  **Footnotes**: Points and error bars represent 50th centile and 10-90th centile range, respectively, of expected survival of a CKD patient with albuminuria under standard of care in the expert elicitation exercise (see response to clarification questions for full details).

		Abbreviations: CPRD: clinical practice research datalink; KM: Kaplan-Meier; uACR: urinary albumin creatinine ratio. **Figure 5: KMs and adjusted survival curves for dapagliflozin – unified broad population analysis 1 (weighted by [redacted]% uACR ≥200 and [redacted]% uACR <200, based on updated CPRD analysis)**  **Footnotes**: Points and error bars represent 50th centile and 10-90th centile range, respectively, of expected survival of a CKD patient with albuminuria under standard of care in the expert elicitation exercise (see response to clarification questions for full details). **Abbreviations**: CPRD: clinical practice research datalink; KM: Kaplan-Meier; uACR: urinary albumin creatinine ratio.

Table 4: Distribution fitting comparison independent of treatment arm, UBPA1

Distribution	AIC	BIC
Gompertz	16615.07	16821.87
Weibull	16616.16	16822.95
Log-logistic	16617.44	16824.24
Gamma	16617.65	16824.45
Log-normal	16652.10	16858.89
Exponential	16663.97	16859.89

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; UBPA: unified broad population analysis.

Three additional approaches for survival modelling were explored, as outlined in Table 5. The results from each of these modelling approaches are presented in the results section below.

Table 5: Adjustment factor for event rates in non-T2DM versus T2DM patients

Modelling approach	Approach for survival modelling	Approach for transition probabilities
UBPA 1	DAPA-CKD and $DECLARE_{CKD}$ datasets combined for survival modelling; Weibull distribution selected given AIC/BIC and long-term plausibility	Transition probabilities derived from DAPA-CKD (applied to all health states in sub-analysis 1 and to CKD stage 4-5 health states in sub-analyses 2 and 3) and $DECLARE_{CKD}$ (applied to CKD stage 2-3b health states in sub-analyses 2 and 3), see Appendix 4. The use of transition probabilities from DAPA-CKD for CKD stage 4-5 health states in sub-analyses 2 and 3 is based on input from [redacted] who considered the transition probabilities from
UBPA 2	Restrict DAPA-CKD dataset to patients with baseline uACR ≥200 mg/g and restrict $DECLARE_{CKD}$ dataset to patients with uACR <200 mg/g to remove dataset overlaps, then combine datasets as per unified broad population analysis 1; fewer distributions converged – Gamma selected as best option	

UBPA 3	DAPA-CKD and DECLARE$_{CKD}$ datasets combined for survival modelling; uACR as a categorical covariable; Weibull distribution selected given AIC/BIC and long-term plausibility	DAPA-CKD to be more generalisable to these health states.
UBPA 4	Same approach as in unified broad population analysis 1	DAPA-CKD and DECLARE$_{CKD}$ datasets combined to derive single set of transition probabilities (see Appendix 5)

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; CKD: chronic kidney disease; T2DM: type 2 diabetes mellitus; uACR: urinary albumin creatinine ratio; UBPA: unified broad population analysis.

Cost-effectiveness results from broad population model

The broad population model was used to evaluate cost-effectiveness of dapagliflozin in the revised target population, as described above, i.e. the analysis was restricted to CKD patients treated with background ACE inhibitor/ARB, unless not tolerated. This restriction was implemented through updated CPRD analyses of patient characteristics, which excluded patients who are not treated with ACE inhibitor/ARB (see Appendix 1 for revised CPRD patient characteristics). The mean age of the CKD cohort from this CPRD analysis was higher than the expected mean age of CKD patients in UK clinical practice, and therefore a more plausible age estimate based on an analysis using a more general definition of CKD was applied as model inputs in the cost-effectiveness analysis (see additional issues table below).

Table 6: Results from unified broad population analyses

#	Modelling approach	Population	ΔCosts (£)	ΔQALYs	ICER
1	Original modelling approach	Previous company base case: overall CKD population	£3,095	0.503	£6,158
2	Original modelling approach	CKD population, treated with ACE inhibitors/ARB (based on updated CPRD patient characteristics), mean age 64	£5,181	0.734	£7,063
3	UBPA1	CKD population, treated with ACE inhibitors/ARB, mean age 64	£2,069	0.454	£4,557

4	UBPA2	CKD population, treated with ACE inhibitors/ARB, mean age 64	£2,888	0.396	£7,290
5	UBPA3	CKD population, treated with ACE inhibitors/ARB, mean age 64	£1,874	0.414	£4,531
6	UBPA4	CKD population, treated with ACE inhibitors/ARB, mean age 64	£3,507	0.515	£6,813
7	UBPA1	CKD patients with uACR ≥200 mg/g, treated with ACE inhibitors/ARB, mean age 64	-£1,183	0.587	Dominant
8	UBPA1	CKD patients with uACR <200 mg/g, treated with ACE inhibitors/ARB, mean age 64	£2,492	0.437	£5,705
9	UBPA1	CKD patients with uACR <200 mg/g, with T2DM, treated with ACE inhibitors/ARB, mean age 64	£2,801	0.517	£5,418
10	UBPA1	CKD patients with uACR <200 mg/g, without T2DM, treated with ACE inhibitors/ARB, mean age 64	£2,091	0.333	£6,285

Abbreviations: ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blockers; CKD: chronic kidney disease; uACR: urinary albumin creatinine ratio; UBPA: unified broad population analysis; T2DM: type 2 diabetes mellitus.

This additional evidence reduces the uncertainty around the clinical efficacy and cost-effectiveness of dapagliflozin with Incremental cost-effectiveness ratios (ICERs) remaining well below the cost-effectiveness threshold in the entire licenced CKD population as well as explicitly for patients with a uACR <200 mg/g. Based on the original modelling approach, the ICER for the total population of patients with CKD stages 1-4 already on ACE inhibitor/ARB therapy is £7,063. When using the UBPA1 approach, the ICER for the total population of patients with CKD stages 1-4 already on ACE inhibitor/ARB therapy is £4,557, whilst in those with CKD, no T2DM and low uACR, the ICER is £6,285. NICE communicated that a FTA could be pursued if the target population was amended to match the DAPA-CKD trial; the decision not to progress with an FTA despite the reduced timelines was taken because the data demonstrate the significant clinical value that dapagliflozin can provide to a patient population with a high unmet need despite ACE inhibitor/ARB therapy, holding the potential to prevent the progression of a chronic and incurable disease with significant cost implications.

Whilst AstraZeneca acknowledges that some residual uncertainty may remain, these additional analyses further demonstrate that dapagliflozin is very likely to represent a highly cost-effective option for treating patients with CKD irrespective of uACR levels. Given the cost-effective estimates, we firmly believe that despite some degree of residual uncertainty in the exact ICER, the risk of decision error remains incredibly low.

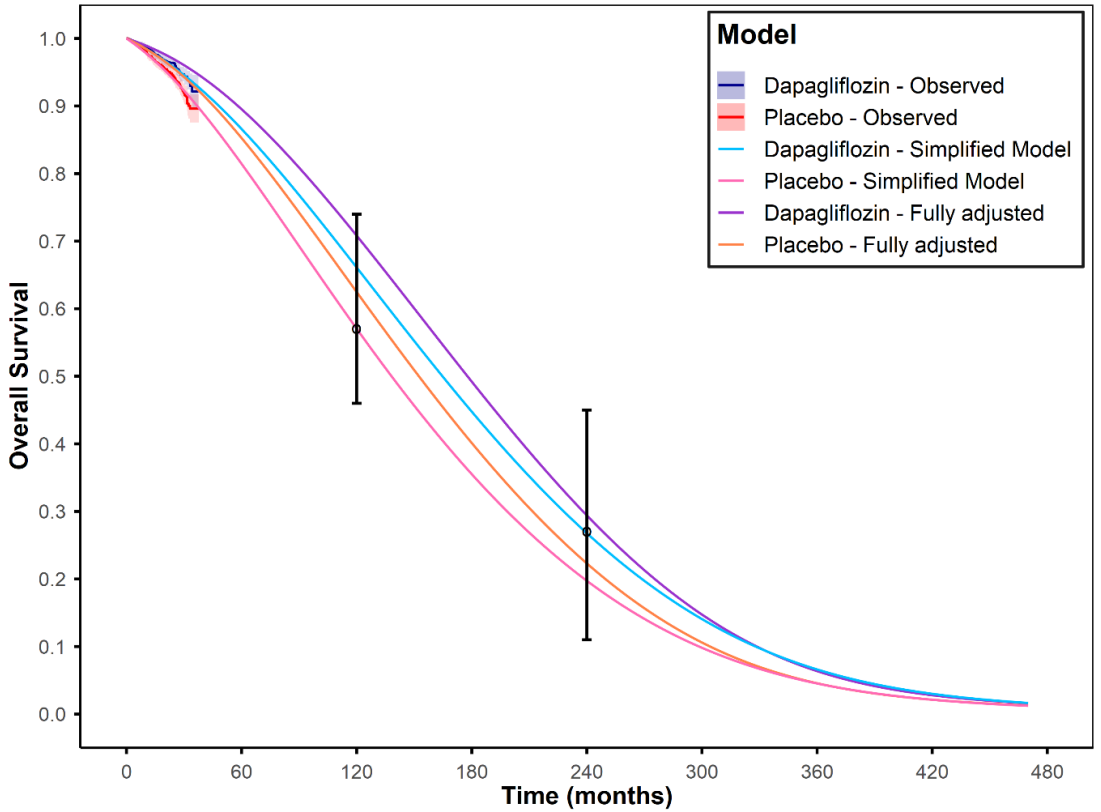
		A recommendation irrespective of uACR levels is aligned to the NHS's ambition to remove healthcare inequalities The NHS long-term plan highlights a commitment to disease prevention and removing healthcare inequalities. The plan explicitly commits to a more concentrated and systematic approach to reducing health inequalities with a promise that action on health inequalities will be central to the NHS. In addition, the recently published NICE 5-year strategy further commits to contributing to reducing healthcare inequalities. We firmly believe that given the highly innovative nature of dapagliflozin for the treatment of patients with CKD, the broad licence granted by the regulators, and the cost-effective estimates generated as result of all of the above analyses; that dapagliflozin offers NICE and the NHS an opportunity to reduce healthcare inequalities for patients with CKD. This is particularly important in the context of uACR testing, given that only approximately 16% of patients with CKD without T2DM and ~50% of those with T2DM receive a uACR test.[3] A restriction for the use of dapagliflozin by uACR would therefore result in a large proportion of patients being unnecessarily prevented from receiving optimal treatment despite an expected treatment benefit irrespective of uACR levels, and a proportion of untested patients likely to have a uACR >200 mg/g. Data from the DAPA-CKD trial shows that of all patients assessed for inclusion in the trial, [redacted]% of those with comorbid T2DM and [redacted]% of those without comorbid T2DM had a uACR of ≥200 mg/g at visit 1 (pre-randomisation)[4]. This illustrates that with a recommendation restricting access to the DAPA-CKD trial population, despite almost half of these patients meeting the uACR criteria, the majority wouldn't receive treatment because they are not being tested. Furthermore, [redacted] In addition, uACR testing rates are lower for patients of black or Asian ethnicity than for those of Caucasian background, and therefore a restriction by uACR is likely to further drive racial inequalities of healthcare across the UK.[5] CKD represents a major population health concern, and restricting access to dapagliflozin would not only prevent those with early stage CKD from receiving early intervention that halts their disease progression, but would also prevent treatment of patients with more advanced stage disease due to poor testing rates.
Key issue 2: Concerns	**YES**	As per the three points within this key issue raised by the ERG, this response is also structured based on:

regarding the company's overall modelling approach and OS predictions		• Use of a time-updated covariable for CKD stage • Mean of covariates issue • Overestimation of overall survival in both arms **Use of time-updated eGFR** Despite the ERG's comment that the use of a time-updated covariable for CKD stage may contribute to the overpredictions of overall survival, due to "problems determining causality", AstraZeneca does not consider the methodology used to be of concern from a statistical perspective. This is because there is no assumption about causality in the cost-effectiveness model. Instead, the transition probabilities and survival models within the cost-effectiveness analysis merely capture the associations observed in the DAPA-CKD trial. <u>Modelling of observed associations</u> In the cost-effectiveness model, a proportion of the treatment effect of dapagliflozin on all-cause mortality is modelled through a delay in CKD progression (using treatment-specific transition probabilities), with more severe CKD stage being associated with higher all-cause mortality. This relationship between CKD stage severity and all-cause mortality is well-established in the literature.[3, 6] Even when treatment-specific transition probabilities are used, there is a residual dapagliflozin treatment effect on all-cause mortality that is not accounted for, i.e. within any CKD stage, there was a lower hazard of death with dapagliflozin compared with placebo. This residual treatment effect is captured as the dapagliflozin coefficient in the survival model with time-updated CKD stage within the cost-effectiveness analysis. These two components of the dapagliflozin treatment effect captured in the cost-effectiveness analysis purely reflect observed associations (i.e. association between dapagliflozin and CKD progression, and the observed residual association between dapagliflozin and all-cause mortality). As such, the use of time-updated CKD stage (post-randomisation) is not a statistical concern, given the joint derivation of the transition probability matrices and the survival model. The company modelling approach was validated by [redacted] to appropriately capture the dynamic and progressive nature of CKD, with changes in risk factors for mortality (e.g. CKD stage) over time. The model predictions were also validated through the clinical expert elicitation of expected long-term survival in CKD patients (see Clarification Qs B4). In contrast, the time-homogeneous multi state model proposed by the ERG would represent an oversimplification CKD, and likely lead to survival predictions with poor face validity (the predictions from a time-

		homogenous model can likely be approximated using the exponential fully-adjusted survival model, see Document B, Figure 23). Joint derivation of transition probabilities and survival model, and application to cost-effectiveness analysis The treatment-specific transition probabilities and the all-cause survival model applied in the cost-effectiveness analyses were derived jointly but sequentially. As outlined in the company submission, a one-month intervalised dataset was created where interval covariates were determined by the last observed value (e.g. of eGFR) at or prior to the interval opening. The occurrence of death within an interval was used to inform the hazard of death among the complete at-risk population and thus parameterise the model of overall survival (OS). Subsequently, the at-risk population for determination of the transition matrices was reduced to those observed to survive the interval, and the rates of eGFR category transition determined by changes in observed eGFR category between interval opening and interval close. These transitions are thus conditional upon survival over the interval, and are consistently applied within the cost-effectiveness model after removal of patients dying within each interval as predicted by the OS equation upon the total at-risk population. Because of the use of last observed eGFR as a covariable in the all-cause survival model, the impact of CKD stage on mortality is taken into account, to ensure there is no double-counting when used alongside the treatment-specific transition probabilities in the cost-effectiveness analysis. Mean of covariate issue The ERG suggested the use of a "corrective group prognosis" model to overcome the mean of covariate issue. In contrast to the "time homogenous multi state" model also proposed by the ERG (see above), the full application of "corrected group prognosis" to the time-varying patient characteristics within the economic model is a much more complex task requiring the prediction of eGFR-conditional predictor joint distributions over time. This was not possible to do within the time available during technical engagement, however, other more complex modelling approaches, such as individual patient simulations, have previously been developed. The CREDEM-DKD model was a microsimulation model developed to estimate the cost-effectiveness of canagliflozin, another sodium-glucose transport protein 2 (SGLT2) inhibitor with a comparable treatment effect as dapagliflozin (see matching-adjusted indirect comparison [MAIC] in company submission), for the treatment of CKD with T2DM, based on individual patient data from the CREDENCE trial. The results from this model shows that canagliflozin was associated with both quality-adjusted life year (QALY) gains and cost-savings over a 10 year time horizon.[7] Similarly, a microsimulation model based on DAPA-CKD individual patient data was originally developed during model conceptualisation, demonstrating similar results as the final cohort Markov model. However, the DAPA-CKD microsimulation model was deprioritised in favour of the cohort Markov model, given the ability of the simpler cohort Markov model to still capture the key characteristics of CKD that impact cost-effectiveness.

		The simple Gompertz survival model, previously presented in response to Clarification Q B31, overcomes the mean of covariate issue by only including time-updated CKD stage, treatment, age and sex as covariables. This means that the values of other covariables are not used to inform the survival modelling. The simple Gompertz model captures the mortality hazard associated with each CKD stage, rather than merely reflecting the marginal differences in hazard associated with the time-updated CKD stage variable itself when modelled alongside other covariables. Figure 6 shows that the simple Gompertz model provides a good fit to the observed trial data and the expected long-term survival as elicited from clinical experts. The cost-effectiveness results from using the simple Gompertz model is highly comparable to the results using the fully adjusted survival model used in the company base case (£6,493/QALY vs £5,841/QALY; see Clarification Qs response, Table 31).

Figure 6: Observed survival in DAPA-CKD versus model OS, controlling for time-varying CKD stage alone (simple Gompertz)



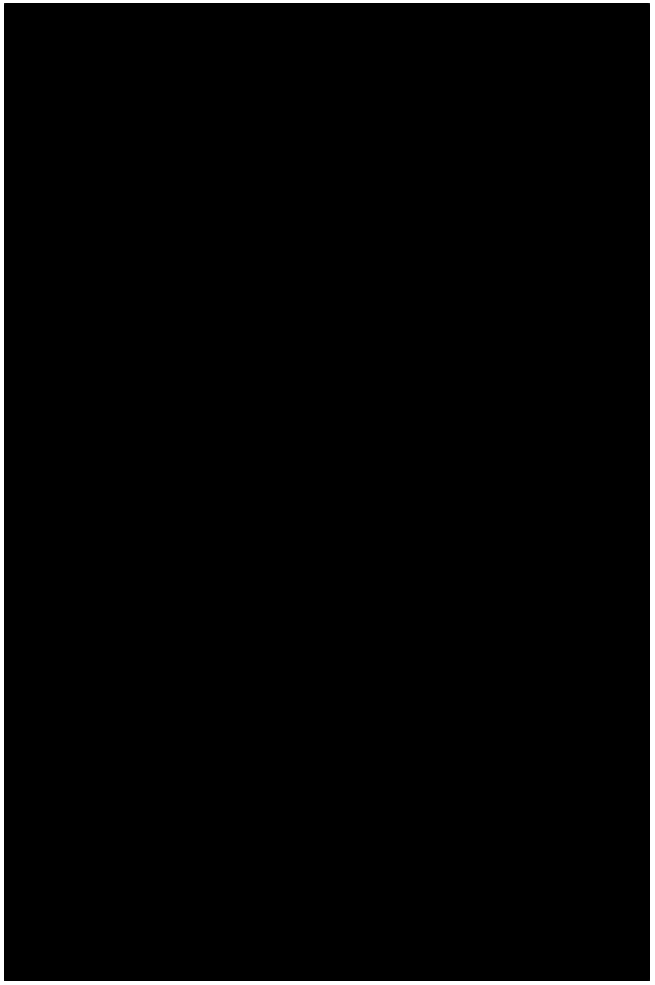
Footnotes: "Observed" – Kaplan-Meier estimator of OS from DAPA-CKD; "Simplified Model" – Gompertz model of OS dependent only upon time, eGFR and treatment status (i.e. without baseline adjustment); "Fully adjusted" – Gompertz model with covariate set used in company base case. Points and error bars represent 50th centile and 10-90th centile range, respectively, of expected survival of a CKD patient with albuminuria under standard of care in the expert elicitation exercise (see response to clarification questions for full details).
Abbreviations: CKD: chronic kidney disease; OS: overall survival.

		One further modelling approach, a standardised mortality ratio (SMR) approach, was explored to address the "mean of covariates" concern from the ERG. For this modelling approach, the assumption of proportional hazards relative to a non-parametric baseline hazard function of age and sex matched lifetable hazard, conditioned upon last-observed (monthly interval) eGFR category and treatment, was made, to derive a hazard ratio for each CKD stage health state relative to the general population. Hazard and cumulative hazard functions were defined as below, i.e. coefficients act to scale the reference (lifetable) hazard proportionally: $h(t\|\boldsymbol{x}) = h_{lt}(t)$*exp($\boldsymbol{x}'\boldsymbol{\beta}$) $H(t\|\boldsymbol{x}) = H_{lt}(t)$*exp($\boldsymbol{x}'\boldsymbol{\beta}$) Models were fitted by maximum likelihood, using the *flexsurv* package framework with the above defined hazard and cumulative hazard user-defined functions. Table 7 summarises the SMR model. The reference lifetables were derived using the Ederer-I marginal lifetable method to generate a survival curve in a matched UK general population. The Ederer-I marginal lifetable survival curve was derived based on: $$S_{LT,marginal} = \frac{1}{N}\sum_{i=1}^{N} S_{LT}(t\|x_i)$$ Where $S_{LT}(t\|x_i)$ is the survival due to life tables of patient i with characteristics (baseline age, sex) x_i within DAPA-CKD, with $x_1, \ldots, x_N$ being all patients within DAPA-CKD. Figure 7 shows the survival curve of a matched UK general population and the survival predictions using the SMR model, which provide a good fit to the observed survival in DAPA-CKD. The cost-effectiveness estimates using the SMR modelling approach is summarised in Table 8 alongside the cost-effectiveness estimates for the DAPA-CKD population using the original modelling approach. The results from these two modelling approaches closely match each other, providing further evidence that the mean of covariates use in the original modelling approach does not bias the cost-effectiveness results.

