Dapagliflozin for treating chronic kidney disease: A Technology Appraisal

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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

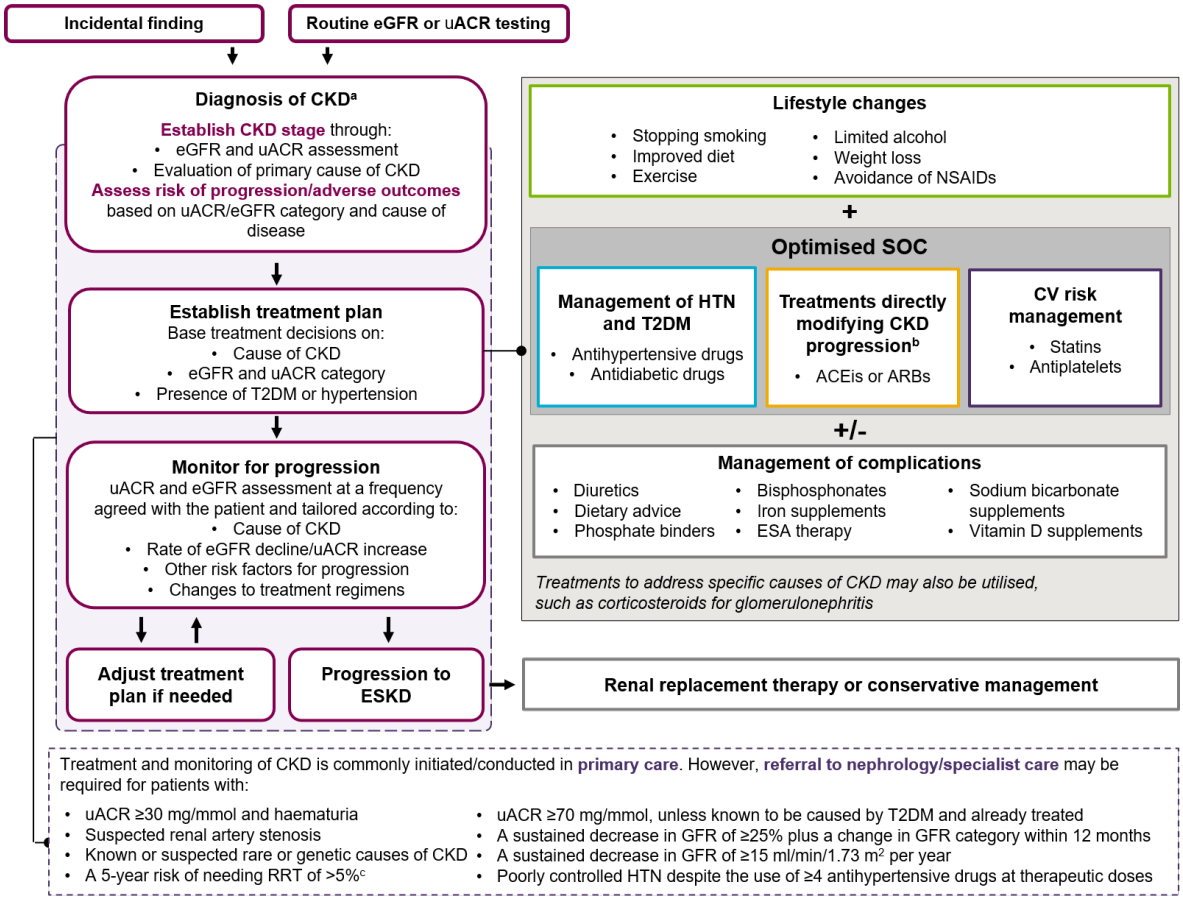
An overview of the treatment pathway is presented in Section B.1.3.3 of the CS.[1] This refers to NICE Clinical Guideline 182 (Chronic kidney disease in adults: assessment and management)[3] and the revised guideline draft for consultation, which is expected to be published in August 2021.[4] The company's 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