Table 7: SMR model fitted to last observed eGFR category and treatment arm

	Estimate	L95%	U95%	SE	Hazard ratio (vs general population) - placebo	Hazard ratio (vs general population) – dapagliflozin
Intercept (<15 eGFR)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment - Dapa 10 mg	[redacted]	[redacted]	[redacted]	[redacted]		
eGFR 15 – 30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
eGFR 30 – 60	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
eGFR ≥60	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: [a]Within the economic model, probabilities less than general population mortality are increased to general population mortality.
Abbreviations: eGFR: estimated glomerular filtration rate; SE: standard error; SMR: standardised mortality ratio.

		Figure 7: Observed survival in DAPA-CKD versus predictions using the SMR model based on DAPA-CKD matched lifetable reference hazard, taking eGFR and treatment into account  **Footnotes:** "Controlled" models – base-case fully adjusted Gompertz models (company base case in response to ERG clarification questions).

Abbreviations: eGFR: estimated glomerular filtration rate; SMR: standardised mortality ratio; TE: technical engagement.

Table 8: Cost-effectiveness estimates from fully adjusted survival equations (original modelling approach) and SMR modelling approach

	Dapagliflozin + SOC (intervention)	Placebo + SOC (comparator)	Incremental	ICER (£/QALY)
Fully adjusted survival equations (original modelling approach), DAPA-CKD patient profile				
Life years	11.529	10.461	1.068	£5,841
QALYs	8.057	7.288	0.768	
Costs (£)	£78,399	£73,910	£4,489	
SMR modelling approach				
Life years	12.345	11.361	0.984	£4,551
QALYs	8.581	7.867	0.715	
Costs (£)	£86,533	£83,280	£3,253	

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years; SMR: standardised mortality ratio; SOC: standard of care.

Overestimation of OS in both arms

The ERG's concern around the overestimation of OS in the dapagliflozin and placebo arms compared to observed data, can be addressed by the simple Gompertz model and the SMR model outlined above. Figure 6 and Figure 7 show that these alternative survival model provide a good fit to the observed trial data and to the expected long-term survival elicited from clinical experts. The cost-effectiveness results based on the use of these alternative survival modelling approaches are consistent with the results from the original company modelling approach, showing that the original company modelling approach does not bias the cost-effectiveness results.

The same conclusion was also reached by the ERG, based on Exploratory Analysis 7 (EA7) in the ERG report, where the ERG applied a hazard ratio of 1.4 to both the dapagliflozin arm and the placebo arm to force the survival model to better fit the observed trial data. The resulting ICER only differed by ~£200/QALY compared with the company base case, providing further evidence that the original company modelling approach does not bias the cost-effectiveness results.

		Given the conclusion from the simple Gompertz model, the SMR model, and the ERG EA7 scenario, that the company's original survival model does not bias the ICER, the company base case modelling approach remains the same, with the use of the fully adjusted survival model (as per response to ERG Clarification Qs).

Appendix 1 – updated CPRD patient characteristics, restricted to CKD patients treated with ACE inhibitors/ARB

The CPRD analysis used in the base case cost-effectiveness model has been amended to include only patients already on ACE inhibitor/ARB therapy.

The following patient subpopulations were also excluded from the analysis in order to more closely mirror the DAPA-CKD trial population in all other ways except CKD stage as measured by eGFR and uACR and to better reflect those that would receive treatment with dapagliflozin for their CKD in clinical practice: T1DM, PKD, NYHA class IV HF and organ transplant.

Table 9: CPRD patient characteristics

Characteristic	CPRD subgroup with ACE inhibitors/ARB		CPRD subgroup with uACR <200 mg/g[a] and with ACE inhibitors/ARB		CPRD subgroup with uACR ≥200 mg/g[a] and with ACE inhibitors/ARB		CPRD subgroup with uACR <200 mg/g[a],with T2DM and with ACE inhibitors/ARB		CPRD subgroup with uACR <200 mg/g[a],without T2DM and with ACE inhibitors/ARB	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Patient characteristics										
Age (years)	[redacted]									
Female	[redacted]									
BMI (kg/m^2)	[redacted]									
Race: White	[redacted]									
Race: Black or African American	[redacted]									
Race: Other	[redacted]									
Smoker	[redacted]									
Clinical characteristics										
CKD 1	[redacted]									
CKD 2	[redacted]									

	CKD 3a	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	CKD 3b	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	CKD 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	CKD 5 (pre-RRT)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Dialysis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Transplant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	uACR: <30 mg/g (3.39 mg/mmol)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	uACR: 30–300 mg/g (3.39–33.9 mg/mmol)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	uACR: ≥300 mg/g (33.9 mg/mmol)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	T2DM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Glomerulonephritis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ACE inhibitor	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ARB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	MRA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Diuretic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Potassium (mmol/L)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Systolic blood pressure (mmHg)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Haemoglobin (g/dL)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	History										
	Prior HF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Prior MI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Prior stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnote: Variables reported in the table are proportions unless otherwise stated. [a]uACR of 200 mg/g=22.6 mg/mmol.
Abbreviations: ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker; BMI: body mass index; CKD: chronic kidney disease; CPRD: clinical practice research datalink; HF: heart failure; MI: myocardial infarction; MRA: mineralocorticoid receptor antagonist; RRT: renal replacement therapy; SE: standard error; T2DM: type 2 diabetes mellitus; uACR: urine albumin creatinine ratio.

Appendix 2 – unified broad population analysis survival model

Table 10: Parameterisations of all-cause survival in unified broad population analysis 1 – Weibull distribution

Covariate	Coefficient	SE	p value
Shape	1.296	0.0458	--
Scale	32709.8	17882.2	--
Dapagliflozin	0.2017	0.0556	<0.001
Age	-0.0286	0.0036	<0.001
Female	0.1531	0.0639	0.008
Race: Black or African American	-0.4742	0.158	0.001
Race: White	-0.3886	0.0987	<0.001
Race: Other	-0.6468	0.1372	<0.001
BMI (kg/m^2)	0.0039	0.0049	0.214
eGFR <15 ml/min/1.73 m^2	-1.0794	0.1976	<0.001
eGFR 15–30 ml/min/1.73 m^2	-0.4876	0.1167	<0.001
eGFR 30–60 ml/min/1.73 m^2	-0.141	0.0687	0.020
Haemoglobin (g/dL)	0.0577	0.0191	0.001
Glomerulonephritis	--	--	--
Systolic blood pressure (mmHg)	-6.58E-04	0.0016	0.343
Potassium (mmol/L)	0.0428	0.0558	0.222
Prior HF	-0.5502	0.0691	<0.001
Prior MI	-0.3289	0.0645	<0.001
Prior stroke	-0.3873	0.0844	<0.001

	Footnotes: Note glomerulonephritis is not included as a factor. No usable data from $DECLARE_{CKD}$ were available so the factor was removed from consideration for the unified data set. **Abbreviations**: BMI: body mass index; eGFR: estimated glomerular filtration rate; HF: heart failure; MI: myocardial infarction; SE: standard error.
Appendix 3 – Simulated treatment outcomes analysis	Poisson regression models fitted from DAPA-CKD data independently for dapagliflozin and placebo as shown below. **Figure 8: Annual event rates per 100 patients with dapagliflozin versus placebo, for the primary endpoint, sustained eGFR decline ≥50% and ESKD**  **Footnotes**: Points correspond to estimated event rates from patient data. Coloured bands represent 95% confidence intervals. The primary endpoint was ≥50% sustained decline in eGFR, ESKD, CV death or renal death. **Abbreviations**: eGFR: estimated glomerular filtration rate; ESKD: end-stage kidney disease; uACR: urinary albumin creatinine ratio. **Source**: AstraZeneca Data on File 2021d: Simulated treatment outcomes analysis summary.[1]

Table 11: Annual event rates per 100 patients with dapagliflozin versus placebo by uACR thresholds

Endpoint	uACR (mg/g)	Annual event rate / 100 patients	
		Placebo	Dapa 10mg
Primary endpoint	30	[redacted]	[redacted]
	300	[redacted]	[redacted]
	1,000	[redacted]	[redacted]
Sustained eGFR decline >50%	30	[redacted]	[redacted]
	300	[redacted]	[redacted]
	1,000	[redacted]	[redacted]
ESKD	30	[redacted]	[redacted]
	300	[redacted]	[redacted]
	1,000	[redacted]	[redacted]

Abbreviations: eGFR: estimated glomerular filtration rate; ESKD: end-stage kidney disease; uACR: urinary albumin creatinine ratio.
Source: AstraZeneca Data on File 2021d: Simulated treatment outcomes analysis summary.[1]

Poisson regression models fitted from DAPA-CKD data independently for dapagliflozin and placebo for the T2DM and non-T2DM cohort as shown below.

Figure 9: Annual event rates per 100 patients with dapagliflozin versus placebo, for the primary endpoint, sustained eGFR decline ≥50% and ESKD, T2DM and non-T2DM

Footnotes: Points correspond to estimated event rates from patient data. Coloured bands represent 95% confidence intervals. The primary endpoint was ≥50% sustained decline in eGFR, ESKD, CV death or renal death.
Abbreviations: eGFR: estimated glomerular filtration rate; ESRD: end-stage renal disease; T2DM: type 2 diabetes mellitus; uACR: urinary albumin creatinine ratio.
Source: AstraZeneca Data on File 2021d: Simulated treatment outcomes analysis summary.[1]

Table 12: Annual event rates per 100 patients with dapagliflozin versus placebo by uACR thresholds, T2DM and non-T2DM

Endpoint	Baseline status	uACR (mg/g)	Annual event rate / 100 patients	
			Placebo	Dapa 10mg
Primary endpoint	Non-T2DM	30	[redacted]	[redacted]
		300	[redacted]	[redacted]
		1,000	[redacted]	[redacted]
	T2DM	30	[redacted]	[redacted]
		300	[redacted]	[redacted]
		1,000	[redacted]	[redacted]
Sustained eGFR decline >50%	Non-T2DM	30	[redacted]	[redacted]
		300	[redacted]	[redacted]
		1,000	[redacted]	[redacted]
	T2DM	30	[redacted]	[redacted]
		300	[redacted]	[redacted]
		1,000	[redacted]	[redacted]
ESKD	Non-T2DM	30	[redacted]	[redacted]
		300	[redacted]	[redacted]
		1,000	[redacted]	[redacted]
	T2DM	30	[redacted]	[redacted]
		300	[redacted]	[redacted]
		1,000	[redacted]	[redacted]

Footnotes: Patient numbers: T2DM: 1455 dapagliflozin, 1451 placebo; non-T2DM: 697 dapagliflozin, 701 placebo.
Abbreviations: eGFR: estimated glomerular filtration rate; ESKD: end-stage kidney disease; T2DM: type 2 diabetes mellitus; uACR: urinary albumin creatinine ratio.

Source: AstraZeneca Data on File 2021d: Simulated treatment outcomes analysis summary.[1]

Appendix 4 – transition probabilities derived from DECLARE$_{CKD}$

Table 13: Transition probabilities derived from DECLARE$_{CKD}$ and DAPA-CKD for sub-analysis 2 and sub-analysis 3 – dapagliflozin

Mean (SE)		To								Reference
		CKD 1	CKD 2	CKD 3a	CKD 3b	CKD 4	CKD 5	Dialysis	Kidney transplant	
Months 0-4										
From	CKD 1	0.9977 (0.0008)	0.0006 (0.0004)	0.0003 (0.0003)	0.0003 (0.0003)	0.0003 (0.0003)	0.0003 (0.0003)	0.0003 (0.0003)	0.0003 (0.0003)	DECLARE$_{CKD}$[8]
	CKD 2	0.0003 (0.0003)	0.9975 (0.0009)	0.0006 (0.0004)	0.0003 (0.0003)	0.0003 (0.0003)	0.0003 (0.0003)	0.0003 (0.0003)	0.0003 (0.0003)	
	CKD 3a	0.0006 (0.0006)	0.0013 (0.0009)	0.9931 (0.0021)	0.0019 (0.0011)	0.0013 (0.0009)	0.0006 (0.0006)	0.0006 (0.0006)	0.0006 (0.0006)	
	CKD 3b	0.0039 (0.0039)	0.0039 (0.0039)	0.0118 (0.0067)	0.9647 (0.0115)	0.0039 (0.0039)	0.0039 (0.0039)	0.0039 (0.0039)	0.0039 (0.0039)	
	CKD 4	0.001 (0.001)	0.003 (0.001)	0.006 (0.002)	0.143 (0.008)	0.843 (0.008)	0.004 (0.001)	0.001 (0.001)	0.001 (0.000)	DAPA-CKD[9]
	CKD 5	0.063 (0.060)	0.125 (0.080)	0.062 (0.058)	0.124 (0.080)	0.375 (0.118)	0.125 (0.080)	0.063 (0.059)	0.062 (0.059)	
	Dialysis	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.995 (0.100)	0.005 (0.000)	Sugrue et al. 2019[6]
	Kidney transplant	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.007 (0.001)	0.993 (0.099)	
Months 5 and onwards										
From	CKD 1	0.9702 (0.001)	0.0287 (0.001)	0.0008 (0.0002)	0.0001 (0.0001)	0.0001 (0.0001)	0 (0)	0 (0)	0 (0)	DECLARE$_{CKD}$[8]
	CKD 2	0.0124 (0.0006)	0.9714 (0.0009)	0.0148 (0.0006)	0.0013 (0.0002)	0.0002 (0.0001)	0 (0)	0 (0)	0 (0)	
	CKD 3a	0.0014 (0.0003)	0.029 (0.0014)	0.9503 (0.0018)	0.0187 (0.0011)	0.0004 (0.0002)	0.0001 (0.0001)	0.0001 (0.0001)	0.0001 (0.0001)	

	CKD 3b	0.0012 (0.0005)	0.0069 (0.0013)	0.0377 (0.003)	0.9465 (0.0035)	0.0062 (0.0012)	0.001 (0.0005)	0.0002 (0.0002)	0.0002 (0.0002)	
	CKD 4	0.000 (0.000)	0.000 (0.000)	0.001 (0.000)	0.035 (0.002)	0.952 (0.002)	0.010 (0.001)	0.001 (0.000)	0.000 (0.000)	DAPA-CKD[9]
	CKD 5	0.001 (0.001)	0.002 (0.001)	0.002 (0.001)	0.001 (0.001)	0.027 (0.005)	0.920 (0.008)	0.045 (0.006)	0.002 (0.001)	
	Dialysis	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.995 (0.100)	0.005 (0.000)	Sugrue et al. 2019[6]
	Kidney transplant	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.007 (0.001)	0.993 (0.099)	

Abbreviations: CKD: chronic kidney disease; SE: standard error.

Table 14: Transition probabilities derived from DECLARE$_{CKD}$ and DAPA-CKD for sub-analysis 2 and sub-analysis 3 – placebo

Mean (SE)		To								Reference
		CKD 1	CKD 2	CKD 3a	CKD 3b	CKD 4	CKD 5	Dialysis	Kidney transplant	
Months 0-4										
From	CKD 1	0.9973 (0.0009)	0.0009 (0.0005)	0.0003 (0.0003)	0.0003 (0.0003)	0.0003 (0.0003)	0.0003 (0.0003)	0.0003 (0.0003)	0.0003 (0.0003)	DECLARE$_{CKD}$[8]
	CKD 2	0.0003 (0.0003)	0.9976 (0.0009)	0.0006 (0.0004)	0.0003 (0.0003)	0.0003 (0.0003)	0.0003 (0.0003)	0.0003 (0.0003)	0.0003 (0.0003)	
	CKD 3a	0.0005 (0.0005)	0.0016 (0.0009)	0.9946 (0.0017)	0.0005 (0.0005)	0.0011 (0.0008)	0.0005 (0.0005)	0.0005 (0.0005)	0.0005 (0.0005)	
	CKD 3b	0.0039 (0.0038)	0.0077 (0.0054)	0.0077 (0.0054)	0.9652 (0.0114)	0.0039 (0.0038)	0.0039 (0.0039)	0.0039 (0.0039)	0.0039 (0.0039)	
	CKD 4	0.001 (0.001)	0.002 (0.001)	0.005 (0.002)	0.127 (0.008)	0.856 (0.009)	0.007 (0.002)	0.001 (0.001)	0.001 (0.001)	DAPA-CKD[9]
	CKD 5	0.043 (0.041)	0.174 (0.077)	0.043 (0.042)	0.044 (0.042)	0.175 (0.077)	0.348 (0.097)	0.130 (0.068)	0.043 (0.041)	
	Dialysis	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.995 (0.100)	0.005 (0.000)	Sugrue et al. 2019[6]

	Kidney transplant	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.007 (0.001)	0.993 (0.099)	
Months 5 and onwards										
From	CKD 1	0.9695 (0.0011)	0.029 (0.0011)	0.0009 (0.0002)	0.0004 (0.0001)	0.0002 (0.0001)	0 (0)	0 (0)	0 (0)	DECLARE$_{CKD}$[8]
	CKD 2	0.0107 (0.0005)	0.9693 (0.0009)	0.0178 (0.0007)	0.0019 (0.0002)	0.0001 (0.0001)	0.0001 (0.0001)	0 (0)	0 (0)	
	CKD 3a	0.0011 (0.0003)	0.0333 (0.0015)	0.9417 (0.002)	0.0228 (0.0012)	0.0008 (0.0002)	0.0001 (0.0001)	0.0001 (0.0001)	0.0001 (0.0001)	
	CKD 3b	0.0014 (0.0006)	0.0068 (0.0012)	0.041 (0.003)	0.9405 (0.0036)	0.0097 (0.0015)	0.0002 (0.0002)	0.0002 (0.0002)	0.0002 (0.0002)	
	CKD 4	0.000 (0.000)	0.001 (0.000)	0.001 (0.000)	0.028 (0.001)	0.954 (0.002)	0.014 (0.001)	0.002 (0.000)	0.000 (0.000)	DAPA-CKD[9]
	CKD 5	0.001 (0.001)	0.001 (0.001)	0.001 (0.001)	0.002 (0.001)	0.038 (0.005)	0.910 (0.008)	0.044 (0.005)	0.003 (0.002)	
	Dialysis	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.995 (0.100)	0.005 (0.000)	Sugrue et al. 2019[6]
	Kidney transplant	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.007 (0.001)	0.993 (0.099)	

Abbreviations: CKD: chronic kidney disease; SE: standard error.

Appendix 5 – transition probabilities derived from DAPA-CKD and DECLARE$_{CKD}$ unified dataset

Table 15: DAPA-CKD and DECLARE$_{CKD}$ unified dataset health state transition matrix – dapagliflozin

Mean (SE)		To								Reference
		CKD 1	CKD 2	CKD 3a	CKD 3b	CKD 4	CKD 5	Dialysis	Kidney transplant	
Months 0-4										
From	CKD 1	0.996 (0.001)	0.002 (0.001)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	

		CKD 2	0.002 (0.001)	0.973 (0.002)	0.023 (0.002)	0.002 (0.001)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	DAPA-CKD[9]/ DECLARE$_{CKD}$[8]
		CKD 3a	0.000 (0.000)	0.030 (0.003)	0.909 (0.005)	0.057 (0.004)	0.003 (0.001)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	
		CKD 3b	0.000 (0.000)	0.003 (0.001)	0.050 (0.003)	0.877 (0.005)	0.069 (0.004)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	
		CKD 4	0.001 (0.001)	0.001 (0.001)	0.004 (0.001)	0.094 (0.006)	0.895 (0.007)	0.003 (0.001)	0.000 (0.000)	0.000 (0.000)	
		CKD 5	0.041 (0.040)	0.083 (0.055)	0.042 (0.040)	0.083 (0.055)	0.209 (0.081)	0.458 (0.100)	0.042 (0.040)	0.042 (0.040)	
		Dialysis	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.995 (0.100)	0.005 (0.000)	Sugrue et al. 2019[6]
		Kidney transplant	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.007 (0.001)	0.993 (0.099)	
	Months 5 and onwards										
	From	CKD 1	0.970 (0.001)	0.029 (0.001)	0.001 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	
		CKD 2	0.011 (0.000)	0.968 (0.001)	0.019 (0.001)	0.001 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	
		CKD 3a	0.001 (0.000)	0.025 (0.001)	0.940 (0.001)	0.033 (0.001)	0.001 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	DAPA-CKD[9]/ DECLARE$_{CKD}$[8]
		CKD 3b	0.000 (0.000)	0.002 (0.000)	0.026 (0.001)	0.943 (0.001)	0.027 (0.001)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	
		CKD 4	0.000 (0.000)	0.001 (0.000)	0.001 (0.000)	0.036 (0.002)	0.952 (0.002)	0.010 (0.001)	0.000 (0.000)	0.000 (0.000)	
		CKD 5	0.001 (0.001)	0.003 (0.001)	0.001 (0.001)	0.002 (0.001)	0.022 (0.004)	0.969 (0.005)	0.001 (0.001)	0.001 (0.001)	
		Dialysis	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.995 (0.100)	0.005 (0.000)	Sugrue et al. 2019[6]
		Kidney transplant	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.007 (0.001)	0.993 (0.099)	

Abbreviations: CKD: chronic kidney disease; SE: standard error.

Table 16: DAPA-CKD and DECLARE$_{CKD}$ unified dataset health state transition matrix – placebo

Mean (SE)		To								Reference
		CKD 1	CKD 2	CKD 3a	CKD 3b	CKD 4	CKD 5	Dialysis	Kidney transplant	
Months 0-4										
From	CKD 1	0.997 (0.001)	0.001 (0.001)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	DAPA-CKD[9] /DECLARE$_{CKD}$[8]
	CKD 2	0.002 (0.001)	0.972 (0.002)	0.023 (0.002)	0.002 (0.001)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	
	CKD 3a	0.000 (0.000)	0.030 (0.002)	0.907 (0.004)	0.060 (0.003)	0.002 (0.001)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	
	CKD 3b	0.001 (0.000)	0.004 (0.001)	0.057 (0.004)	0.881 (0.005)	0.056 (0.004)	0.001 (0.001)	0.000 (0.000)	0.000 (0.000)	
	CKD 4	0.001 (0.001)	0.002 (0.001)	0.003 (0.001)	0.087 (0.007)	0.899 (0.007)	0.007 (0.002)	0.001 (0.001)	0.001 (0.001)	
	CKD 5	0.045 (0.043)	0.091 (0.060)	0.046 (0.044)	0.045 (0.043)	0.227 (0.087)	0.455 (0.104)	0.045 (0.043)	0.046 (0.044)	
	Dialysis	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.995 (0.100)	0.005 (0.000)	Sugrue et al. 2019[6]
	Kidney transplant	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.007 (0.001)	0.993 (0.099)	
Months 5 and onwards										
From	CKD 1	0.972 (0.001)	0.027 (0.001)	0.001 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	DAPA-CKD[9] /DECLARE$_{CKD}$[8]
	CKD 2	0.009 (0.000)	0.967 (0.001)	0.021 (0.001)	0.003 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	

	CKD 3a	0.001 (0.000)	0.026 (0.001)	0.936 (0.001)	0.036 (0.001)	0.002 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	
	CKD 3b	0.000 (0.000)	0.002 (0.000)	0.028 (0.001)	0.937 (0.001)	0.032 (0.001)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	
	CKD 4	0.000 (0.000)	0.001 (0.000)	0.002 (0.000)	0.028 (0.001)	0.956 (0.002)	0.013 (0.001)	0.000 (0.000)	0.000 (0.000)	
	CKD 5	0.001 (0.001)	0.003 (0.001)	0.003 (0.001)	0.001 (0.001)	0.033 (0.004)	0.958 (0.005)	0.001 (0.001)	0.001 (0.001)	
	Dialysis	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.995 (0.100)	0.005 (0.000)	Sugrue et al. 2019[6]
	Kidney transplant	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.007 (0.001)	0.993 (0.099)	

Abbreviations: CKD: chronic kidney disease; SE: standard error.

Appendix 6 – mean age from CPRD analysis of patients with eGFR<90 ml/min/1.73 cm²

This CPRD analysis captures patients with eGFR 15–90 ml/min/1.73 cm². The following patient subpopulations were also excluded from the analysis in order to more closely mirror the DAPA-CKD trial population in all other ways except CKD stage as measured by eGFR and uACR and to better reflect those that would receive treatment with dapagliflozin for their CKD in clinical practice: T1DM, PKD, NYHA class IV HF and organ transplant.

Table 17: Mean age of patients in CPRD with eGFR <90 ml/min/1.73 cm²

Characteristic	CPRD subgroup with ACE inhibitors/ARB	
	Mean	SE
Age (years)	64	[redacted]

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Mean age of target population	N/A	Yes	Following further clinical input, AstraZeneca became aware that the mean age of patients included with in the CPRD analysis conducted to inform the patient characteristics in the original cost-effectiveness model was significantly overestimated. This is because patients were only included if they had a formal diagnosis of CKD stages 1 to 4 and were on ACE inhibitor/ARB therapy. However, it has been reported that over 40% of people with CKD in England are undiagnosed, with the majority of those with asymptomatic early stage CKD unlikely to receive a formal diagnosis until more advanced stages of disease.[10] In order to receive a diagnosis of CKD during the earlier stages of disease (i.e. stages 1 or 2) a uACR test is required. Based on the National CKD Audit 2017, 86% of patients have annual eGFR tests.[3] In contrast, out of those who receive an eGFR test only 15% of patients without T2DM and 54% of patients with T2DM, receive a uACR test, and as such, few patients with early CKD are identified.[3] Consequently, patients with CKD stages 1 and 2 are significantly underrepresented in the CPRD analysis, accounting for just [redacted]% and [redacted]% of the total CKD stages 1–4 population, respectively,[11] whilst published estimates suggest 4% and 14% of CKD patients are expected to have stage 1 and 2 disease, respectively.[10] CKD is a chronic, progressive disease, and patients with earlier stage disease are on average considerably younger than those with later stage disease. In the CPRD analysis conducted by AstraZeneca for use in the cost-effectiveness model, the mean age of patients with CKD stage 1 and 2 is [redacted] and [redacted] years, respectively, compared with [redacted] and [redacted] years in those with CKD stages 3 and 4.[11] This means that the CPRD data are confounded by the under representation of stages 1 and 2 in the CPRD

			analysis compared with the real-world; thereby artificially increasing the mean age of the total CPRD population to 77 years. Clinical experts consulted by AstraZeneca advised that the mean age of patients predicted by the CPRD data is not representative of those expected in clinical practice. Experts suggested that an age between 60–70 years would be more clinically plausible. These estimates are aligned with those predicted within clinical studies, and published literature. For example, the mean age of patients enrolled in the DAPA-CKD trial (n=4,304) was 61 years,[12] and was between [redacted] and [redacted] years in patients enrolled with the DECLARE-TIMI 58 trial who were classified as having CKD based on the Kidney Disease: Improving Global Outcomes (KDIGO) criteria (i.e. patients with an eGFR <60 ml/min/1.73 m^2 and/or a uACR >30 mg/g).[8] In addition, a UK primary care longitudinal cohort study conducted in 2013–2017 (N=861), reported that the mean age of patients aged >60 years with CKD stage 1–4 was 74 years.[10] However, this is also likely to overestimate the mean age of all patients in clinical practice due to patients being required to be >60 years old to be included within the study. To provide a more accurate estimate of the mean age of patients who are likely to receive treatment with dapagliflozin, AstraZeneca conducted a new CPRD analysis which included patients with CKD stages 1–4 based on an eGFR of <90 and >15 ml/min/1.73 cm^2, without the requirement for a formal CKD diagnosis. This approach was adopted due to the reasons set out above. This new analyses demonstrated the average age of patients with impaired renal function was 64 years, and is aligned with the expectation shared by UK clinical experts and falls within the range predicted by DAPA-CKD, DECLARE, and the UK longitudinal cohort study (61–74 years).[10, 11] By identifying patients in this way, those with early stage CKD who are not being identified and diagnosed because of low uACR testing rates are included, providing a more accurate representation of the whole real-world patient cohort who could benefit from treatment with dapagliflozin. This estimate is thought to be the most representative of clinical practice for this target population and allows age estimates for each subgroup (T2DM, non-TDM, uACR <200 mg/g, uACR >200 mg/g) to be determined (see Appendix 6). Therefore, these data have been used in the base case modelling approach and the additional broad population modelling approaches

			provided as part of AstraZeneca's response to the ERGs key issue 1 regarding the uncertainty surrounding the target population,

Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER
Key issue 1: Uncertainty surrounding the target population and the effectiveness of dapagliflozin in patients excluded from DAPA-CKD	The previous company base case used the patient characteristics from the overall CKD population from CPRD, without and criteria for background ACE inhibitor/ARB use.	Amendment of target population to CKD patients with background ACE inhibitor/ARB, unless not tolerated. The CPRD patient characteristics used for modelling was updated to capture the subgroup of CKD patients with ACE inhibitor/ARB (see Appendix 1). Mean age was assumed to be 64 (see other issues table above).	New ICER: £7,063/QALY Change from previous ICER: +£904/QALY
Key issue 1: Uncertainty surrounding the target population and the effectiveness of dapagliflozin in patients excluded from DAPA-CKD	Unified board population analysis, whereby DAPA-CKD and DECLARE$_{CKD}$ datasets were combined for survival modelling and derivation of a single set of transition probabilities (unified broad population analysis 1).	Details of the unified broad population analysis approach are provided in the response table above.	New ICER: £4,557/QALY Change from previous ICER: -£1,602/QALY
Company's preferred base case following technical engagement	Incremental QALYs: 0.734	Incremental costs: £5,181	Revised company base case ICER: £7,063/QALY Change from previous ICER: +£904/QALY

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NICE National Institute for Health and Care Excellence

Clinical expert statement & technical engagement response form

Dapagliflozin for treating chronic kidney disease [ID3866]

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on dapagliflozin in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form:

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

Please return this form by **5pm** on **Friday 27 August 2021**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Important information on completing this expert statement

- 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 want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

PART 1 – Treating a patient with chronic kidney disease (CKD) and current treatment options	
About you	
1. Your name	**James Burton**
2. Name of organisation	**University of Leicester / University Hospitals of Leicester**
3. Job title or position	**Professor of Renal Medicine and Honorary Consultant Nephrologist**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with chronic kidney disease? ☒ a specialist in the clinical evidence base for chronic kidney disease or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☒ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**
The aim of treatment for CKD	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Irrespective of the underlying cause of CKD (e.g., diabetes, hypertension, intrinsic kidney disease etc) CKD is slowly progressive and leads to irreversible loss of functional kidney tissue, kidney failure and premature death. One of the important aims of treatment of CKD includes strategies to delay progression. As CKD is an independent risk factor for cardiovascular (CV) events (now recognised as one of the core targets in the national CVD-PREVENT programme), slowing the progression of CKD will reduce the burden of CV morbidity and mortality. Although death from CV disease is more common than progression to end stage kidney disease, those people with kidney failure who need dialysis or a kidney transplant account for approximately half of the entire NHS spend on CKD. So, strategies to slow that progressive decline of kidney function will prevent cardiovascular events and hospitalisations from heart failure, reduce mortality, improve the quality of life of those people who end up not needing dialysis or a kidney transplant and represent a significant cost saving to the NHS.
9. What do you consider a clinically significant treatment	eGFR slowly decreases with ageing as a normal biological process linked to cellular and organ senescence and so a decline is not always associated with a particular disease process. Cross sectional longitudinal studies (of which there are many) estimate this loss to begin at around the age of 30-40 years and to be in the order of magnitude of ~1ml/min per year.

response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Superimposed chronic diseases that impact on kidney function will, of course, accelerate that decline. Data published suggest that the average decline in eGFR is at least double that in diabetics (between 1.9 to 3.3 mL/min, PMID31221677) and the ARIC study showed that loss was increased in people with hypertension by 0.1 to 0.5mLs per year (PMID31031087). This is important because even a mild decline, defined as 0.1mL/min to 3 mL/min is associated with both increased mortality and cardiovascular events (PMID30608199). So, any decline of >1mL/min/year is clinically relevant as it represents a change more than that associated with the ageing process and any reduction in that slope of decline would represent a significant treatment response. The treatment effect seen in the DAPA-CKD trial, where the annual change in the mean eGFR was -3.59mL/min in the placebo group vs -1.67mL/min in the dapagliflozin group therefore represents a highly significant treatment response.
10. In your view, is there an unmet need for patients and healthcare professionals in chronic kidney disease?	Absolutely. Current therapies for chronic kidney disease (CKD) target multiple pathogenic pathways, but only retard disease progression; an improved understanding of CKD pathogenesis is needed to optimise treatment. In addition, we know from the National Diabetes and CKD audits that measurement of albuminuria in people with CKD is not being done. Only around half of people with diabetes have their urine albumin measured according to NICE recommendations and even less in those people with CKD not attributed to diabetes. Because urine albumin concentration (uACR) is so strongly associated with adverse outcomes (even in those people with a normal eGFR), as a community there is a desperate need to improve uACR monitoring in order to better understand an individuals risk and personalise treatment.
What is the expected place of dapagliflozin in current practice?	
11. How is the condition currently treated in the NHS?	In additional to the treatment of any underlying intrinsic renal disease, the current management to delay progression is essentially outlined in NICE NG203: treatment of hypertension and good control of diabetes (if they are diabetic), both of which include prescription of an ACEi or an ARB in most cases and; management of cardiovascular risk with lipid lowering therapy and an antiplatelet for secondary prevention of CV disease.

• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Three professional organisations / institutions have produced guidelines that are relevant to the management of CKD in the UK. NICE – very recently published NG203 Kidney Disease: Improving Global Outcomes (KDIGO) have 2 documents including 'CKD Evaluation and Management' published in 2012 and the more recent 'Diabetes in CKD' published in 2020. The UK Kidney Association (formally UK Renal Association) that has published commentaries on both KDIGO and NICE guidelines as they relate to the management of people with kidney disease in the UK as well as stand alone guidelines. I would signpost the committee to the draft document now published on the UK Kidney Association website about the use of SGLT2 inhibition on adults with kidney disease (https://ukkidney.org/node/1129)
• 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.)	In truth the pathway is not that well defined because the landscape of evidence is evolving so quickly. I think this is highlighted by the recent NICE NG203 document that includes a statement on the rapidly evolving landscape of evidence and the need for review and updates. The clarity that could come from this appraisal will help to ensure a unified approach to treatment pathways across the UK, which will be crucial to ensuring timely delivery of this therapy to patients. It is clearer for people with diabetes and kidney disease. The use of SGLT2i has been recommended for some time as first line therapy (after metformin) if glucose targets are not met for people in whom CKD (or heart failure) predominates because of the evidence of renal benefits seen in the cardiovascular outcome trials (accepting that this was at a time when licencing was restricted to people with more preserved eGFR). This was clarified further in the 2020 KDIGO guideline on Diabetes and CKD, which recommended metformin AND an SGLT2i, with the latter being important irrespective of glycaemic control due to the clear reno-protective and cardio-protective effects. The KDIGO

	guideline group stated that *'all or nearly all well-informed patients would choose to receive treatment with an SGLT2i.'.* The pathway for people with heart failure is also clear as guidelines would recommend SGLT2i for all people with symptomatic heart failure and reduced ejection fraction. The pathway is less clear for those people with CKD without diabetes or heart failure (e.g. those with hypertensive kidney disease) although as mentioned above, the UK Kidney Association is working to plug that gap. I don't believe that there is a difference in opinion between professionals across the NHS who would all agree that the treatment of CKD should now include the use of SGLT2i in the vast majority of cases, irrespective of diabetes status or the presence of heart failure.
• What impact would dapagliflozin have on the current pathway of care?	This would be two-fold. Firstly, it would enable the initiation of an SGLT2i down to an eGFR of 15mLs/min and with the potential for continuation when renal replacement therapy is commenced. This broadens the availability to those people who will benefit. Secondly, it would widen the use of SGLT2i to those people with kidney disease but without diabetes, who we know will benefit from the addition of an SGLT2i to their management.
12. Will dapagliflozin be used (or is it already used) in the same way as current care in NHS clinical practice?	The use of dapagliflozin will be in addition to the way it is currently used.
• How does healthcare resource use differ between dapagliflozin and current care?	For those with diabetes, it will now extend the use to prevent renal complications / CKD progression and allow its use in those people with more advanced kidney disease but, more importantly, also extend use to those people without diabetes for the same reasons.

• In what clinical setting should dapagliflozin be used? (For example, primary or secondary care, specialist clinics.)	The majority of patients with kidney disease for whom dapagliflozin is indicated will be diagnosed, managed and monitored in primary care because they will not trigger the criteria for referral to secondary care. In my opinion, it is crucial that primary care practitioners / GPs have clear pathways to follow and an ability to prescribe this when indicated. There will be cohorts who require specialist input (transplant recipients, those with more advanced CKD, prior history of DKA, those requiring high dose diuretics, for example) but these can be clearly signposted and advice given to seek specialist input.
• What investment is needed to introduce dapagliflozin? (For example, for facilities, equipment, or training.)	Enabling confidence in primary care prescribers is key as the use of SGLT2i in diabetes and HF is still low. This will require the production of clear pathways, a clear and unified message coming from secondary care and specialist societies. In addition, there needs to be a concerted effort to highlight guidelines and pathways once they are produced; for example the CKD audit shows that statin therapy is not prescribed in almost a third of high risk people with CKD and for over two thirds of very high non-diabetic younger people with CKD, despite clear NICE guidance concerning their use. The issue of uACR is also very significant and needs investment. According to the National CKD Audit, only 31% of people with CKD and diabetes have follow up uACR tests and for those without diabetes, uACR testing rates are <15%. So we are in a position where people with CKD at significant risk of mortality, cardiovascular events and progression to end stage kidney disease are either a) not having their albuminuria measured at all or b) having it measured once but then not rechecked. Data from the Australian diabetes, obesity, and lifestyle study (AusDiab) which included >11k adults aged 25 and older suggested that 25.3% of people with diabetes had albuminuria, that it is present early in the course of the disease and is progressive. In the current climate, there can be no doubt that restricting the use of dapagliflozin to those with the presence of albuminuria (accepting that the DAPA-CKD trial recruited people with an ACR of >200mg/g) will mean that a significant number of people who would benefit from the treatment, will not have access to it. Given the low numbers needed to treat (see below) and the follow up period for the DAPA-CKD trial, this will have real consequences for individuals with kidney disease.
13. Do you expect dapagliflozin to provide clinically meaningful	Yes. Dapagliflozin represents a significant improvement to outcomes over and above current standard of care.