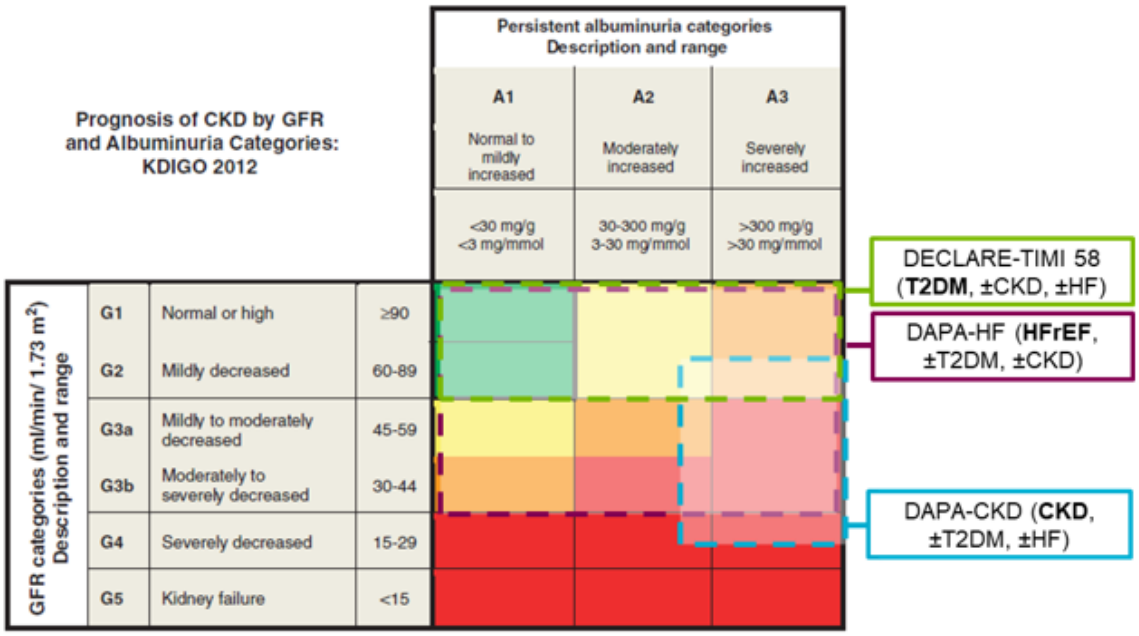
Decision problem: The CS[1] defines the population of interest as adults with CKD who are receiving individually optimised SoC. This is line with the final NICE scope.[17]

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).

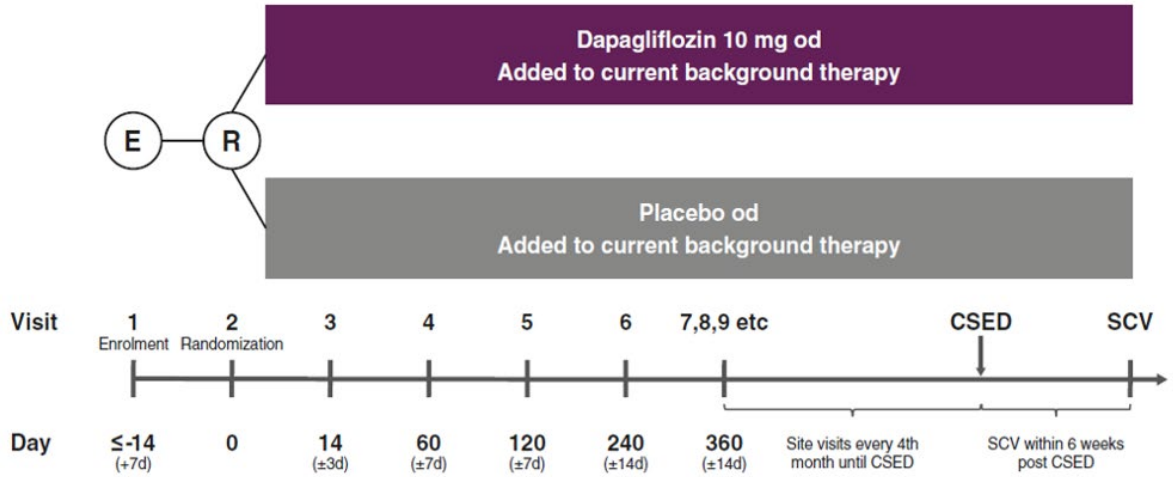
Trial interventions and concomitant treatments