benefits compared with current care?	
• Do you expect dapagliflozin to increase length of life more than current care?	Yes. The evidence of mortality and cardiovascular benefits in people with kidney disease, both with and without diabetes is clear from the trial data.
• Do you expect dapagliflozin to increase health-related quality of life more than current care?	Similarly, there is a significant impact of dialysis commencement and hospitalisations for heart failure on health-related quality of life. Reducing the number of people progressing to kidney failure using dapagliflozin will very likely increase health related QoL.
14. Are there any groups of people for whom dapagliflozin would be more or less effective (or appropriate) than the general population?	Both the CREDENCE and DAPA-CKD trials demonstrated very low numbers needed to treat to prevent both a primary outcome event (22 and 19 respectively), demonstrating that it is an effective treatment for both diabetics and now also non-diabetics. The population recruited into the trial included a mix of people with a wide range of eGFR with an appropriate baseline demographic mix (although more men than women).
The use of dapagliflozin	
15. Will dapagliflozin 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	I can't see that there would be any real barriers to use in terms of difficulties of use. For people with CKD, it will be the same or easier as it effectively part of standard of care for everyone. This is easy for both primary and secondary care practitioners as the prescribing will be the same across patients with a range of conditions and multi-morbidity (diabetes, CKD and heart failure). I do not see any practical implications / barriers for use. In terms of concomitant medications, the vast majority will be on an ACEi / ARB for the management of their CKD or co-morbid conditions as standard care. However, the UK draft Kidney Association guideline rightly points out that the benefits of SGLT2i on the progression of kidney disease may well extend to those not on an ACEi / ARB. So, whilst

clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	concomitant treatment with an ACEi / ARB is preferable, in the event that these drugs are contra-indicated or not tolerated, the use of dapagliflozin should not necessarily be prohibited. The additional benefits that patients may experience from the use of dapagliflozin (e.g., weight loss) would lead me to believe that patients would find this therapy acceptable and that the clear benefits would outweigh the risk of mycotic infections and potential for DKA. This is highlighted again by the statement from KDIGO that nearly all well-informed patients would choose to receive treatment with an SGLT2i. There is no impact on additional tests or monitoring over and above current guidance. Despite the recognised dip in eGFR when initiating an SGLT2i, there is no evidence that more frequent monitoring is required at that stage. Indeed, it could be argued that more frequent should be avoided as it may lead to premature discontinuation, denying the therapy to an individual who would clearly benefit in the longer term.
16. Will any rules (informal or formal) be used to start or stop treatment with dapagliflozin? Do these include any additional testing?	In the context of CKD, many clinicians may wish to see a raised uACR in conjunction with a reduced eGFR before initiation. Given the poor testing of uACR, this will almost certainly delay the commencement of therapy for a significant proportion of those patients that would benefit. It is likely that the drug would be discontinued on commencement of kidney replacement therapy.
17. Do you consider that the use of dapagliflozin will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Progression to end stage kidney disease represents a significant burden on physical health (mortality and CV morbidity, infections etc) and quality of life. Any slowing of progression to dialysis is a substantial benefit. Also, I cannot see any mention of the impact of weight loss. Additional sub-group analyses of the DECLARE-TIMI study showed a significant reduction in weight of ~2kg in the dapagliflozin group. Given the burden of obesity in this cohort, it may represent an additional health related benefit.
18. Do you consider dapagliflozin to be innovative in its potential to make a significant and substantial	The claim that the use of SGLT2is are the most significant advance in the management of CKD progression since ACEi is not overstated; this is a genuine breakthrough. The impact of CKD both on its own and as a cardiovascular

impact on health-related benefits and how might it improve the way that current need is met?	risk factor are significantly underappreciated. The clear evidence that dapagliflozin can modulate this process across the spectrum of CKD certainly has the potential to make a significant and substantial impact.
• Is dapagliflozin a 'step-change' in the management of the condition?	Absolutely and for the reasons stated above.
• Does the use of dapagliflozin address any particular unmet need of the patient population?	Absolutely it does. For the first time we now have a licenced product that can impact on the risk of kidney disease progression that can be initiated all the way down to 15mL/min, irrespective of albuminuria
19. How do any side effects or adverse effects of dapagliflozin affect the management of the condition and the patient's quality of life?	I am not sure that the side effects are any more burdensome than those that we already consider to be standard of care. Medications such as ACEi / ARB already have 'sick day guidance' as part of their use and so this will not be unfamiliar practice for those people prescribing or taking dapagliflozin. Appropriate guidance is included in the draft UKKA guidance document. Although there is a risk of mycotic infection, these are easily treated and as I have said before, the KDIGO Group state that the benefits far outweigh the risk with well-informed patients almost certainly choosing to be on therapy.
Sources of evidence	
20. Do the clinical trials on dapagliflozin reflect current UK clinical practice?	The DAPA-CKD trial represents standard of care in the UK (in fact better than standard of care as the use of ACEi / ARB in both treatment and placebo arms was higher than real world data would suggest) up to the point of addition of dapagliflozin.

• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	The outcomes of the DAPA-CKD trial were all clinically relevant; 50% reduction in renal function, progression to kidney failure requiring renal replacement therapy or cardiovascular / renal death. Safety outcomes were also collected and the very reassuring data on incidence of DKA / serious infection / amputation were reported in the paper and supplementary materials
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not that I am aware of.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No.
22. Are you aware of any new evidence for the comparator treatment(s)?	No. It might be worth noting here that the EMPA-KIDNEY trial (The study of heart and kidney protection with empagliflozin), has completed recruitment of participants (adults with or without diabetes) with an eGFR of >=20 to <45 with or without albuminuria.

23. How do data on real-world experience compare with the trial data?	There is no real-world evidence in the UK at the moment as dapagliflozin is not being used in the context of the DAPA-CKD trial.
Equality	
24a. Are there any potential equality issues that should be taken into account when considering this treatment?	There are none that come to mind
24b. Consider whether these issues are different from issues with current care and why.	N/A
Topic-specific questions	
25. The population in the company submission is aligned with the NICE final scope: adults with CKD who are receiving individually optimised standard care. This includes people irrespective of urine albumin-to-	The first question is simpler to answer and covered to some extent in section 12 above. The national CKD audit suggests that >85% of people at risk of CKD are having their eGFR tested and that 70% of those cases of CKD were given an appropriate code (although there is significant variation in that). Overall 81.3% of people coded with CKD had a repeat blood test in the preceding 12 months. The data for uACR testing show a rather different picture. Only 31.1% of people with coded CKD stages 3-5 had a uACR in the previous year and, as mentioned above, for those people at risk of CKD, the figures are even lower. That means that if clinicians are relying on an ACR measurement to decide whether or not to prescribe dapagliflozin for the management of CKD, then that crucial piece of information will be lacking in over two-thirds of patients. One side to this debate would be to 'just get the ACR measured' although strategies to do this in the past (QOF) have had limited success. In addition, CPRD data from >80k people with diabetes showed that in those with poor glycaemic

creatinine ratio (uACR) or estimated glomerular filtration rate (eGFR). However, the clinical effectiveness evidence in the economic model comes from the DAPA-CKD trial, which is restricted by uACR and eGFR level (uACR must be from 22.6 mg/mmol to 565 mg/mmol, eGFR must from 25 ml/min/1.73m^2 to 75 ml/min/1.73m^2). • How often is uACR and eGFR testing done for people with CKD? • Is the dapagliflozin treatment effect observed in DAPA-CKD likely to be generalisable to people with uACR or eGFR levels outside the range recruited in DAPA-CKD?	control (HbA1C >8.0%) it took an average of 1.6 years to intensify treatment with an addition oral antihyperglycaemic agent (Kunti et al PMID:23877982). Given that the use of urine dipstick tests is not reliable enough to inform whether dapagliflozin should be initiated and no other point-of-care tests for uACR are in use in primary care, the same clinical inertia is likely to happen with the use of dapagliflozin for people with CKD. The second question is whether the effect seen in the DAPA-CKD trial can be extrapolated to those with lower uACR / eGFR values. The first consideration is whether the proposed mechanism of action would be blunted for those individuals with a lower uACR or eGFR. The molecular mechanisms of action of SGLT2 inhibition are well covered in the draft guideline from the UKKA on the use of SGLT2i in people with CKD; the key mechanisms are modulation of tubuloglomerular feedback as well as generating a natriuresis / diuresis, both of which are maintained across a wide range of single nephron GFR values (although less in more advanced disease). There are also other proposed mechanisms that may provide cardiovascular benefits beyond renal physiology. These include reduction in adipose tissue mass including epicardial fat, reduction in systemic inflammation by affecting oxidative stress, changes in myocardial Na/H exchange that are associated with heart failure are examples (see Cowie M et al. SGLT2 inhibitors: mechanisms of cardiovascular benefit beyond glycaemic control). As with RAASi inhibition, it is likely that these pleiotropic effects will benefit those with eGFR / uACR levels outside of those recruited into the DAPA-CKD trial. Although the DAPA-HF trial did not measure uACR at baseline, neither did it exclude participants on that basis. It is therefore reasonable to assume that the trial population included a number of participants without albuminuria and so the mechanisms that underpin the cardiovascular benefits in DAPA-HF are present, irrespective of ACR or indeed the presence of albuminuria at all. This is entirely in keeping with the draft UKKA guideline that recommends initiating an SGLT2i to modify risk of heart failure in those with CKD without albuminuria, irrespective of diabetic status. I note the comments from the ERG on this question and the draft guidance from the UKKA; current evidence only exists for dapagliflozin use in a non-diabetic population for those with proteinuria and in those with CKD up to stage 4 because DAPA-CKD excluded patients with uACR <22.6 mg/mmol and eGFR <25 and >75 mL/min. As with all trials, this was likely not done because of an expectation that it would be less effective or unsafe in those individuals, but rather to enrich the trial population and ensure event rates in a given time period. Given that the recent license

(for example, very high-risk patients with CKD stage 5)	extension does not restrict based on ACR and allows initiation down to an eGFR of 15mLs/min, I can only assume that the panel were convinced enough of the generalisability. Also, the UKKA draft guideline suggests that when used to slow kidney disease progression or heart failure risk, SGLT2i can be continued until the need for dialysis or kidney transplantation arises, with the rationale that both CREDENCE and DAPA-CKD showed that SGLT2 inhibition is safe in their recruited populations and that SGLT2i were shown to prevent the need for dialysis or kidney transplantation. As the cardiorenal benefits identified in their primary outcomes are not modified by baseline eGFR at recruitment, it would be reasonable to expect some ongoing benefit in CKD stage 5 (i.e. an eGFR down to 15mL/min or even less) not requiring renal replacement therapy.
26. The DECLARE TIMI-58 trial suggests a beneficial effect with dapagliflozin regardless of uACR level. However, all patients in DECLARE TIMI-58 had type 2 diabetes mellitus (T2DM). Therefore, there is a lack of direct or indirect evidence for dapagliflozin in people <u>without</u> T2DM regardless of uACR level. • Is the dapagliflozin treatment effect observed in DAPA-CKD likely to be generalisable to people without T2DM with lower	Unlike DAPA-CKD, the DECLARE trial contained no restrictions on baseline uACR levels for inclusion in the study; the mean eGFR was 85mL/min but a significant number of patients enrolled (1265) had an eGFR of <60mL/min. Secondary renal analyses of DECLARE showed that dapagliflozin seemed to prevent and reduce progression of kidney disease compared with placebo in patients with type 2 diabetes, most of whom had preserved kidney function. Interestingly, there was no interaction between treatment groups and uACR for the renal specific endpoint, suggesting that the cardio- and renoprotective effects were seen in people with type 2 diabetes regardless of uACR. We now appreciate that the effect on renal outcomes is independent of glycaemic control and so it would not be unreasonable to assume that the effect of dapagliflozin would also benefit people without T2DM in the same way although there are no trial data to support that assertion directly.

uACR levels (less than 22.6mg/mmol)?	
27. The clinical evidence for dapagliflozin in patients with CKD from DAPA-CKD excludes patients with type 1 diabetes mellitus (T1DM). • Is the dapagliflozin treatment effect observed in DAPA-CKD likely to be generalisable to people with T1DM?	I am not an expert in this area but there are no large clinical trials reporting renal outcomes of SGLT-2 inhibitors in people with type 1 DM. Post-hoc analyses of DEPICT-1 and -2 trials showed that the addition of dapagliflozin to insulin resulted in a reduction of uACR compared to placebo but with an increased risk of DKA. The lack of trial evidence on renal outcomes in people with type 1 DM mean that the data are not generalisable at this point in time.
28. In DAPA-CKD, most of the patients had an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blockers (ARB) at baseline. However, in the Clinical Practice Research Datalink dataset used in the company submission, about	I hope that I have covered this in section 15, although concomitant treatment with an ACEi / ARB is preferable, in the event that these drugs are contra-indicated or not tolerated, the use of dapagliflozin should not necessarily be prohibited.

half the population were having either of these therapies. • Is the dapagliflozin treatment effect observed in DAPA-CKD likely to be generalisable to people not having background therapy with ACE inhibitors or ARBs?	

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
29. Key issue 1: Uncertainty surrounding the target population and the effectiveness of dapagliflozin in patients excluded from DAPA-CKD • Do you have any general comments on this issue?	The difference between DAPA-CKD trial population and the recent licence (initiating in those with an eGFR >=15mLs/min, irrespective of albuminuria) has, I think, come as a surprise to the nephrology community; any narrative around the use of dapagliflozin in those individuals is extrapolated from other data. As a result of that, there will almost certainly be differences of opinion and guideline groups will inevitably go with evidence. As a contributor to a number of guidelines, including the UKKA SGLT2i in CKD group, the consensus and ultimately the recommendations are almost always going to align with where the data point, and that is completely right. Taking a more pragmatic view though, there are a few things that are important here, in my mind - There is absolutely no doubt that an ACR cut off will cause clinical inertia and deny therapy to a large number of individuals with CKD who align with the DAPA-CKD entry criteria. - It is reasonable to assume that the benefits continue in people with low eGFR as the studies retained those individuals and adverse events did not flag increased risk of harm.

	- The evidence is mounting that the benefits are also going to extend to those without proteinuria (from the HF studies), accepting that the data are not there yet (just like we have seen with ACEi / ARB) And so, if I had a non-diabetic patient who I thought was at high risk of progression but had a uACR below the threshold for inclusion in the DAPA-CKD, would I want them to be on dapagliflzin based on current evidence? The answer is yes.
30. Key issue 2: Concerns regarding the company's overall modelling approach and OS predictions • Do you have any general comments on this issue?	None
31. Are there any important issues that have been missed in ERG report?	Not that I can think of.
PART 3 -Key messages	
32. In up to 5 sentences, please summarise the key messages of your statement: • In people with CKD, dapagliflozin has been shown to significantly reduce the risk of a number of clinically meaningful outcomes; this represents a crucial advance in the management of this CKD.	

- These benefits have now been demonstrated in people without diabetes and with much lower levels of kidney function, highlighting the benefits well beyond glycaemic control.
- Strategies to prevent progression to kidney failure in people with CKD are key to improving outcomes and QoL and the ERG reports suggests that this treatment is a cost-effective way to achieve that goal.
- Sub-optimal detection and monitoring of CKD in the UK population will deny access to this beneficial treatment in people with kidney disease, especially if uACR cut-offs are stipulated; incentives to improve that are a priority.
- Whilst the trial population of DAPA-CKD did not include people without albuminuria and stage 5 CKD there is an argument that the mechanisms and pleiotropic effects of dapagliflozin would extend to these individuals.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

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NICE National Institute for Health and Care Excellence

Clinical expert statement & technical engagement response form

Dapagliflozin for treating chronic kidney disease [ID3866]

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on dapagliflozib in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form:

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

Please return this form by **5pm** on **Friday 27 August 2021**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Important information on completing this expert statement

- 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 want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

PART 1 – Treating a patient with chronic kidney disease (CKD) and current treatment options	
About you	
1. Your name	**Dr Rosa Maria Montero**
2. Name of organisation	**St George's University Hospital NHS Foundation Trust, London**
3. Job title or position	**Consultant Nephrologist**
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with chronic kidney disease? ☒ a specialist in the clinical evidence base for chronic kidney disease or technology? ☒ other (please specify): **ABCD/UKKA Committee Member, UKKA – CKD SIG.**
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
The aim of treatment for CKD	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Ideally the main aim of treatment is to cure CKD however there are many different disease processes that underlie the term CKD. Preventing progression of CKD is imperative in order to prevent the disease burden and risk factors associated with CKD. In addition, in preventing progression or slowing this down, less people will require renal replacement therapy such as dialysis or transplantation that are costly treatments. 2% of the total NHS budget was spent on renal replacement therapy (RRT) RCP 2008. Approximately 3 million people in the UK have CKD requiring dialysis, therefore prevention of CKD to end-stage kidney disease (ESKD) would have a significant impact on saving resources.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm,	Preventing a sustained decrease in eGFR of 30-50%, doubling of creatinine, ESKD or death secondary to renal causes.

or a reduction in disease activity by a certain amount.)	
10. In your view, is there an unmet need for patients and healthcare professionals in chronic kidney disease?	Yes. There is an increasing ageing population who are developing CKD that can progress to ESKD, requiring RRT. This together with increasing rates of T2DM in younger age groups will inevitably increase CKD with T2DM that is the leading cause of ESKD. 1.8 million people in the UK have CKD, with an estimated further million being undiagnosed. Forty to 45 thousand premature deaths occur in people with CKD. The need to diagnose people with CKD nationally requires an increase in healthcare professionals to deliver this service and specialised input in stabilising CKD to avoid progression. With disproportionate levels of CKD compared to staffing there is clearly an unmet need.
What is the expected place of dapagliflozin in current practice?	
11. How is the condition currently treated in the NHS?	The main challenge with CKD is early diagnosis to enable prevention. Implementation of urine ACR, effective treatment of blood pressure with ACEi/ARB/ARBs and monitoring is the mainstay of treatment. Specialist opinion for people with CKD G4 and G5/heavy proteinuria/rapidly declining GFR or poorly controlled hypertension is sought from primary care. Promoting self-management e.g. lifestyle changes, BP control, decreasing cardiovascular disease (statins/aspirin), Treatment of asymptomatic hyperuricaemia is at times implemented, albeit no robust evidence illustrating the variable practice however, the mainstay of treatment continues to be supportive rather than active reversal of disease. Some diseases that are classified under CKD e.g glomerulonephritis use disease specific treatment however, as these fail, the common pathway of CKD leading to RRT is implemented.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE guidelines, UK eCKD guide – Renal Association and SIGN guidelines. ABCD/RA guidelines in Management of hyperglycaemia in adults with diabetes kidney disease. Reference has also been made to the KDIGO guidance until NICE publishes local UK guidance. In addition, the recently released CKD NICE guideline 2021.

• 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.)	Primary Care referrals inside and outside London differ between Practices despite national guidance on management and referrals to secondary/tertiary care. The introduction of ACEi/ARBs is now generally established as primary care has become more familiar with CKD and is fully supported by secondary/tertiary care. Many Practices are beginning to use ACR however, this has taken some time and some referrals continue to lack this information despite guidance. Across the Renal community there is alignment of practice with NICE CKD guidance.
• What impact would dapagliflozin have on the current pathway of care?	Diabetologists have adopted dapagliflozin as one of the SGLT2i in their armamentarium for glycaemic control and now with cardiorenal benefit the guidance is for this agent to be used as a second agent to metformin. Dapagliflozin has revolutionised Heart Failure management with Cardiologists rapidly producing trials looking at its benefits across cardiac disease and consequently prescribing this irrespective of GFR/ACR. SGLT2i have been widely accepted by the Renal community following DAPA-CKD, EMPA-REG outcome and EMPA-Kidney, the latter whose results are eagerly waited for by the community. CREDENCE, EMPEROR reduced and the DIAMOND study have all illustrated and supported the benefits of SGLT2i in renal practice. In view of this dapagliflozin would be introduced earlier on and potentially before CKD develops via other specialists. Were CKD to be the primary diagnosis this would likely be introduced if there are existing co-morbidities in addition to CKD. Current practice would introduce this agent following optimisation of ACEi/ARBs as standard of care, however, it is more likely that this may have been introduced prior to ACEi/ARBs from other specialities before referral is made to nephrologists. As dapagliflozin is licenced to start at lower levels of GFR this would make this a preferential choice of SGLT2i as the renal community have adopted a class effect approach to benefit. With increasing studies supporting dapagliflozin this agent is likely to be the most commonly used as is ramipril amongst ACEI/ARB. In those with DM and CKD alone with normotension and normal ACR dapagliflozin would likely be used before ACEI/ARB/ARBs in the present of other co-morbidities. Education however, is imperative for this to be embedded in the current pathway of care.
12. Will dapagliflozin be used (or is it already used) in the same	SGLT2i are being increasingly used with nephrologists using a variety of SGLT2i currently. Canagliflozin from CREDENCE has shown safety and benefit with GFRs as low as 30ml/min/1.73m2 that has encouraged it's use. However, following the results of DAPA-CKD use down to a GFR of 25ml/min/1.73m2 has promoted canagliflozin's use as has the cardio-protective effect in heart failure that is a fair proportion of those with CKD. EMPA-KIDNEY is also likely to change practice providing another option for clinicians. In view of the momentum of benefit from SGLT2i

way as current care in NHS clinical practice?	dapagliflozin is likely to be introduced by Primary Care in earlier stages of CKD as more education and confidence is provided from Tertiary Care to start this agent. Familiarity of side effects and process/monitoring required to introduce dapagliflozin will enable this to be embedded in clinical practice. NICE guidance will formalise current practice in supporting its use in CKD as an established benefit in decreasing progression of kidney disease.
• How does healthcare resource use differ between dapagliflozin and current care?	Current care is embedded in the system whereas dapagliflozin's side effect profile will require increased resource initially to embed this practice via national education. Once this has been understood, adopted and familiarised then the healthcare resources used to introduce this will be minimised with the benefit seen in long term by reducing progression of CKD and RRT.
• In what clinical setting should dapagliflozin be used? (For example, primary or secondary care, specialist clinics.)	Dapagliflozin should be available to be used in Primary and Secondary Care and within Specialised clinics as ACEi/ARBs are used. The benefit of this drug should not be restricted to Secondary Care. The main barrier is education of side effects/monitoring and confidence in use of these medications by the prescriber. The SGLT2i 'dip' is long and advice to check GFR during this period requires education, as the decline associated with this is greater than ACEi/ARBs and having familiarity of this effect needs to be understood with guidance in order for these drugs not to be stopped.
• What investment is needed to introduce dapagliflozin? (For example, for facilities, equipment, or training.)	Clear guidance in checking renal function, ACR and when to use this in CKD, diabetes and heart failure management is required to introduce dapagliflozin. The main investment is education across the sector for both healthcare professionals and patients. In order for rapid introduction nationally, specialists/CCG events between Secondary and Primary Care are required. Whilst these things take time, a rapid referral or advice service should be made available to Primary Care whereby Secondary/Tertiary care may commence, monitor and advise until confidence in Primary Care is gained. Expecting Primary Care to embrace dapagliflozin with its treatment side effects will slow down the introduction of this medication to those that require it most and thus a hybrid introduction is required i.e. Specialist education whereby this education is imparted to primary care and community nurses i.e. diabetes/heart failure services as well as patient education of availability and understanding side-effects. Patient education programmes for SGLT2i in the diabetes sphere have shown great uptake and minimised side effects (DEPICT-1 and 2).

13. Do you expect dapagliflozin to provide clinically meaningful benefits compared with current care?	Yes DAPA-CKD shows ≥50% sustained reduction in people with CKD progressing to ESKD requiring RRT in combination with ACEi/ARBs. Current treatment with ACEi/ARBs reduces proteinuria and BP control, that has been well established since the 1980's showing benefit in T2DM and T1DM with proteinuria renal disease. Dapa-HF has shown significant reduction in cardiovascular mortality in heart failure with reduced ejection fraction and decreased hospitalisations. People with Heart Failure have developed CKD and vice-versa thus dapagliflozin can provide beneficial treatment for both. Dapagliflozin benefits those who have DM and CKD by delaying progression of CKD.
• Do you expect dapagliflozin to increase length of life more than current care?	According to DECLARE TIMI-58 there is a reduced cardiovascular mortality and hospitalisations in those with heart failure and T2DM with history of atherosclerotic cardiovascular disease. DAPA-CKD reduced progression, ESKD and renal and cardiovascular mortality supporting that dapagliflozin will increase longevity enhancing current care and maintaining a more healthy and independent/less co-morbid population.
• Do you expect dapagliflozin to increase health-related quality of life more than current care?	CKD progression results in an increase in polypharmacy prior to requiring RRT. RRT is a life changing event that dramatically reduces quality of life and also impacts on employment and mental health. Risks associated with RRT are not insignificant and although transplantation improves quality of life compared with people on dialysis this continues to require life long high risk medications with the consequential sequelae of risks associated with this e.g. risk of cancer. Transplantation rarely lasts a life time and thus slowing CKD to avoid reaching RRT is significant. The role of dapagliflozin on immunosuppressed patients is currently unknown. Genital mycotic infections in immunosuppressed patients have the potential to be infections with high morbidity and mortality. A failing transplant although may be labelled as CKD requires recognition that the potential side effects may be deleterious in those immunosuppressed. In those with recurrent genital infections or urinary tract infections the effect on quality of life may outweigh the long-term benefits of the drug.
14. Are there any groups of people for whom dapagliflozin would be more or less effective (or appropriate) than the general population?	In view of the significant risk profile of SGLT2i in particular with respect to genital mycotic infections this requires further studies in immunosuppressed patients e.g. transplant patients and those with glomerulonephritis. Small centre studies are underway to determine whether these are safe and whether the benefits currently seen in dapagliflozin are seen in this group of patients. Those on immunosuppression for different reasons are at increased risk of cardiovascular mortality and hence if dapagliflozin is safe, maintaining renal function in these patients would be beneficial. It is unclear whether SGLT2i will be effective in patients with APKD providing another area to be studied. Those with no residual urine output may not benefit from being on dapagliflozin e.g. those on haemodialysis. Further studies would be required in this area and drug interactions.

The use of dapagliflozin	
15. Will dapagliflozin 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.)	Dapagliflozin will be the same to use as other medications as side effects and monitoring are understood. With the introduction of any medication education will allow effective introduction. Routine blood and ACR urine tests would be expected in those with CKD and thus there would be no need to arrange additional testing of these introducing this. Bone health and awareness of osteoporotic fracture risk. Currently there are no requisites for DEXA scanning and the management and identification of osteoporosis is well established in primary care. Foot health is already embedded in diabetes practice with foot checks and in these patients Primary care would revert to specialists to start dapagliflozin and in all likelihood the Diabetologists would have already decided who would be suitable or not. Bladder health is important as those with recurrent urinary tract infections would not be eligible. Careful consideration needs to be taken by those with neuropathic bladders and recurrent genital mycotic infections. Urine samples are sent from primary care for confirmation of urinary tract infections. DKA – this requires more extensive education and clear instruction of how often or how frequent monitoring should occur. Shared care/self empowerment of patients is required if this is to be started so that this responsibility is not solely on the physicians. In addition, looking and knowing what Fournier’s gangrene looks like and advising patients is extremely important as although rare, the implications are serious.

16. Will any rules (informal or formal) be used to start or stop treatment with dapagliflozin? Do these include any additional testing?	Sick Day rules apply. Any of the side effects above or development of these are likely to stop e.g DKA, AKI. Following an AKI the renal function would need to return to baseline before re-starting. Often medications that have been stopped during an AKI e.g Metformin/ACEi/ARBs are delayed in restarting thus further education is required to recommence medications but this will not be specific to dapagliflozin. Until studies are available to show benefit in lower GFRs/RRT there is likely to be variability in practice as to whether to continue or stop. This is not dissimilar to ACEi/ARB whereby STOP ACE is addressing whether this should be stopped or continued with low GFRs to preserve renal function. Starting dapagliflozin on RRT will be controversial however, there will be centres that will prescribe off licence as many of the medications in renal are.
17. Do you consider that the use of dapagliflozin will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	The impact of CKD is not appreciated until later in the progression of CKD and thus it is important to know about the psychological stress having this diagnosis can induce. Patients knowing they are on a beneficial drug improves aspects of psychological health while this also sets expectations that they will be stable, it is important to balance optimism with fact otherwise patients will assume they will never progress with this medication and although benefit has been shown, a proportion of patients continued to progress.
18. Do you consider dapagliflozin to be innovative in its potential to make a significant and substantial impact on health-related benefits	It is unclear as to whether the benefits seen with dapagliflozin is a SGLT2i class effect or whether it is specific to dapagliflozin. EMPA-KIDNEY will provide further evidence of the impact of SGLT2i's. This class of drug thus far has provided signals showing benefits to reduce CKD progression. CKD is a silent disease that people only appreciate as they progress to ESKD. The health benefit may not be appreciated by patients which may lead to non concordance

and how might it improve the way that current need is met?	issues however, the Renal community are well aware of the massive positive impact of introducing this agent in the early stages of CKD will have, with it providing many health related benefits.
• Is dapagliflozin a 'step-change' in the management of the condition?	Dapagliflozin is a 'game changer' for CKD.
• Does the use of dapagliflozin address any particular unmet need of the patient population?	Yes, those with progressive CKD, heart failure, T2DM and in DEPICT -1 and -2 suggesting safety and benefit for T1DM.
19. How do any side effects or adverse effects of dapagliflozin affect the management of the condition and the patient's quality of life?	Genital infections and DKA were found in DECLARE TIMI-58 that were less compared to canagliflozin. Fournier's gangrene is a rare but serious bacterial infection requiring urgent treatment. These complications may affect the quality of life of patients and would lead to cessation of dapagliflozin. There are many diets that are adopted in the general population e.g. ketogenic diet and this should be avoided in view of DKA together with those at risk of dehydration and poor adherence to medication, those who are pregnant, those without contraception and/or those on steroids. Some patients may not be willing to adopt these changes and in turn this can affect the patient's quality of life. Education therefore is essential prior to starting these medications. Recurrent genital infections may require cessation of dapagliflozin as this may not only affect the patient's quality of life but lead to more antibiotic use or excess treatment that would outweigh any benefit.

	Were patients to sustain fractures or require an amputation the change in quality of life for the patient would be dramatic and could lead to increased morbidity and mortality however, those at risk would need to be counselled or avoid the medications.
Sources of evidence	
20. Do the clinical trials on dapagliflozin reflect current UK clinical practice?	The clinical trials reflect a proportion of practice in the UK with physicians introducing dapagliflozin or advising Primary Care to commence patients on these. There is also the extended use whereby some centres in view of the trial's beneficial effects have applied this to other renal populations outside of those in the trial. The trial has encouraged most practice to introduce dapagliflozin at any GFR up to 25ml/min/1.73 m2 or in those with isolated albuminuria. The patients however would be on ACEi/ARBs as per the trial as those being started on this agent with diabetes and heart failure would already be on this to maximal tolerated dose.
• If not, how could the results be extrapolated to the UK setting?	Follow up once commencing these agents is erratic with variable information provided to GPs and physicians regarding monitoring. Set guidance will provide more robust safety.
• What, in your view, are the most important outcomes, and were they measured in the trials?	Decline in renal function - yes, Onset of RRT – yes, Death caused by renal or cardiovascular causes – yes, Quality of life/psychological impact measures – no, Effect/interaction with immunosuppression medications – no, Effect on dialysis and transplant patients - no
• If surrogate outcome measures were used, do they adequately predict	Yes

long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No, assuming all dapagliflozin trials are reviewed outside of DAPA-CKD.
22. Are you aware of any new evidence for the comparator treatment(s)?	Sparsentan – combination of ARB and endothelin receptor antagonist is currently underway to determine whether there is a treatment effect on CKD and thus going forward this would/could be a comparator of non-inferiority or potentially synergistic effect. Entresto – combination of sacubitril and valsartan (neprilysin inhibitor and ARB) is commonly being used in heart failure treatment and in those with CKD showing some preservation of renal function and could be used as a comparator or alternatively as an adjunct to determine whether there is synergy to improve CKD.
23. How do data on real-world experience compare with the trial data?	Dapagliflozin is being used with additional medications used in heart failure and diabetes. People with CKD have multiple co-morbidities and include those on immunosuppression. Immunosuppression may have affected the outcome however, further evidence is rapidly required to provide reassurance to the community. Dapagliflozin may not be suitable for those with APKD taking tolvaptan.

Equality	
24a. Are there any potential equality issues that should be taken into account when considering this treatment?	No. All CCGs should be able to access these drugs for everyone who is suitable to benefit from them. National tariffs should allow deprived and affluent areas to access these drugs as many deprived areas have higher numbers of patients with CKD. Dapagliflozin decreases intraglomerular pressure, decreases body weight and increases haemostasis enhancing glucosuria and natriuresis. No signals were seen amongst different ethnic groups or gender in the studies.
24b. Consider whether these issues are different from issues with current care and why.	No difference.
Topic-specific questions	
25. The population in the company submission is aligned with the NICE final scope: adults with CKD who are receiving individually optimised standard care. This includes people irrespective of urine albumin-to-creatinine ratio (uACR) or estimated glomerular filtration rate (eGFR). However, the clinical	

effectiveness evidence in the economic model comes from the DAPA-CKD trial, which is restricted by uACR and eGFR level (uACR must be from 22.6 mg/mmol to 565 mg/mmol, eGFR must from 25 ml/min/1.73m^2 to 75 ml/min/1.73m^2). • How often is uACR and eGFR testing done for people with CKD? • Is the dapagliflozin treatment effect observed in DAPA-CKD likely to be generalisable to people with uACR or eGFR levels outside the range recruited in DAPA-CKD? (for example, very high-risk patients with CKD stage 5)	Globally 700 million people have CKD. UACR and GFR testing are clinically performed at the point of diagnosis. In practical experience the GFR is generally tested more regularly than the UACR with the latter re-tested should a decline in the GFR be detected. The recently released NICE CKD guidance reflects national practice whereby GFR and urinary ACR is used to determine the stage, the cardiovascular risk, overall mortality and the frequency of testing Very high risk CKD stage G5 patients not on dialysis may benefit from these agents as they have an overall increased mortality risk. However, the renal benefits would be questionable at this level in view that there will be scarring in the kidney, many of which will be atrophic and the tubular function much reduced. Without a study it would be extremely difficult to predict whether starting dapagliflozin at CKD stage G5 would be able to stabilise kidney function as these patients have reached end-stage kidney disease. If patients were on dapagliflozin and they progressed to CKD stage G5 it is unclear as to whether they would potentially continue to benefit from the reduced cardiovascular mortality or improvement in their heart failure.

	Conceivably there may be a benefit of dapagliflozin in CKD stage G5 as there are some retrospective case reports whereby ACEi/ARB have been seen to maintain cardiovascular benefits however the UK STOP ACEi trial results are awaited. Starting dapagliflozin at CKD stage G5 would be a concern in view of the 'dip' seen when starting this. Should dapagliflozin be started before CKD stage G5 and continued then the benefit may be present. The risks at CKD stage G5 of developing an intercurrent AKI are high and again may limit the use in this group. In addition, those with T1DM with CKD stage G5 have prolonged effects of insulin as the kidneys fail to metabolise this. The combination of insulin and dapagliflozin may result in a greater hazard and thus if dapagliflozin were to be licensed in this group great care and instruction would need to be taken to explicitly exclude certain causes of CKD since no trial evidence would be available to support this recommendation. Patients in CKD stage G5 have a higher level of polypharmacy that also needs to be considered. Cessation of dapagliflozin may improve renal function in view of its haemodynamic affect and allow further preparations for RRT to be made in a timely fashion. Further trial evidence is needed to safely determine the effects on this population. Those started and currently maintained on dapagliflozin progressing to stages G4 and G5 will enable the effects of dapagliflozin to be determined at this level of function.
26. The DECLARE TIMI-58 trial suggests a beneficial effect with dapagliflozin regardless of uACR level. However, all patients in DECLARE TIMI-58 had type 2 diabetes mellitus (T2DM). Therefore, there is a lack of direct	

or indirect evidence for dapagliflozin in people without T2DM regardless of uACR level. • Is the dapagliflozin treatment effect observed in DAPA-CKD likely to be generalisable to people without T2DM with lower /uACR levels (less than 22.6mg/mmol)?	The benefits of dapagliflozin are described in those with and without T2DM in DAPA-CKD. The albuminuric ranges span A2 and A3 classification of CKD. A2 classically termed microalbuminuria as 3 to <30mg/mmol. It would be plausible drawing parallels with ACEi/ARB treatment (IRMA-2, CALM, EUCLID, UKPDS) that using dapagliflozin in those with microalbuminuria i.e 3-30mg/mmol would derive benefit from this treatment. This would be below the already stated uACR levels in DAPA-CKD (22.6mg/mmol). It is possible that normoalbuminuric patients with CKD could benefit however there is no evidence to currently support this. SGLT2 receptors are only found within the proximal tubule in the kidney. The beneficial effects seen in studies have used inhibition of these receptors. ACEI/ARB/ARBs have been shown to reduce albuminuria in spite of normotension providing effects of haemodynamic stability of the kidney. The haemodynamic effects of SGLT2i reduce sodium reabsorption in the proximal tubule stimulating tubuloglomerular feedback initiating afferent arteriole vasoconstriction and reduction in hyperfiltration. Reduction in hyperfiltration, decreased inflammation and fibrotic response of proximal tubule are all beneficial to maintaining renal function and reduction of albuminuria (Fioretto 2016). Irrespective of albuminuria these effects are reno-protective hence treatment in normoalbuminuric patients with CKD could theoretically provide benefit albeit no trial evidence. uACR however should not be abandoned as this is prognostic and licensing without uACR will not determine the baseline and whether there is change or development of albuminuria that is important in CKD and may result in initiation of further medications to reduce albuminuria and/or stabilise CKD potentially synergistically with dapagliflozin.

27. The clinical evidence for dapagliflozin in patients with CKD from DAPA-CKD excludes patients with type 1 diabetes mellitus (T1DM). • Is the dapagliflozin treatment effect observed in DAPA-CKD likely to be generalisable to people with T1DM?	The haemodynamic effect induced by SGLT2i will also be beneficial to those with diabetes kidney disease that includes patients with T1DM. Dapagliflozin has already been used as an adjunct to insulin for T1DM in DEPICT-1 and 2 trials. These trials showed similar reductions in hyperglycaemia and body weight without significant risks of DKA than the overall trial population and since 2019 has been approved for use in T1DM. A DKA education programme was developed for T1DM patients to recognise DKA (Jendle 2021). Pooled data from DEPICT-1 and 2 over 52 weeks showed a reduction in ACR from baseline whilst on dapagliflozin supporting the likely efficacy of dapagliflozin in patients with CKD and T1DM (Edelman 2018).
28. In DAPA-CKD, most of the patients had an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blockers (ARB) at baseline. However, in the Clinical Practice Research Datalink dataset used in the company submission, about	Optimisation with ACEi/ARBs has long been found to have a profound effect in reducing not only BP and cardiovascular disease but also reducing proteinuria that impacts on slowing the disease. Activation of the RAAS system in CKD has been well established. Although DAPA-CKD did not use SGLT2i alone, the mechanism of action is different from RAAS inhibition and will have an effect on glucosuria however, whether the same benefit is seen with a single agent is unclear. The combination of both may enhance the efficacy of dapagliflozin resulting in significant reduction in overall mortality and reduction in progression reported.

half the population were having either of these therapies. • Is the dapagliflozin treatment effect observed in DAPA-CKD likely to be generalisable to people not having background therapy with ACE inhibitors or ARBs?	The benefits of dapagliflozin in DECLARE TIMI-58 did not distinguish those on ACEi/ARB although the study recruited 81% of patients with ACEi/ARB. 20% in the dapagliflozin arm therefore were not on an ACEi/ARB that was identical to the control arm. Currently no subgroup analysis has been performed. Future studies or observational studies looking at people with T2DM and without proteinuria may determine whether there is an effective impact on the outcomes from DAPA-CKD. The reduction in proteinuria is unlikely to be more using a single agent however this would need to be proven.

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
29. Key issue 1: Uncertainty surrounding the target population and the effectiveness of dapagliflozin in patients excluded from DAPA-CKD • Do you have any general comments on this issue?	Caution should be taken on introducing dapagliflozin or any SGLT2i on those on immunosuppression, in view of the side effect of genital mycotic infections. Consideration for a further study should be taken in view of this. Education prior to starting these medications is essential for compliance and close monitoring. In dialysis patients that have no residual renal function the benefits are unlikely to be seen despite a high risk population however a future study may determine this. A selective glucose transport-1 inhibitor may be more effective in this population. In patients with T2DM without CKD, these medications may provide protection against the development of CKD in this population. Time will determine this as diabetologists begin using SGLT2i for glycaemic control.