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

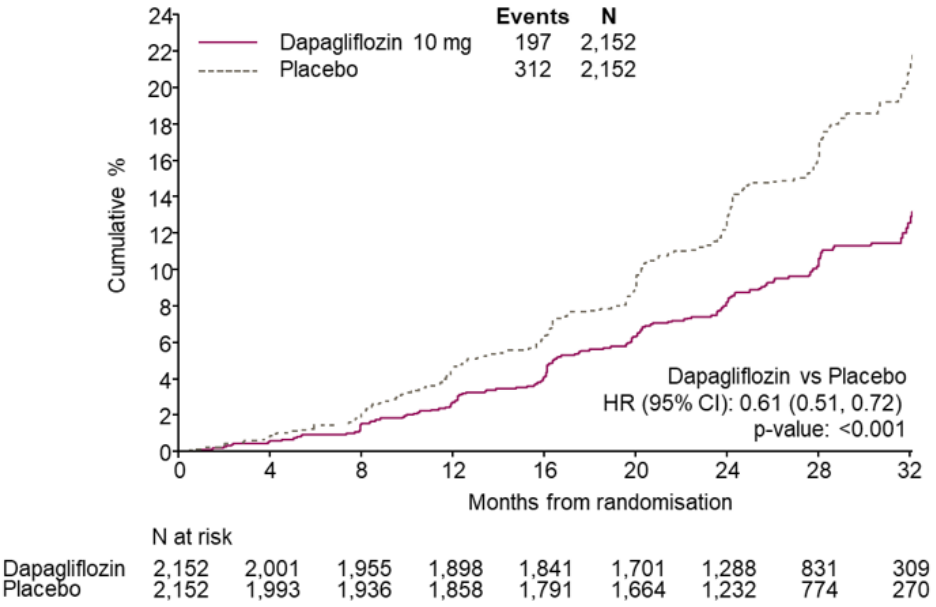
4.2.3 Effectiveness results: DAPA-CKD

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]

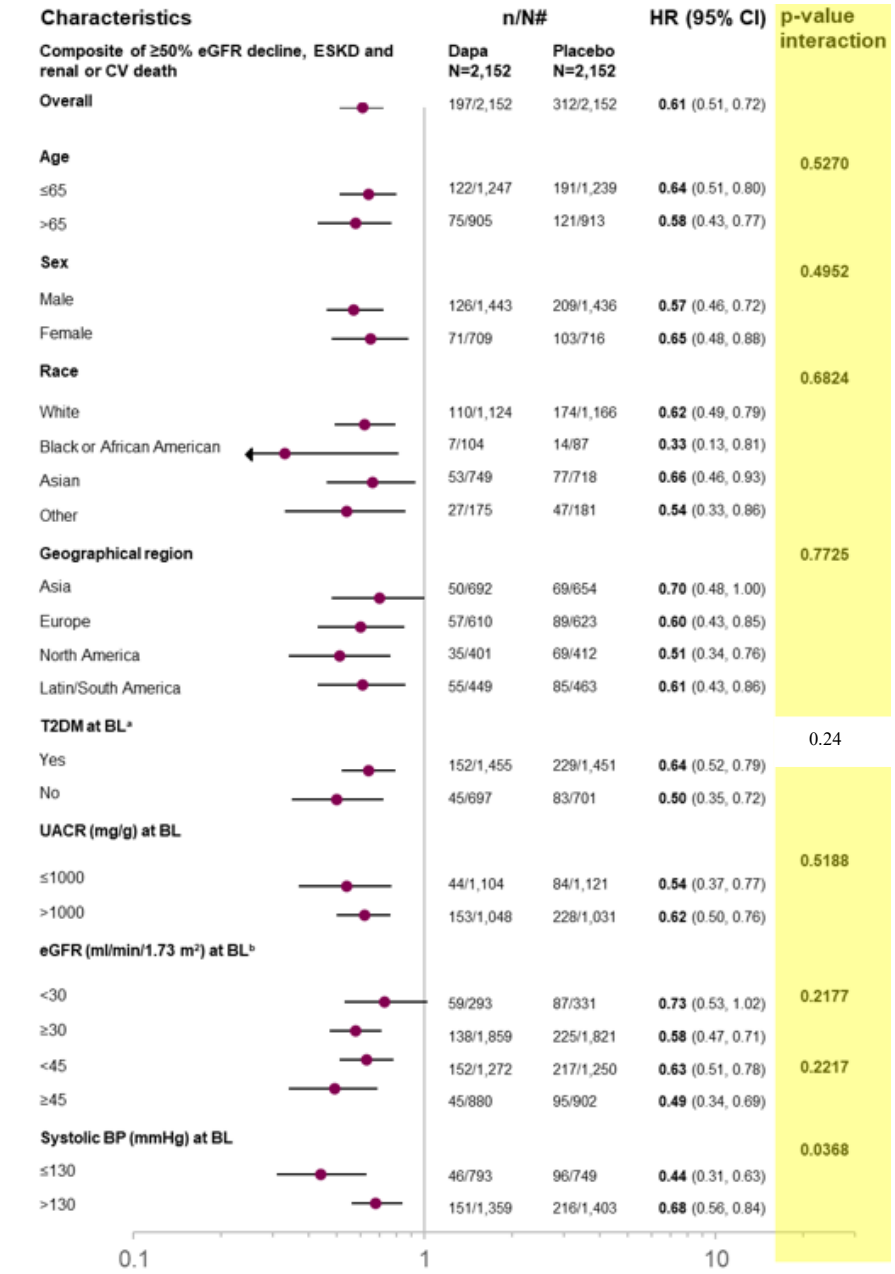
[redacted]

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]

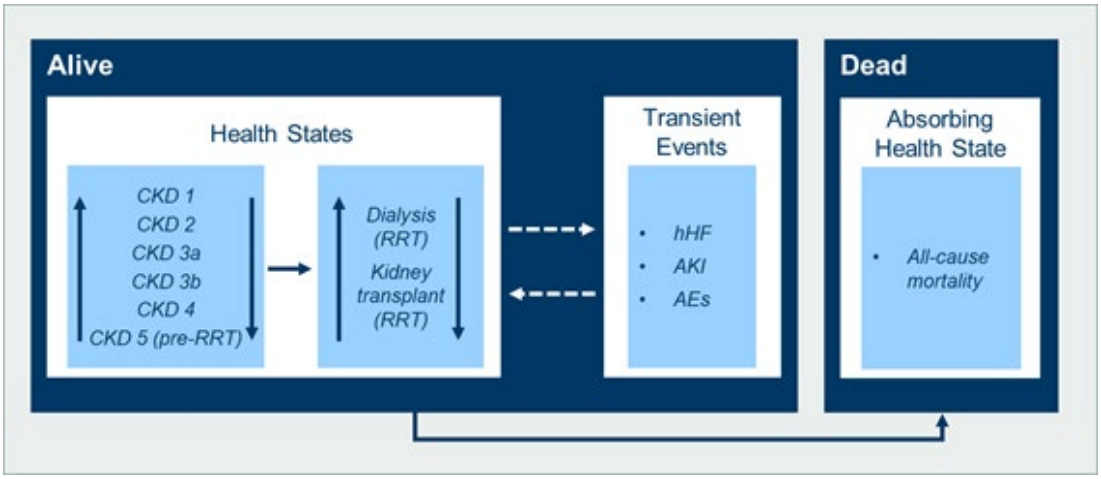
Intervention

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	[redacted]	
CKD 3a	[redacted]	
CKD 3b	[redacted]	
CKD 4	[redacted]	
CKD 5 (pre-RRT)	[redacted]	
Dialysis	0.46	Lee *et al.*[39]
Transplant	0.71	
Disutilities applied to transient events		
hHF	[redacted]	DAPA-CKD[19]
AKI	[redacted]	
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	[redacted]	
UTI	[redacted]	