30. Key issue 2: Concerns regarding the company's overall modelling approach and OS predictions • Do you have any general comments on this issue?	
31. Are there any important issues that have been missed in ERG report?	Drug interactions and specific questions regarding those on immunosuppression as many kidney diseases fall under CKD hence a caveat with the term CKD would be encouraged in view of the infection side effects.
PART 3 -Key messages	
32. In up to 5 sentences, please summarise the key messages of your statement: • Dapagliflozin provides great benefit to our CKD populations and should be used in primary/secondary/tertiary care • Education is key to effectively introducing this to healthcare professionals but also empowering patients (DEPICT-1 and 2 in T1DM illustrates increased patient awareness and monitoring for DKA) • Benefit may be seen in normo- and microalbuminuria CKD albeit paucity of evidence however ACR should be measured prior to commencing dapagliflozin and monitoring should continue in the form of GFR and ACR	

- Without trial evidence starting dapagliflozin in CKD stage G5 cannot be recommended from a renal progression point of view although there may be a benefit for maintaining dapagliflozin to reduce cardiovascular mortality this is not proven and cannot be recommended currently.
- I would advocate a further trial for immunosuppressed patients as they are at high risk of infection and although there may be cardiovascular and renal mortality benefits these need to be weighted by mortality secondary to infection.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

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Jendle JH Dapagliflozin as an Adjunct Therapy to Insulin in Patients with Type 1 Diabetes Mellitus: Efficacy and Safety of this Combination. touchREVIEWS in Endocrinology. 2021;17(1):12-20 DOI: https://doi.org/10.17925/EE.2021.17.1.12

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Technical engagement response form

Dapagliflozin for treating chronic kidney disease [ID3866]

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About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Primary Care Diabetes Society**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**1. Speaker honoraria from: AstraZeneca, Boehringer Ingelheim, Janssen, Lilly, MSD, Novo Nordisk, SB Communications, OmniaMed, Roche, Napp, NB Medical, Amgen** **2. Advisory board honoraria from: AstraZeneca, Lilly, Boehringer Ingelheim, Janssen, MSD, Novo Nordisk, Takeda, Sanofi,** **3. Educational grants from: Boehringer Ingelheim, Lilly, Novo Nordisk, Takeda** **4. Conference registration and subsistence from:, Boehringer Ingelheim, Janssen, Lilly, Novo Nordisk, Takeda**

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Key issues for engagement

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Key issue	**Does this response contain new evidence, data or analyses?**	Response
Key issue 1: Uncertainty surrounding the target population and the effectiveness of dapagliflozin in patients excluded from DAPA-CKD	YES, but unpublished yet.	1. RAAS-I: The DAPA-CKD population focused on those optimised with RAAS-Is. Indeed 97% had optimal RAAS-I. The ERG therefore questioned the applicability in those without OPTIMAL RAAS-I in the real world.The counter argument however is that the benefits of DAPA-CKD were noted over and above any benefits of RAAS-I (IDNT and RENAAL), where further improvements would have been difficult to achieve. Indeed, in a recent further meta-analysis (unpublished yet) we showed with aggregate published data that the combination of SGLT2 and RAAS inhibitors may be similar in efficacy and safety if not superior to SGLT2-Is alone. *Seidu S. Kunutsor SK, Topsever P, Khunti K. Benefits and harms of SGLT2 and RAAS inhibitors versus SGLT2 inhibitors alone in patients with type 2 diabetes: A systematic review and meta-analysis of randomised controlled trials (UNPUBLSIHED)* 2. The findings int the DAPA-CKD analysis may not be applicable to patients with Polycystic kidney disease, lupus nephritis, ANCA- associated vasculitis, Immunosuppressive therapy and ≤6 months as these populations were excluded.

		3. People with ACR less than 22.6 mg/mmol were excluded. In the real world this will be the vast majority of patient, therefore the results may not be applicable.
Key issue 2: Concerns regarding the company's overall modelling approach and OS predictions	**No**	Please provide your response to this key issue, including any new evidence, data or analyses Altering the model fit to an alternative modelling approach would involve a considerable amount of additional analysis by the company but this analysis will not significantly alter the overall economic conclusions drawn from the analysis. Indeed, it is expected that the findings in such a model will even be better in favour of Dapagliflozin as the population in the real world is usually not as well optimised on RAAS-I, leaving room for further benefit from any nephron-protective drugs.

Additional issues

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Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

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..	..	..	[INSERT / DELETE ROWS AS REQUIRED]
Company's preferred base case following technical engagement	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide the revised company base-case ICER resulting from combining the changes described, and the change from the company's original base-case ICER

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About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**London Kidney Network (hosted by St Georges NHS Hospital Trust)**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Nil**

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Key issues for engagement

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Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Uncertainty surrounding the target population and the effectiveness of dapagliflozin in patients excluded from DAPA-CKD	NO	We support the ERG's concern that there is a critical evidence gap in key groups not included in the DAPA-CKD trial; including eGFR >75, lower albumin-to-creatinine ratio, Type 1 diabetes, transplanted patients, and those with autosomal dominant polycystic kidney disease. We are aware that the newly announced licence extension granted by MHRA is liberal, however we recommend that recommendations from NICE reflect the existing evidence base. DAPA-CKD is the only existing primary outcome study including people without diabetes, therefore its criteria should be considered when extrapolating the evidence to a wider patient base. As per the company submission and acknowledged by the ERG, DAPA HF and DECLARE TIMI 58 results suggest benefits that stretched beyond the patients included in the DAPA-CKD trial (albeit not primary outcome findings). We note that the UK Kidney Association has produced draft guidance for consultation "SGLT2-I and Kidney Disease" It acknowledges that large study placebo-control trials in people with CKD and/or heart failure are ongoing which will likely contribute further evidence for the use of Dapagliflozin in the groups not recruited to the DAPA-CKD trial. With respect to certain populations excluded by DAPA-CKD, the draft UK Kidney Association Guidance suggests (based on evidence they have graded as 1c) that if

		people with Type 1 diabetes are offered an SGLT2-I, they should only be used under specialist care and with explicit direction regarding ketone monitoring. Another concern raised by the LKN is with the limited exploration of the impact of potential health inequities on outcomes: • The DAPA-CKD trial have not yet undertaken a significant post-hoc analysis based on sex, which has recently been demonstrated in other cardiovascular trials to be significantly different between men and women. We suggest that if this is possible, this work should be completed and presented. • The ethnic minority representation in the trial was low, and ongoing data collection is important to support their role in different groups, particularly where disease mechanisms may differ e.g. APOL1 and sickle cell disease.
Key issue 2: Concerns regarding the company's overall modelling approach and OS predictions	NO	We are not clear if the modelling has considered the cost of optimising RAAS blockade agents as should precede dapagliflozin prescription. We refer to the need to consider the cost of visits, the risk of acute kidney injury and any associated treatment costs for hyperkalaemia. This could be particularly important when considering the ERG's comments on the different between the DAPA-CKD trial population and real-world primary care patients. The model makes use of estimates from this paper; "Economic Modelling of Chronic Kidney Disease: A Systematic Literature Review to Inform Conceptual Model Design". It would be useful to know the ERG's thoughts on the appropriateness of use of the paper.

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Company's preferred base case following technical engagement	**Incremental QALYs: [QQQ]**	**Incremental costs: [£££]**	**Please provide the revised company base-case ICER resulting from combining the changes described, and the change from the company's original base-case ICER**

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Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Novartis Pharmaceuticals UK Limited**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

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Key issue 1: Uncertainty surrounding the target population and the effectiveness of dapagliflozin in patients excluded from DAPA-CKD	**NO**	The DAPA-CKD trial provides evidence of efficacy of dapagliflozin only for people with an eGFR (at treatment initiation) of ≥25 to ≤75 ml/min/1.73m^2 and a urine albumin-to-creatinine ratio (UACR) of ≥200 mg/g (≥22.6 mg/mmol) to ≤5,000 mg/g (≤565 mg/mmol), when administered in addition to a maximum tolerated dose of an ACE inhibitor or ARB, unless medically contraindicated. The DAPA-CKD trial population ultimately represents an enriched patient population selected for its higher unmet need and greater potential to benefit from treatment, given the focus on patients with proteinuria – a well-established risk factor for disease progression – despite treatment with the current, NICE-recommended first-line standard of care (ACE inhibitor or ARB) at the maximally tolerated dose.[1] It is unclear whether a treatment effect of the same magnitude would have been observed in a lower-risk population without proteinuria, in a population naive to treatment with current standard of care, or in a population whose kidney disease was already more advanced (eGFR <25 ml/min/1.73m^2) at time of treatment initiation. Equally, it is unclear whether cost-effectiveness estimates relying on efficacy data from DAPA-CKD are generalisable to people who would have been excluded from the trial. We noted the ERG's observation that, as opposed to other model parameters, transition probabilities between CKD stages were not adjusted to

		account for differences between the DAPA-CKD trial population and the company's broader target population. We consider it implausible that the same transition probabilities from the DAPA-CKD trial would apply independent of a population's eGFR and UACR levels (also the company submission (p. 17) recognises that higher UACR and lower eGFR are associated with an increased risk of CKD progression). As cost-effectiveness for the company's full target population thus cannot be reliably evaluated given the lack of clinical evidence, we agree with the ERG that it would be appropriate to amend the economic model to reflect a narrower population in line with the characteristics of the DAPA-CKD trial population. If judged to be a cost-effective use of NHS resources, a NICE recommendation for dapagliflozin which is in line with the DAPA-CKD trial criteria would also be consistent with the positioning recommended by the London Kidney Network in its professional organisation submission and feedback from the ERG's clinical advisors as summarised in the ERG report. [1] Chronic kidney disease: assessment and management (2021). NICE guideline NG203.
Key issue 2: Concerns regarding the company's overall modelling approach and OS predictions	**NO**	No comments.

Dapagliflozin for treating chronic kidney disease: A Technology Appraisal

Addendum: ERG comments on the company's technical engagement response

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
Authors	Paul Tappenden, Professor of Health Economic Modelling, ScHARR, University of Sheffield, Sheffield, UK Edith Poku, Research Fellow, ScHARR, University of Sheffield, Sheffield, UK Jean Hamilton, Research Fellow, ScHARR, University of Sheffield, Sheffield, UK Aline Navega Biz, Research Associate, ScHARR, University of Sheffield, Sheffield, UK Mark Clowes, Information Specialist, ScHARR, University of Sheffield, Sheffield, UK Kate Ren, Senior Research Fellow, ScHARR, University of Sheffield, Sheffield, UK
Correspondence Author	Paul Tappenden, Professor of Health Economic Modelling, ScHARR, University of Sheffield, Sheffield, UK
Date completed	8th August 2021

Introduction

In July 2021, the company submitted their response to technical engagement (TE) for the appraisal of dapagliflozin for treating chronic kidney disease (CKD).[1] As part of their response, the company submitted the following:

- A written document which describes additional analyses which are intended to address the two key issues raised in the Evidence Review Group (ERG) report:[2]
    - Issue 1: The company's TE response[1] provides additional statistical analyses which estimate the relative effectiveness of dapagliflozin in patients with a urine albumin-to-creatinine ratio (uACR) which is lower than the minimum threshold of 22.6mg/mmol (200mg/g) applied in the DAPA-CKD trial.[3] The TE response also presents the methods and the results of a broad economic analysis of dapagliflozin versus standard of care (SoC) in the company's revised target population, based on a new model.
    - Issue 2: The company's TE response[1] provides further discussion and survival analyses in response to the ERG's concerns regarding the multivariable overall survival (OS) model presented in the company's submission (CS).[4]
- A new executable economic model which includes additional functionality to evaluate dapagliflozin across a range of patient populations and subgroups, including data from a subset of patients enrolled in DECLARE TIMI 58.[5]
- Instructions for implementing the company's additional economic analyses using the company's executable model.

This ERG addendum provides a summary and critique of the company's TE response.[1]

Key issue 1: Uncertainty surrounding the target population and the effectiveness of dapagliflozin in patients excluded from DAPA-CKD

The original CS[4] proposed the positioning of dapagliflozin as an additional treatment option for adult patients with CKD, regardless of estimated glomerular filtration rate (eGFR), uACR levels and the presence or absence of comorbid type 2 diabetes mellitus (T2DM). As discussed in the ERG report,[2] the DAPA-CKD trial[3] does not provide evidence of efficacy for dapagliflozin in: people with urine albumin excretion <22.6mg/mmol (200mg/g); people with end stage kidney disease (ESKD); people with prior organ transplantation, or people with type 1 diabetes mellitus (T1DM). Almost all (97%) patients in DAPA-CKD were receiving angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) therapy at baseline. The CS presented further supporting evidence from DAPA-HF[6] and DECLARE-TIMI 58[5] which was intended to demonstrate the generalisability of the treatment effect of dapagliflozin regardless of uACR, eGFR or background therapy.

In response to concerns raised in the ERG report,[2] the company has amended their proposed positioning of dapagliflozin to reflect a narrower population of patients with CKD who are currently receiving ACE inhibitor/ARB therapy. The company has also amended the analysis of the Clinical Practice Research Datalink (CPRD) to reflect this population in their economic analysis. This dataset is used to inform patient characteristics and to adjust the risks of mortality and transient events. The amended CPRD dataset also includes additional exclusion criteria to better reflect the eligibility criteria applied in DAPA-CKD.[3] The company's TE response[1] (page 3) states that *"AstraZeneca believe that a recommendation from NICE for use of dapagliflozin in patients already treated with an ACE inhibitor/ARB for their chronic kidney disease (CKD) if tolerated, reflects a patient population that's broadly similar to the DAPA-CKD trial population."* The ERG agrees that the amended population reflected in the new model is more similar to the DAPA-CKD trial with respect to the use of ACE inhibitor/ARB therapy; however, the revised target population remains much broader than the population of patients recruited into DAPA-CKD.

Specifically, the company has not restricted the amended target population for dapagliflozin by uACR. The company's TE response[1] highlights that the European Medicines Agency (EMA), the Medicines and Healthcare products Regulatory Agency (MHRA) and the US Food and Drug Administration (FDA) have granted a marketing authorisation for dapagliflozin without restriction by uACR. The company's TE response[1] includes the following quote from the MHRA (the ERG notes that this quote is not referenced in the company's TE response and so the precise source is not clear): [redacted] The company's TE response (page 4) states that as a result of the regulators' assessment, the company believes that *"sufficient clinical evidence has been presented to support a recommendation in patients with CKD, irrespective of diabetes status and uACR levels."* The ERG acknowledges that the relevant marketing authorisation for dapagliflozin is broader than the eligibility criteria applied in the DAPA-CKD trial,[3] but notes that evidence is weak or lacking for some populations. As noted in the ERG report,[2] there is no evidence for the efficacy of dapagliflozin in patients without T2DM and with uACR<22.6mg/mmol. This group represents a substantial proportion of the company's revised target population for dapagliflozin.

Within their TE response,[1] the company presents additional analyses which are intended to provide evidence for the clinical and cost-effectiveness of dapagliflozin in patients with low uACR. The company's response includes two sets of additional analyses:

(1a) Additional statistical analyses to predict outcomes for patients with low uACR

(1b) Additional economic analyses for the broad CKD population (irrespective of uACR) based on pooled data from DAPA-CKD[3] and a subset of patients enrolled in DECLARE TIMI 58.[5]

These analyses are described below.

(1a) Additional analyses to predict outcomes for patients with low uACR

The company undertook a simulated treatment outcomes analysis, using a Poisson model to fit the estimated annual event rate conditional on uACR as a continuous variable using data from DAPA-CKD.[3] The uACR range was then extended to 30-5,000 mg/g (beyond the minimum cut-off used in the DAPA-CKD inclusion criteria) and the event rate ratio between dapagliflozin and placebo at each uACR level was determined. The analysis was stratified by T2DM status at baseline for three outcomes: (i) the composite primary endpoint of sustained eGFR decline ≥50%, ESKD, cardiovascular (CV) death and renal death; (ii) sustained eGFR decline ≥50% and (iii) ESKD.

Detailed results of this analysis are presented in Figures 1 and 2 and Tables 1 and 2 of the company's TE response.[1] The results of the stratified analysis are reproduced in Figure 1.

Figure 1: Ratio of annual event rates per 100 patients with dapagliflozin versus placebo, for the primary endpoint, sustained eGFR decline ≥50% and ESKD, stratified by T2DM status (reproduced from company's TE response, Figure 2)

eGFR: estimated glomerular filtration rate; ESRD, end-stage renal disease; uACR: urinary albumin creatinine ratio

Briefly, the results of the company's additional analyses indicate that:

[redacted]

On the basis of these analyses, the company concludes that [redacted] The findings of these analyses were then used to justify modelling a treatment benefit with dapagliflozin as add on to ACE inhibitor/ARB therapy across a broader population than that included in the DAPA-CKD trial.[3] The findings of this analysis are particularly relevant to the assumptions applied in Subgroups 2 and 3 of the company's updated economic analysis, as described in Section 1b of this addendum.

ERG comments on the company's additional statistical analyses

The ERG believes that the findings of the company's additional analyses can be interpreted as supporting a hypothesis that dapagliflozin might work in people with lower uACR than that of the population recruited into DAPA-CKD.[3] However, these are model-based analyses which involve extrapolating event rates to a population for whom there is no evidence of efficacy for dapagliflozin. As such, these findings should be interpreted with some caution.

(1b) Summary of company's updated economic analysis

As part of their TE response,[1] the company submitted a new economic model which attempts to reflect the revised target population in whom the company is seeking a positive recommendation - that is - patients with CKD who are currently treated with ACE inhibitor/ARB therapy, irrespective of uACR. The new economic model, which is described as a "unified broad population analysis" (UBPA), is a weighted economic analysis across three subgroups of patients, with weights for each subgroup determined according to their prevalence in the amended CPRD dataset:[7]

- Subgroup 1: Patients with uACR≥200 mg/g, with or without T2DM
- Subgroup 2: Patients with uACR<200 mg/g, with T2DM
- Subgroup 3: Patients with uACR<200 mg/g, without T2DM.

The company's TE model leverages data from a subset of patients with T2DM in DECLARE TIMI 58 (excluding patients with eGFR>60 and uACR<30),[5] referred to as "$DECLARE_{CKD}$", together with the other evidence sources used in the company's original economic model (including DAPA-CKD[3] and the CPRD[7]). The new TE model adopts the same general structure as the company's original model,[4] but involves the re-estimation of patient characteristics, transition probabilities, mortality risks and transient event risks for each subgroup. Generally speaking, Subgroup 1 (patients with uACR≥200 mg/g, with or without T2DM) reflects the population of patients recruited into DAPA-CKD. The other two subgroups reflect patients who are included in the company's revised target population who have low uACR (split according to whether patients have T2DM or not). Patients in these two subgroups would not have been eligible for entry into the DAPA-CKD trial. Subgroup 2 reflects patients with low uACR and with T2DM, some of whom would have been eligible for DECLARE TIMI 58. The ERG notes that dapagliflozin already has a positive NICE recommendation in triple therapy (in combination with metformin and sulfonylurea) for people with T2DM, without restriction by uACR.[8] Subgroup 3 reflects a population of patients with low uACR and without T2DM; this population was not reflected in either DECLARE TIMI 58 or DAPA-CKD. The company's TE model uses a mix of data from $DECLARE_{CKD}$ and DAPA-CKD to inform transitions and mortality risks across the subgroups. Individual trial datasets are not used specifically to inform event risks in any of the three subgroups.

Table 1 provides a general summary of how evidence from the amended CPRD dataset,[7] DAPA-CKD[3] and $DECLARE_{CKD}$[5] is used to inform patient characteristics, survival and transition probabilities in the TE model. Of particular note, the model assumes that for Subgroup 3 (patients with uACR<200 mg/g without T2DM), the relative effectiveness of dapagliflozin versus SoC is assumed to be the same as that for patients with T2DM, based on the statistical analysis of events rates by uACR level described in Section 1a of this addendum. A "non-T2DM correction factor", which was derived from an analysis of patients with T2DM and patients without T2DM in DAPA-CKD was used to estimate absolute risks of mortality and hospitalisation for heart failure (hHF) for SoC in this subgroup. In addition, the model uses patient characteristics from the CPRD for patients with CKD receiving ACE inhibitor/ARB therapy for most covariates, but assumes a lower mean age based on a wider group of patients (those with eGFR<90ml/min/1.73cm^2 on ACE inhibitor/ARB therapy) based on a different analysis of patients included in the CPRD.