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

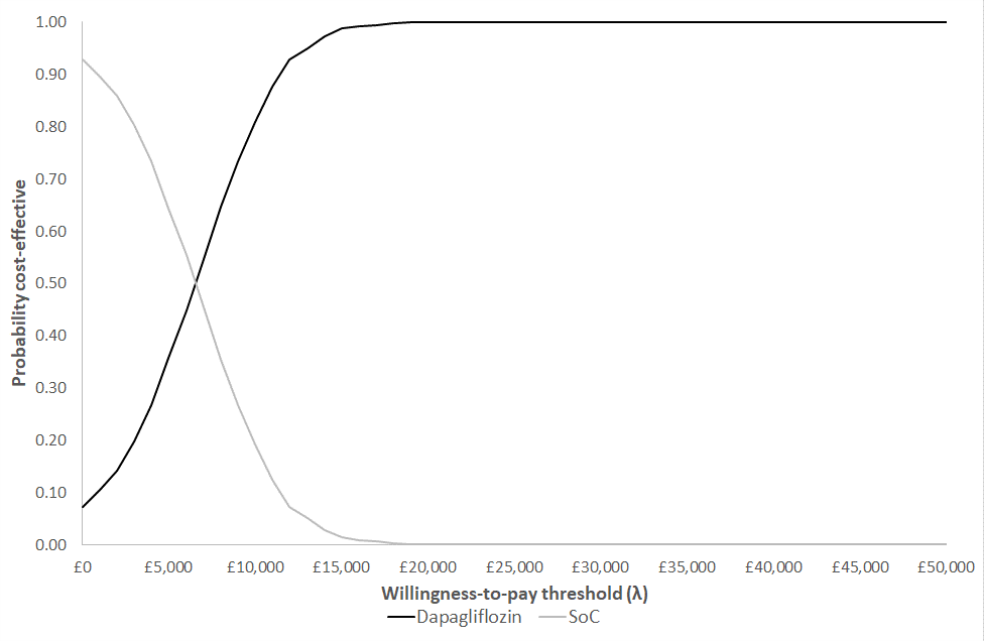
Model estimate	Dapagliflozin	SoC	Incremental
LYGs*	11.67	10.19	1.47
QALYs CKD stages 1-5 (pre-RRT)	6.15	5.39	0.76
QALYs dialysis	0.41	0.40	0.01
QALYs transplant	0.25	0.25	0.00
QALY losses AEs and transient events	-0.01	-0.01	0.00
Total QALYs	6.80	6.03	0.77
Drug costs	£3,212	£126	£3,086
CKD management 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)

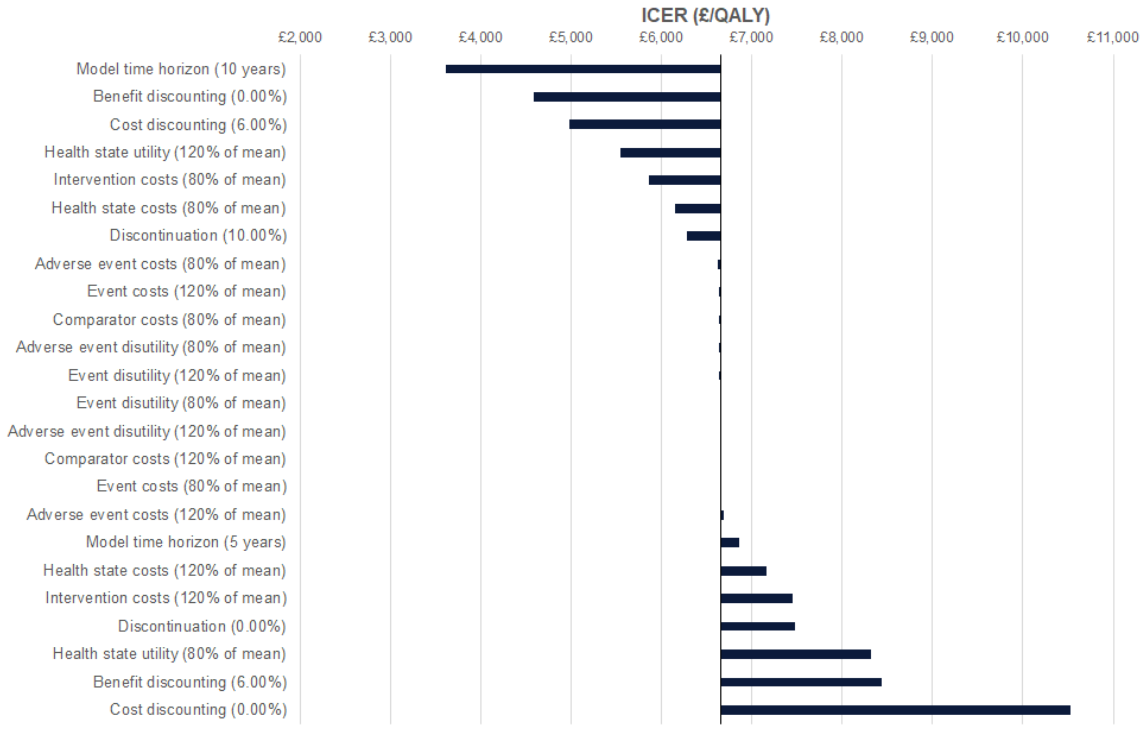


SoC - standard of care

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

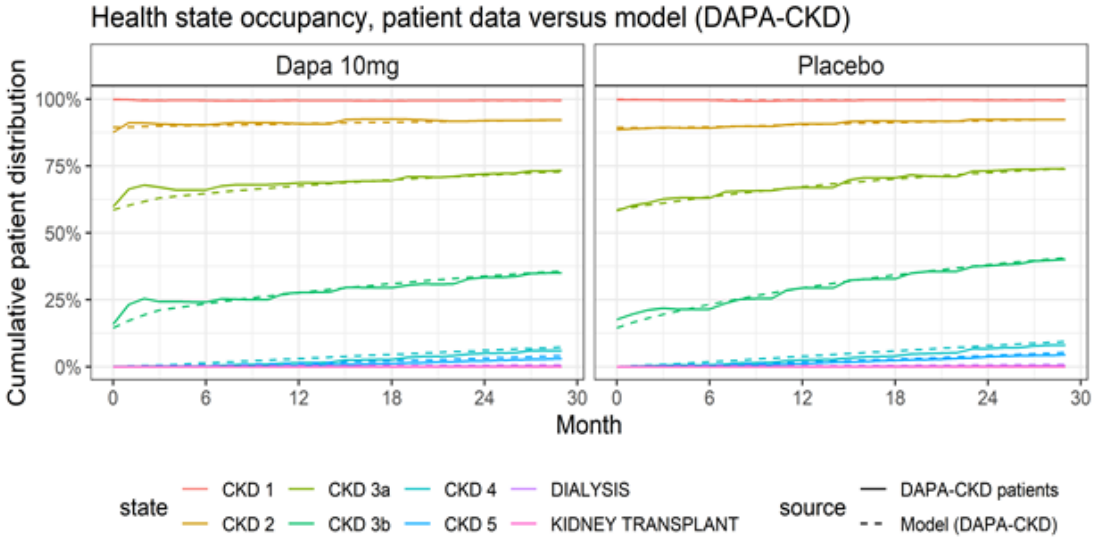
treatment of early CKD takes place), prescribing and some outpatient costs, the CKD-specific health state costs used in the model are likely underestimated. As dapagliflozin is predicted to extend OS, this suggests that the ICER would increase if these missing costs were included. In their clarification 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