Table 1: Summary of company's weighted subgroup approach, UBPA1

Patent subgroup	Patient characteristics and subgroup weighting	Survival	Transition probabilities
Subgroup 1 - uACR≥200mg/g	Patients with uACR≥200mg/g on ACEi/ARB therapy in CPRD dataset[7] Mean age assumed to be [redacted] years† Subgroup weighting=[redacted]	Multivariable Weibull model fitted to pooled data from DAPA-CKD[3] and DECLARE$_{CKD}$,[5] including covariates for treatment group, uACR, T2DM and other patient characteristics. Weibull model selected on basis of statistical goodness of fit and through reference to clinical experts' expectations of survival for patients with CKD and albuminuria[9]*	DAPA-CKD[3] used to inform all transitions out of CKD stages 1-5 (as per the original model) Not adjusted by CPRD
Subgroup 2 - uACR<200mg/g with T2DM	Patients with uACR<200mg/g with T2DM on ACEi/ARB therapy in CPRD dataset[7] Mean age assumed to be [redacted] years† Subgroup weighting=[redacted]		DECLARE$_{CKD}$[5] used to inform transitions out of CKD stages 1-3b; DAPA-CKD[3] used to inform transitions out of between CKD stages 4-5. Not adjusted by CPRD
Subgroup 3 - uACR<200mg/g without T2DM	Patients with uACR<200mg/g without T2DM on ACEi/ARB therapy in CPRD dataset[7] Mean age assumed to be [redacted] years† Subgroup weighting=[redacted]	Same survival model as Subgroups 1 and 2, but including non-T2DM mortality adjustment factor of [redacted] (lower event rate compared with diabetic patients)[1]	Assumed to be the same as Subgroup 2 Not adjusted by CPRD
[redacted]			

† Age based on a separate CPRD query including people with eGFR <90 ml/min/1.73cm^2, without the requirement of a formal diagnosis of CKD
uACR - urine albumin-to-creatinine ratio; ACEi - angiotensin converting enzyme inhibitor; ARB - angiotensin receptor blocker; CKD - chronic kidney disease; T2DM - type 2 diabetes mellitus

The company's TE response[1] reports the results of economic analyses using five different modelling approaches:

(i) Original approach: This is the approach used in the company's original base case whereby event risks were estimated using data from DAPA-CKD only,[3] as described in the CS[4]

(ii) UBPA1: As described in Table 1

(iii) UBPA2: This approach is the same as UBPA1, but with the DAPA-CKD[3] and DECLARE$_{CKD}$[5] datasets restricted to avoid overlap. OS is modelled using a gamma distribution rather than a Weibull model

(iv) UBPA3: The difference between this method and UBPA1 is not clear from the wording in Table 5 of the company's TE response[1]

(v) UBPA4: This approach is the same as UBPA1, but with transition probabilities estimated from a single pooled dataset from DAPA-CKD[3] and DECLARE$_{CKD}$,[5] rather than using separate sources to inform certain transitions.

In addition, results are presented separately for each of the three subgroups which comprise the company's revised target population, based on UBPA1. A further analysis is also presented for patients with CKD patients with uACR<200mg/g who are treated with ACE inhibitors/ARBs (relating to Subgroups 2 and 3 together).

Table 2 presents the disaggregated results of the company's economic analyses for each of the three subgroups which comprise the company's revised target population (using UBPA1), together with the weighted results. Table 3 presents a summary of results obtained using alternative modelling approaches UBPA2-4, and the additional analysis for patients with uACR<200mg/g treated with ACE inhibitors/ARBs. The company's analyses indicate that based on UBPA1, the deterministic incremental cost-effectiveness ratios (ICERs) for dapagliflozin versus SoC in Subgroups 1-3 are each below £7,000 per QALY gained; the weighted ICER for dapagliflozin versus SoC is estimated to be £4,557 per QALY gained. The other analyses indicate that the ICER is consistently less than £8,000 per QALY gained, irrespective of the approach used to estimate transition probabilities and mortality risks.

Table 2: Company's results for UBPA1 – subgroup results and weighted ICER (generated by the ERG using the company's TE model)

Subgroup / population	Subgroup weighting	Option	QALYs	Costs	ICER
Subgroup 1 - Patients with uACR≥200mg/g	[redacted]	Dapagliflozin	7.05	£60,245	-
		SoC	6.47	£61,428	-
		Incremental	0.59	-£1,183	Dominant
Subgroup 2 - Patients with uACR<200mg/g with T2DM	[redacted]	Dapagliflozin	8.52	£28,574	-
		SoC	8.00	£25,772	-
		Incremental	0.52	£2,801	£5,418
Subgroup 3 - Patients with uACR<200mg/g without T2DM	[redacted]	Dapagliflozin	9.76	£33,134	-
		SoC	9.43	£31,043	-
		Incremental	0.33	£2,091	£6,285
Weighted results UBPA1	N/a	Dapagliflozin	8.83	£33,975	-
		SoC	8.37	£31,907	-
		Incremental	0.45	£2,069	**£4,557**

QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; SoC - standard of care; uACR - urine albumin-to-creatinine ratio; T2DM - type 2 diabetes mellitus; UBPA - unified broad population analysis

Table 3: Company's results for other analyses presented in the company's TE response (generated by the ERG using the company's TE model)

Scenario description	Inc. QALYs	Inc. costs	ICER
Original approach	0.50	£3,095	£6,158
Original approach, ACEi/ARB treated, age=[redacted]	0.73	£5,181	£7,063
UBPA2, ACEi/ARB treated, age=[redacted]	0.40	£2,888	£7,290
UBPA3, ACEi/ARB treated, age=[redacted]	0.41	£1,874	£4,531
UBPA4, ACEi/ARB treated, age=[redacted]	0.51	£3,507	£6,813
UBPA1, uACR<200mg/g, ACEi/ARB treated, age=[redacted]	0.44	£2,492	£5,705

QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; uACR - urine albumin-to-creatinine ratio; UBPA - unified broad population analysis; ACEi - angiotensin converting enzyme inhibitor; ARB - angiotensin receptor blocker; Inc. - incremental

ERG critique of company's TE model

The ERG notes the following issues regarding the company's TE model:

- The ERG was able to generate the results for each of the scenarios/subgroups presented in the TE response[1] using instructions provided by the company. The ERG attempted to implement the three subgroup analyses shown in Table 1 using the ERG's double-programmed model, but the results were notably different to those obtained from the company's TE model. However, this does not necessarily indicate the presence of errors in the company's TE model and the ERG's double-programmed ICERs were only markedly higher for Subgroup 3 (ERG's double-programmed ICER=£13,414 per QALY gained; company's ICER=£6,285 per QALY gained). The ERG did not have sufficient time to further explore the reasons for these differences.
- The ERG's main concern remains unchanged - whilst the company has highlighted that the marketing authorisation for dapagliflozin reflects a broad CKD indication without restriction by uACR,[10] the pivotal trial of dapagliflozin in CKD - DAPA-CKD[3] - excluded patients with a uACR<22.6mg/mmol (200mg/g). DECLARE TIMI 58[5] did not restrict trial inclusion by uACR and a subset of patients from this study is used to inform the company's TE model (see Table 1). However, all patients in this trial had T2DM. DAPA-HF[6] has not been used to inform the TE model. As discussed above, there is no evidence of efficacy for dapagliflozin in patients without T2DM and with a uACR<22.6mg/mmol (<200mg/g - Subgroup 3). The ERG believes that this is problematic as the Appraisal Committee may have concerns about recommending a treatment in a population for whom there is no evidence of efficacy. As shown in Table 2, [redacted] of the weighting for the QALYs and costs in the company's TE analysis is applied to a population of patients who were not eligible for the DAPA-CKD trial (Subgroups 2 and 3), and [redacted] of the overall weighting is applied to Subgroup 3, which reflects a population in whom there is no evidence for dapagliflozin from any trial.
- The ERG does not believe that the company's weighted analysis is appropriate. Instead, the ERG believes that it would be more appropriate to consider the cost-effectiveness of dapagliflozin within the individual subgroups which together make up the company's overall proposed target population. These considerations should take into account the availability and strength of evidence for the efficacy for dapagliflozin within each subgroup. A positive recommendation in Subgroup 3 will require a judgement regarding the plausibility of the assumption of efficacy for dapagliflozin based on the interpretation of the findings of the company's Poisson model analyses presented in Section 1a.
- The company's updated model uses an amended CPRD dataset which has been restricted to patients receiving ACE inhibitor/ARB therapy.[7] As described in the ERG report[2] (Section 5.2.4), this CPRD dataset is used to inform baseline characteristics and to adjust event risks (mortality, AKI and hHF) in the model. The amended dataset suggests a mean age of [redacted]

years (see TE response,[1] Table 9). However, the company's economic model assumes a mean age of [redacted] years, based on a different group of CPRD patients - those with eGFR<90 ml/min/1.73cm^2, without the requirement of a formal diagnosis of CKD. All other patient characteristics are based on the older population of CKD patients receiving ACE inhibitor/ARB therapy. The company's TE response[1] (page 39) notes that *"patients were only included if they had a formal diagnosis of CKD stages 1 to 4 and were on ACE inhibitor/ARB therapy. However, it has been reported that over 40% of people with CKD in England are undiagnosed, with the majority of those with asymptomatic early stage CKD unlikely to receive a formal diagnosis until more advanced stages of disease."* The values obtained from the CPRD analyses and those used in the economic model are shown in Table 6 in Appendix 1. The ERG has several concerns regarding the company's use of the CPRD data:

- The ERG does not consider it appropriate to include a mix of patient characteristics from two separate groups of patients in the CPRD.[7] In particular, the company's model appears to implicitly assume that the distribution of characteristics for patients in the CPRD with CKD who are receiving ACE inhibitor/ARB therapy (age [redacted] years) will be the same as that for the younger cohort who do not have a formal diagnosis of CKD (age [redacted] years). The ERG considers this to be very unlikely.
- The CPRD analysis used to inform age in the model (people with eGFR<90ml/min/1.73cm^2, without the requirement of a formal diagnosis of CKD) is likely to include an unknown proportion of people who are receiving ACE inhibitor/ARB therapy for other indications (e.g. diabetes, heart failure and/or hypertension) but who do not have CKD. The ERG does not believe that these patients should form part of the company's revised target population.
- Given the mix of different CPRD datasets used to inform the patient characteristics in the analysis, it is unclear which target population is actually reflected in the TE model.
- The ERG re-ran the company's TE model using the older mean ages for the subgroups obtained from the CPRD queries for CKD patients receiving ACE inhibitors/ARBs (shown in Table 6 in Appendix 1). The results for Subgroups 1 and 2 were generally similar to the company's estimates; however, the ICER for Subgroup 3 increased from £6,285 per QALY gained to £44,748 per QALY gained (see Table 4). This shows the importance of modifying the patient age parameter on the cost-effectiveness of dapagliflozin in this subgroup.
- The company's TE response[1] (pages 39-40) argues that the amended ACE inhibitor/ARB CPRD dataset is not representative of the CKD population in whom dapagliflozin would be used, in particular, due to the under-representation of patients with early stage CKD. The ERG believes that if the CPRD dataset is not representative of the anticipated target population, this raises questions regarding the justification for

undertaking an adjusted analysis and the reliability of the results obtained from it. This concern applies to all of the company's CPRD adjusted analyses, including those reported in the original CS.[4]

- The company has developed a new multivariable survival model using pooled data from $DECLARE_{CKD}$ and DAPA-CKD.[3, 5] The ERG notes the following concerns regarding this approach:
    - The company has trimmed the data from DECLARE TIMI 58[5] by excluding patients with eGFR>60 and uACR<30 to derive the $DECLARE_{CKD}$ dataset used in the economic analysis. It appears that the company has undertaken simple pooling of the data from $DECLARE_{CKD}$ and DAPA-CKD.[3] Simple pooling of data from separate trials will break randomisation, which may lead to bias in the survival modelling and the group-specific transition probabilities.
    - In the company's original analysis, covariates were selected for inclusion in the multivariable survival model using a backwards stepwise procedure and clinical judgement. In the TE model, it has been assumed *a priori* that the same covariates identified from the analysis of DAPA-CKD[3] should also apply in the pooled dataset of DAPA-CKD and $DECLARE_{CKD}$. The ERG is unclear whether this would be the case, had the selection procedure been repeated.
    - The company selected the Weibull distribution for inclusion in the TE model on the basis of consideration of goodness-of-fit statistics and through reference to estimates of expected survival obtained from clinical experts.[9] The company's original model[4] applied a Gompertz distribution. As described in the company's TE response,[1] clinicians were asked to provide expectations of survival in CKD patients with albuminuria (more severe patients), not the broader CKD population in whom the company is seeking a positive recommendation. Figures 4 and 5 of the company's TE response show that the Weibull model leads to predictions of OS which are close to, or higher than, the upper 95% CIs of the estimates obtained from the clinical experts. Given the differences between the populations considered in the elicitation exercise and the economic model, it is unclear whether the new Weibull OS model provides plausible estimates of OS for the company's proposed target population.
- The company's TE model uses the same approach to derive transition probabilities as the original model, albeit using $DECLARE_{CKD}$[5] to inform some transitions in Subgroups 2 and 3.
    - The ERG's clinical advisors commented that rapid CKD progression is more common in people with T2DM than people without T2DM (as demonstrated by Go *et al*.[11]). As such, it is unlikely to be appropriate to assume the same transition probabilities will apply to Subgroups 2 and 3. The ERG notes that it is unclear what else the company

could do to derive transition probabilities for Subgroup 3, as neither DAPA-CKD[3] nor DECLARE TIMI 58[5] relate to people with low uACR and without T2DM.

- Given that the company has stated that OS and CKD transitions were jointly determined, this suggests that when the approach used to derive transitions is amended, this should lead to a different set of coefficients for the multivariable survival model (i.e. the survival model for UBPA4 should be different to that for UBPA1). However, the executable model appears to apply the same multivariable OS model, irrespective of the approach used to derive transition probabilities. The ERG is unsure why this is the case.
- As discussed in the ERG report[2] (Section 5.3.4), none of the transition probabilities are adjusted to reflect the CPRD population.

Table 4: Additional ERG analyses of Subgroups 1-3 using age from CPRD dataset of patients with CKD receiving ACE inhibitors/ARBs (UBPA1)

Subgroup	Option	Company's analyses assuming age=[redacted] years			ERG analyses using age from CPRD dataset of patients with CKD receiving ACEi/ARBs (see Table 6, Appendix 1)		
		QALYs	Costs	ICER	QALYs	Costs	ICER
Subgroup 1 - Patients with uACR≥200mg/g	Dapagliflozin	7.05	£60,245	-	6.00	£48,426	-
	SoC	6.47	£61,428	-	5.51	£49,389	-
	Incremental	0.59	-£1,183	**Dominant**	0.49	-£962	**Dominant**
Subgroup 2 - Patients with uACR<200mg/g with T2DM	Dapagliflozin	8.52	£28,574	-	6.34	£21,016	-
	SoC	8.00	£25,772	-	6.02	£18,771	-
	Incremental	0.52	£2,801	**£5,418**	0.31	£2,245	**£7,189**
Subgroup 3 - Patients with uACR<200mg/g without T2DM	Dapagliflozin	9.76	£33,134	-	6.29	£21,229	-
	SoC	9.43	£31,043	-	6.27	£20,060	-
	Incremental	0.33	£2,091	**£6,285**	0.03	£1,169	**£44,748**

ERG - Evidence Review Group; CPRD - Clinical Practice Research Datalink; CKD - chronic kidney disease; ACEi - angiotensin converting enzyme inhibitor; ARB - angiotensin receptor blocker; uACR - urine albumin-to-creatinine ratio; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; SoC - standard of care; T2DM - type 2 diabetes mellitus

Key issue 2: Concerns regarding the company's overall modelling approach and OS predictions

As discussed in the ERG report[2] (Section 5.3.4), treatment effects for dapagliflozin on OS are modelled via two mechanisms: (a) directly – through the application of a hazard ratio (HR) to each state-specific OS model except transplant, and (b) indirectly – through the application of transition matrices which lead to slower disease progression for dapagliflozin compared with SoC. The ERG report raises the following concerns: (i) that including post-randomisation covariates can lead to problems in determining causality - if part of the causal effect of treatment is through CKD stage, this approach will block that effect, and the resulting model coefficients may not be meaningful; (ii) the company's multivariable survival model uses a "mean of covariates" approach which has been shown to lead to

bias when estimating survival distributions, and (iii) the company's unadjusted economic model for the DAPA-CKD population,[3] excluding adjustment to the CPRD population,[7] overestimates OS in both treatment groups (see ERG report,[2] Figure 17). The ERG report suggests that this overestimation is likely to be a consequence of issues (i) and/or (ii) above. This overestimation of OS raises some doubts regarding the confidence that should be placed on the results obtained from the company's economic model.

The company's TE response[1] provides further discussion and analyses to address the ERG's concerns about the company's original survival modelling and the resulting OS predictions. In summary, the company's TE response makes the following points:

- The company does not consider the methodology used to be of concern from a statistical perspective because there is no assumption about causality in the cost-effectiveness model and the transition probabilities and survival models in the economic model reflect associations observed in the DAPA-CKD trial.[3]
- The relationship between CKD stage and all-cause mortality is well established in the literature.
- After accounting for CKD stage, there is a residual treatment effect on OS for dapagliflozin, as represented by the dapagliflozin coefficient in the multivariable OS model.
- The company's modelling approach was validated by clinical and methodological experts and the modelled OS predictions were validated through expert elicitation.
- Whilst not done, the multistate modelling approach, which is suggested as a potential solution in the ERG report, would likely lead to implausible OS predictions.
- Because last observed eGFR was included as a covariate in the multivariable OS model, there is no double-counting when used alongside the treatment-specific transition probabilities in the economic model.
- Applying the ERG's preferred "corrected group prognosis" method to the model would be very complex. This has not been done.
- The previous CREDEM-DKD microsimulation model[12] suggests that canagliflozin is associated with QALY gains. A microsimulation model based on DAPA-CKD was considered during model conceptualisation, but was deprioritised in favour of the cohort Markov model presented in the CS.[4]
- The simple Gompertz model presented in response to clarification question B31, which includes only time-updated CKD stage, treatment, age and sex as covariates, provides a good fit to the observed data from DAPA-CKD[3] (see company's TE response,[1] Figure 6).
- A separate survival model based on a standardised mortality ratio (SMR) approach provides a good fit to the data from DAPA-CKD[1] (see company's TE response,[1] Figure 7). This provides

similar ICERs to the company's original multivariable approach (see company's TE response,[1] Table 8).

- The ERG's concerns regarding overestimation of OS can be addressed through reference to the company's simple Gompertz model or the SMR model. The company also notes that similar results were obtained from ERG Exploratory Analysis 7 (EA7) which forced model-predicted OS to better fit the OS data. As the results of these analyses are similar, the company's preferred approach is to retain the multivariable OS model approach in their base case analysis.

The company's TE response[1] presents cost-effectiveness results for the DAPA-CKD population (without adjustment using the CPRD[7]) using two alternative survival modelling approaches: (i) the company's original multivariable OS approach and (ii) the SMR approach. The results of these analyses are summarised in Table 5. Both analyses indicate that the ICER for dapagliflozin versus SoC in the DAPA-CKD population is less than £6,000 per QALY gained.

Table 5: Cost-effectiveness results for the DAPA-CKD population using the company's multivariable OS model and using the SMR model

Subgroup / population	Option	QALYs	Costs	ICER
Original multivariable OS model	Dapagliflozin	8.06	£78,399	-
	SoC	7.29	£73,910	-
	Incremental	0.77	£4,489	**£5,841**
SMR model	Dapagliflozin	8.58	£86,533	-
	SoC	7.87	£83,280	-
	Incremental	0.71	£3,253	**£4,551**

QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; OS - overall survival; SMR - standardised mortality ratio; SoC - standard of care

With respect to the arguments put forward in the company's TE response,[1] the ERG notes the following:

- The ERG's main concern is that the company's multivariable model, without adjustment using the CPRD dataset,[7] does not fit the observed data from DAPA-CKD.[1] The precise cause of this poor fit is not fully clear, but it remains a matter of concern to the ERG. The potential problems associated with the inclusion of a time-updated (post-randomisation) covariate and the mean of covariates approach were postulated as potential reasons why the economic model over-predicts OS in the DAPA-CKD population. The ERG notes that if these two problems are not the underlying cause of the poor fit, then the cause relates to some other issue which has not been identified by the ERG or the company. Nonetheless, the issue of the poor fit of the multivariable OS model has not been resolved in the company's TE response.[1]
- As discussed in the ERG report (Section 5.3.4),[2] the fully specified survival model and the code used to fit the multivariable OS model were not provided by the company. This limits the extent to which the ERG is able to investigate the precise cause of the poor fit.

- The ERG is not concerned specifically that survival is being modelled through two different mechanisms. The ERG's concern is that the inclusion of post-randomisation covariates in survival models which estimate treatment effects is contrary to standard practice and may lead to bias in the estimation of the treatment effect parameter (the dapagliflozin HR estimated from the multivariable model). This is because of problems in determining causality in the statistical model itself. The company's TE response does not clearly address this point and instead refers only to how the statistical analysis outputs are applied in the economic model. The ERG also notes that the EMA's guidance on the adjustment of baseline covariates cautions against adjusting for post-randomisation covariates because they may be affected by the treatments included in the trial, which in turn, makes the treatment effect difficult to interpret.[13] The EMA guidance suggests such analyses might be considered in secondary analyses.
- The ERG is unclear how the reference to the CREDEM-DKD model QALY estimates in the company's TE response[1] is relevant to the issue of poor OS predictions in the company's economic model of dapagliflozin. The ERG notes that a separate publication describing the development and validation of the CREDEM-DKD model[14] also highlights potential problems associated with including time-updated covariates in survival models (referred to by the authors as "endogeneity bias").
- The ERG agrees that the SMR model, the simple Gompertz model and the ERG's EA7 each provide a better fit to the observed survival data in DAPA-CKD,[3] compared with the company's preferred multivariable approach. Whilst the ICERs are generally similar across all approaches, the ERG is unsure why the company prefers the approach which does not fit the observed data.
- As discussed in the ERG report (Section 1.7),[2] the ERG believes that even if the issues identified in the company's model were resolved, the ICER for dapagliflozin would probably remain below £20,000 per QALY gained in the DAPA-CKD population.