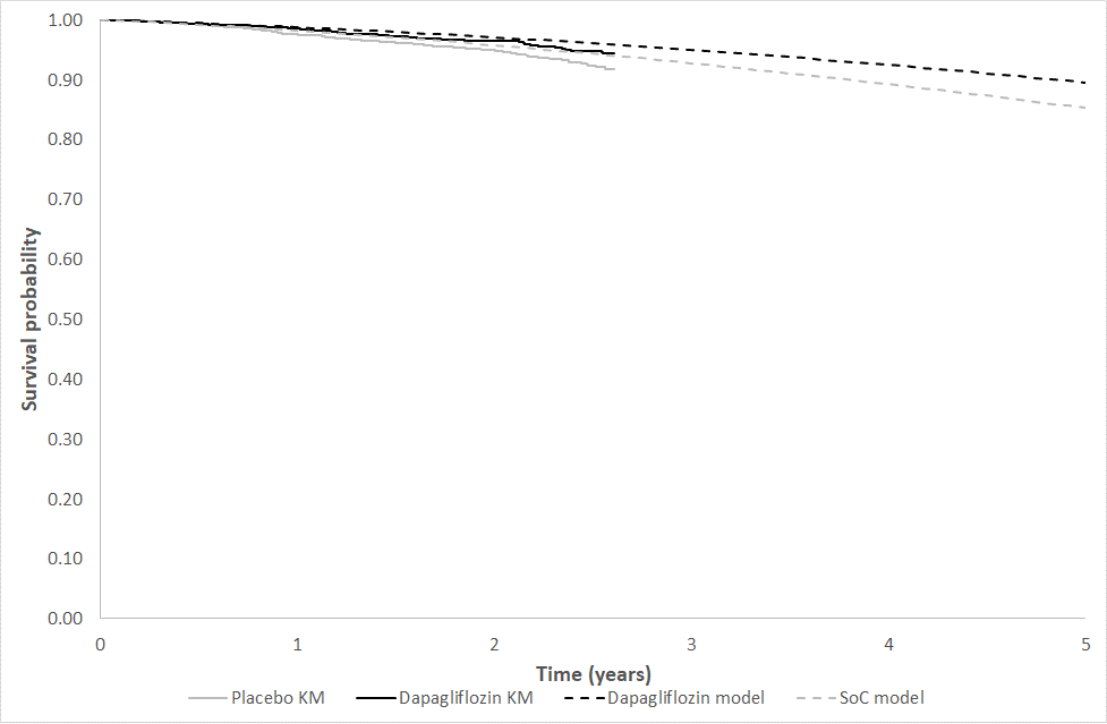
The CS[1] provides limited evidence to demonstrate the extent to which the economic model can predict the CKD stage and OS outcomes observed in DAPA-CKD.[19] The company's clarification response[16] (question B30) presents a plot showing the observed CKD stage over time from DAPA-CKD versus the equivalent 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.

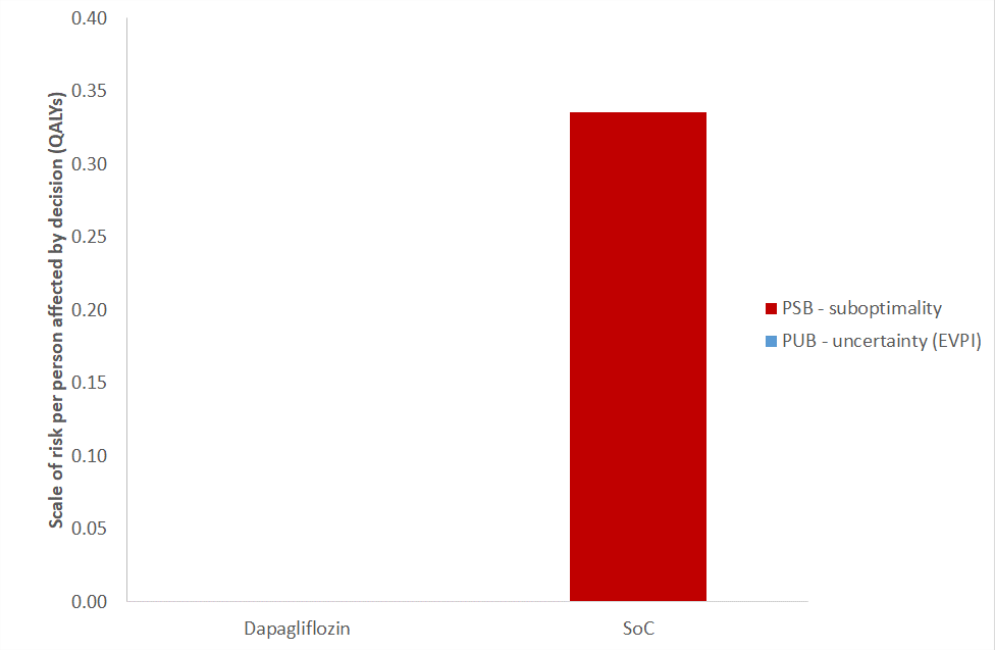
- Irrespective of the assumed WTP threshold, almost all of the payer burden of uncertainty is associated with selecting the sub-optimal treatment, which in this case is expected to be SoC. In other words, the NHS stands to lose more health by adopting a sub-optimal treatment given current information (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.