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Appendix 1: Patient characteristics obtained from revised CPRD analyses and additional analyses undertaken by the ERG

Table 6: CPRD patient characteristics used in company's TE model

Patient characteristic	Subgroup 1 - patients with uACR≥200mg/g		Subgroup 2 - patients with uACR<200mg/g with T2DM		Subgroup 3 - patients with uACR<200mg/g without T2DM	
	CRPD value*	Model value	CRPD value	Model value	CRPD value	Model value
Age (years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI (kg/m2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race: White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race: Black or African American	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race: Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Smoker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CKD 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CKD 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CKD 3a	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CKD 3b	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CKD 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CKD 5 (pre-RRT)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dialysis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Transplant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
uACR 30-300mg/g	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
uACR >=300mg/g	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Type 2 diabetes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glomerulonephritis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ACE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MRA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diuretic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Potassium	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SBP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hemoglobin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior HF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior MI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior Stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

** Patient characteristics based on amended CPRD analysis, restricted to CKD patients receiving ACE inhibitor/ARB therapy. Amended dataset includes further exclusions based on DAPA-CKD eligibility criteria: patients with T1DM, polycystic kidney disease, New York Heart Association Class IV heart failure and organ transplant*
† Age based on patients in CPRD with eGFR <90 ml/min/1.73cm.^{2}

NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

Dapagliflozin for treating chronic kidney disease [ID3866]

Thank you for agreeing to give us your views on this treatment 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.

About this Form

In **part 1** we are asking you to complete questions about living with or caring for a patient with the condition.

In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.

The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a patient perspective could help either:

- resolve any uncertainty that has been identified
  or
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.
-

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

If you have any questions or need help with completing this form please email the public involvement team via pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please return this form by **5pm** on **Friday 27 August 2021**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee. The text boxes will expand as you type.

Important information on completing this expert statement

- 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 want 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 15 pages.

PART 1 – Living with or caring for a patient with chronic kidney disease and current treatment options	
About you	
1.Your name	**Ann Harpur-McGrath**
2. Are you (please tick all that apply):	**X**☐ a patient with chronic kidney disease? ☐ a patient with experience of the treatment being evaluated? ☐ a carer of a patient with chronic kidney disease? ☐ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation.	Kidney Care UK
4. Has your nominating organisation provided a submission? Please tick all options that apply.	☐ No, (please review all the questions below and provide answers where possible) X☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing

5. How did you gather the information included in your statement? (please tick all that apply)	X☐ I am drawing from personal experience. X☐ I have other relevant knowledge/experience (e.g. I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ **X** I have not completed part 2 of the statement
Living with the condition	
6. What is your experience of living with chronic kidney disease? If you are a carer (for someone with chronic kidney disease) please share your experience of caring for them.	I' m a renal patient, CKD stage 4, my grandmother ,father, Aunt have died from CKD another Aunt is transplanted and my daughter in her 20's has already symptoms. I spent 9 years working as a nurse and specialist practitioner in a dialysis unit. I have seen many suffer with the longstanding problems due to CKD, dialysis and failed transplantation, and I live with the physical and emotional impact of suffering with CKD it's complications that many endure. Loss of my beloved father, my job, impact on my family, fatigue, medication regime to name a few. Fear and anxiety of knowledge of what's ahead, as well as being physically debilitated. I also have experience in working in committees and am a member of the Patient Advisory Group for KCUK, recently invited on to NIKPA committee, a member of Renal Arts Group@QUB and my local renal unit support group so regularly meet other patients with CKD and am aware of their stories.

Current treatment of the condition in the NHS	
7a. What do you think of the current treatments and care available for chronic kidney disease on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	Managed care under GP or Renal Consultant and between both, following Nice Guidelines. Pre dialysis, hospital appointments, monitoring, medications, lifestyle changes, restrictions. Dialysis, three days a week 4+ hours at a unit or at home, supported by renal team. Multiple medications daily and restrictions on diet, fluid and lifestyle. Transplantation, multiple medications daily, multiple hospital appointments and blood samples. Not a cure, another treatment now CKD patient again. Conservative end of life care, for patients unsuitable for dialysis , transplantation or choose to refuse treatments. My Aunt died at 61 had home CAPD complications led to dialysis at local unit, more complications and hospital admissions she decided to stop all treatments. Many patients arrive at the point of dialysis without any prior knowledge of disease or treatments. Diet and lifestyle changes, medical interventions year's before could prevent or delay many patients progression.
8. If there are disadvantages for patients of **current NHS treatments** for chronic kidney disease (for example how dapagliflozin is given or taken, side effects of treatment etc) please describe these	Many patients arrive at the point of dialysis without any prior knowledge. Diet and lifestyle changes, medical interventions year's before could prevent or delay progression Dialysis is very demanding on patients physically, mentally and lifestyle invasive. Not to mention expenses on NHS Kidney patients are at very high risk of death from cardio vascular disease which my father suffered immensely. He suffered a heart attack at 47 which caused **Peripheral vascular disease** and he required bilateral amputation of his legs and caused his premature death at 52.

Advantages of dapagliflozin	
9a. If there are advantages of dapagliflozin over current treatments on the NHS please describe these. For example, the impact on your Quality of Life, your ability to continue work, education, self-care, and care for others? 9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does dapagliflozin help to overcome/address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these.	A new way of treating kidney disease that benefits patients, by delaying further decline in kidney function and progression to end stage kidney failure/dialysis is very exciting for myself and many other patients. Development of new treatments for kidney disease has greatly changed from my grandmother's death in the 1960s aged 45 and these positive findings for this treatment offers real hope to patient's like myself and my daughter. Progression to dialysis. Watching others on dialysis, many for years. It is a very invasive treatment and costly. It requires specialist nurses and no matter how poorly you feel you must attend the three lengthy sessions each week. Many are on dialysis for life and have great distances to travel in all weather. They have no choice.
Disadvantages of dapagliflozin	
10. If there are disadvantages of dapagliflozin over current treatments on the NHS please describe these? For example, are there any risks with	Possible urinary tract infections as they can lead to further kidney damage.

dapagliflozin? If you are concerned about any potential side affects you have heard about, please describe them and explain why.	
Patient population	
11. Are there any groups of patients who might benefit more from dapagliflozin or any who may benefit less? If so, please describe them and explain why. Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Diabetic patients would have an advantage. Patients with heredity conditions known to the renal teams may have an advantage than others who present at end stage without attending a doctor.
Equality	
12. Are there any potential equality issues that should be taken into account when considering chronic kidney disease and dapagliflozin? Please explain if	**CKD** affects all genders, age group, socioeconomic background, races. BAME would seem to be more prevalent group and have poorer outcomes.

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 More general information about the Equality Act can and equalities issues can be found at https://www.gov.uk/government/publications/easy-read-the-equality-act-making-equality-real and https://www.gov.uk/discrimination-your-rights.	
Other issues	
13. Are there any other issues that you would like the committee to consider?	

PART 2 – Technical engagement questions for patient experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the patient organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
14. Key issue 1: Uncertainty surrounding the target population and the effectiveness of dapagliflozin in patients excluded from DAPA-CKD • Do you have any general comments on this issue?	

15. Key issue 2: Concerns regarding the company's overall modelling approach and OS predictions • Do you have any general comments on this issue?	
15. Are there any important issues that have been missed in ERG report?	

PART 3 -Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- CKD is a very debilitating, causing much suffering from both the symptoms caused and from treatments such as dialysis and transplantation. It is a life long, life changing diagnosis.
- Many current treatments are around symptoms presented , this explores prevention by delaying declining kidneys, hopefully reducing symptoms.
- CKD changes lives for many people when a diagnosis occurs. Many symptoms are prevented with health education, eating and maintaining a healthy life style monitoring by health professionals. But CKD is life limiting and present every day.
-

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Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

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NICE National Institute for Health and Care Excellence

Patient expert statement

Dapagliflozin for treating chronic kidney disease [ID3866]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on 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.

Information on completing this expert statement

- 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	**MARK SMITH**
2. Are you (please tick all that apply):	☒ a patient with the condition? ☐ a carer of a patient with the condition? ☒ a patient organisation employee or volunteer?

	☐ other (please specify):
3. Name of your nominating organisation	KIDNEY CARE UK
4. Did your nominating organisation submit a submission?	☒ yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☐ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	I have a Kidney and Pancreas transplant. Despite this I am still classed as having Stage 3 CKD and as such experience, on occasion, symptoms of such. Some days I can be absolutely fine, and others I can be tired, lethargic, moody and irritable, dizzy and I find that although I still don't become ill any more often than I did pre CKD I find that I struggle to recover from illness for a longer period of time. I find that people don't understand living with CKD and on those days see me as being a 'typical man'. They don't understand how draining those days can be. The constant medication makes it a daily condition, as in you have to focus on the condition every day, for medication, exercise, and general well-being

Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	At present as described in the KCUK (Kidney Care UK) statement the main treatment of CKD ultimately is either dialysis or transplantation. Neither of these are choices patients want to have to make, though of course a transplant is a better option that Dialysis but still has issues around medication, steroids, medication whilst dialysis can be debilitating in most cases. So an option which delays either of these would be a preferable option. Anything that delays this potential would be welcome.
10. Is there an unmet need for patients with this condition?	Not that I am aware of.
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	An inhibitor that reduces Cardiovascular complications is very welcome, especially when this might prolong life in many patients. As a transplantee quality of life is important, as if quantity. The longer we can put off the inevitable the better. I think this is the main advantage of this technology.
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	None that I am aware. There is a need to look into potential risk and side effects in patients to minimise negative impact on those patients.
Patient population	
13. Are there any groups of patients who might benefit	I think pre-dialysis or pre transplant patients would benefit more from this than post-transplant but this would only be marginal as it would be a way of limiting cardiovascular decay. It might also benefit post-transplant patients by adding a level of protection to longevity they may not have had otherwise.

more or less from the technology than others? If so, please describe them and explain why.	
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	**None that I am aware of.**
Other issues	
16. Are there any other issues that you would like the committee to consider?	No.
Key messages	
17. In up to 5 bullet points, please summarise the key messages of your statement: • The advantage of a cadio-vascular inhibitor has the potential to increase life span of all CKD patients. • A potential issue around an extra medication in some patients could be an issue.	

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Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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Your privacy

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☐ **Please tick this box** if you would like to receive information about other NICE topics.

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NICE National Institute for Health and Care Excellence

Clinical expert statement & technical engagement response form

Dapagliflozin for treating chronic kidney disease [ID3866]

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on dapagliflozib in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form:

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

Please return this form by **5pm** on **Friday 27 August 2021**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Important information on completing this expert statement

- 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 want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

PART 1 – Treating a patient with chronic kidney disease (CKD) and current treatment options	
About you	
1. Your name	**Andrew Lewington**
2. Name of organisation	**Leeds Teaching Hospitals Trust**
3. Job title or position	**Consultant Renal Physician**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with chronic kidney disease? ☐ a specialist in the clinical evidence base for chronic kidney disease or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
The aim of treatment for CKD	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The treatment is currently licensed to treat type 2 diabetes mellitus as monotherapy or with another hypoglycaemic agent. It is also used to treat type one diabetes mellitus in patients on insulin and in the treatment of patients with heart failure with a decreased ejection fraction in line with NICE TA679 Evidence from a number of trials have indicated that the treatment can delay the progression of chronic kidney disease
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm,	A significant treatment response for a patient with chronic kidney disease would be to slow the progression of the disease towards kidney failure and the need for dialysis. Reduce the progression by 25% over one year would be significant

or a reduction in disease activity by a certain amount.)	
10. In your view, is there an unmet need for patients and healthcare professionals in chronic kidney disease?	There is an urgent and that need for patients and healthcare professionals in Chronic kidney disease. There is a lack of medications that can slow the progression of chronic kidney disease.
What is the expected place of dapagliflozin in current practice?	
11. How is the condition currently treated in the NHS?	The treatment of chronic kidney disease is limited to encouraging a healthy lifestyle, tight blood pressure control, reduction of cardiovascular risk factors e.g. lowering cholesterol
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE clinical guidelines just recently updated
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway of care is currently well defined and there is little difference between the opinions of professionals across the NHS who treat patients with chronic kidney disease. However there is a lack of knowledge amongst non-kidney specialist healthcare professionals about the significance of chronic kidney disease and therefore the importance of management can be overlooked unless these patients are referred to a kidney specialist for further advice.
• What impact would dapagliflozin have on the current pathway of care?	The medication would have a significant impact in reducing the progression of chronic kidney disease and the incidence of kidney failure. It would also reduce the risk of a cardiovascular event.

12. Will dapagliflozin be used (or is it already used) in the same way as current care in NHS clinical practice?	Currently the medication is not used in NHS clinical practice for the treatment of chronic kidney disease per se. The medication is not currently on the trust formulary and would require a specific application along with economic modelling to understand the impact.
• How does healthcare resource use differ between dapagliflozin and current care?	The medication would be added to existing medications that are prescribed to the patient. They would need to be monitoring of the patient in terms of potential side-effects.
• In what clinical setting should dapagliflozin be used? (For example, primary or secondary care, specialist clinics.)	The medication could be used in primary and secondary care but with the input from kidney specialists.
• What investment is needed to introduce dapagliflozin? (For example, for facilities, equipment, or training.)	If the medication was to be used in primary care there would need to be investment in education on the potential side effects and monitoring.
13. Do you expect dapagliflozin to provide clinically meaningful benefits compared with current care?	Yes On the evidence from recent trials
• Do you expect dapagliflozin to increase length of life more than current care?	Yes based on the evidence from the recent trials

• Do you expect dapagliflozin to increase health-related quality of life more than current care?	Yes based on the evidence from recent trials
14. Are there any groups of people for whom dapagliflozin would be more or less effective (or appropriate) than the general population?	Patients with type two diabetes mellitus as my therapy or along with other hypoglycaemic agents Patients with chronic kidney disease with and without diabetes Patients with heart failure with reduced ejection fraction Patients with type one diabetes mellitus on insulin without chronic kidney disease
The use of dapagliflozin	
15. Will dapagliflozin 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.)	There will be more monitoring required in terms of the side-effects of potential volume depletion and hypoglycaemia It will be very simple to prescribe as it can be used alongside current medications with the caveat that the blood glucose levels must be measured The majority of the patients in the study were on an angiotensin-converting enzyme inhibitor or a angiotensin receptor blocker. It does appear that patients will need to be on on one of these medications

16. Will any rules (informal or formal) be used to start or stop treatment with dapagliflozin? Do these include any additional testing?	They will need to be clarity on which patients are eligible to commence the medication and when to stop the medication in terms of the kidney function, eGFR
17. Do you consider that the use of dapagliflozin will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Yes based on the evidence from the trials.
18. Do you consider dapagliflozin 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?	The medication would make a significant impact on the progression of chronic kidney disease and reducing the cardiovascular outcomes associated with having kidney disease.
• Is dapagliflozin a 'step-change' in the management of the condition?	Yes

• Does the use of dapagliflozin address any particular unmet need of the patient population?	Yes they provide patients with chronic kidney disease a real opportunity to take a medication that will slow the progression of the kidney disease and reduce the risk of cardiovascular disease
19. How do any side effects or adverse effects of dapagliflozin affect the management of the condition and the patient's quality of life?	Based on the evidence from the trials I do not think that the medication will significantly affect the patient's quality of life in a negative way in terms of side-effects
Sources of evidence	
20. Do the clinical trials on dapagliflozin reflect current UK clinical practice?	Yes they reflect current UK clinical practice.
• If not, how could the results be extrapolated to the UK setting?	Not applicable
• What, in your view, are the most important outcomes, and were they measured in the trials?	The primary outcome measures were very important and are clinically significant
• If surrogate outcome measures were used, do they adequately predict	Not applicable

long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatment(s)?	Not applicable
23. How do data on real-world experience compare with the trial data?	I think they are comparable
Equality	

24a. Are there any potential equality issues that should be taken into account when considering this treatment?	Chronic a disease is more prevalent in patients from the black and Asian minority ethnic groups. The recent publication on the medication indicated that 52% of the patients were white. I do not know the percentage of patients with chronic kidney disease who are white compared to other ethnicities. This would need to be examined.
24b. Consider whether these issues are different from issues with current care and why.	It will be important to reach out to the underserved communities who are undiagnosed with chronic kidney disease to provide them with the potential treatment
Topic-specific questions	
25. The population in the company submission is aligned with the NICE final scope: adults with CKD who are receiving individually optimised standard care. This includes people irrespective of urine albumin-to-creatinine ratio (uACR) or estimated glomerular filtration rate (eGFR). However, the clinical effectiveness evidence in the economic model comes from the DAPA-CKD trial, which is	Testing for uACR is recommended By the NICE chronic kidney disease clinical guideline. This will depend upon the stage of chronic kidney disease. Patients with more severe chronic kidney disease will be referred to secondary care clinics and will have their urine checked for proteinuria or albuminuria on every attendance. I'm uncertain as to how often the urine is checked in primary care for patients with chronic kidney disease. My personal view is that the medication should only be using those patients who meet the criteria. I would like more guidance on the lowest level of kidney function that the medication can be prescribed in due to the risk of side-effects

restricted by uACR and eGFR level (uACR must be from 22.6 mg/mmol to 565 mg/mmol, eGFR must from 25 ml/min/1.73m^2 to 75 ml/min/1.73m^2). • How often is uACR and eGFR testing done for people with CKD? • Is the dapagliflozin treatment effect observed in DAPA-CKD likely to be generalisable to people with uACR or eGFR levels outside the range recruited in DAPA-CKD? (for example, very high-risk patients with CKD stage 5)	
26. The DECLARE TIMI-58 trial suggests a beneficial effect with dapagliflozin regardless of uACR	I suspect the medication would be effective in patients irrespective of the degree of proteinuria due to its affect on reducing intraglomerular hypertension

level. However, all patients in DECLARE TIMI-58 had type 2 diabetes mellitus (T2DM). Therefore, there is a lack of direct or indirect evidence for dapagliflozin in people without T2DM regardless of uACR level. • Is the dapagliflozin treatment effect observed in DAPA-CKD likely to be generalisable to people without T2DM with lower uACR levels (less than 22.6mg/mmol)?	
27. The clinical evidence for dapagliflozin in patients with CKD from DAPA-CKD excludes patients with type 1 diabetes mellitus (T1DM). • Is the dapagliflozin treatment effect observed	I would imagine that it would be applicable to patients with type one diabetes mellitus but the studies need to be performed

in DAPA-CKD likely to be generalisable to people with T1DM?	
28. In DAPA-CKD, most of the patients had an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blockers (ARB) at baseline. However, in the Clinical Practice Research Datalink dataset used in the company submission, about half the population were having either of these therapies. • Is the dapagliflozin treatment effect observed in DAPA-CKD likely to be generalisable to people not having background therapy with ACE inhibitors or ARBs?	I'm not sure I fully understand the question. Do you mean that any 50% of the patients were on either an angiotensin converting enzyme inhibitor or on an angiotensin receptor blocker. If that was the case then it would appear that the medication does work whether you are on one of these medications or not. If the majority of patients were on either of these other medications then I would be more inclined to interpret it as an additive effect

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
29. Key issue 1: Uncertainty surrounding the target population and the effectiveness of dapagliflozin in patients excluded from DAPA-CKD • Do you have any general comments on this issue?	

30. Key issue 2: Concerns regarding the company's overall modelling approach and OS predictions • Do you have any general comments on this issue?	
31. Are there any important issues that have been missed in ERG report?	

PART 3 -Key messages

32. In up to 5 sentences, please summarise the key messages of your statement:

- The studies on these medications recognise an unmet clinical need in patients with chronic kidney disease
- The results from the studies demonstrate the opportunity to slow the progression of chronic kidney disease
- There are few side-effects from using these medications in patients with chronic kidney disease
- The use of these medications also reduce the risk of cardiovascular disease in patients with chronic kidney disease
- There are other areas of kidney disease where these medications could be useful e.g. following acute kidney injury

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

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