Finerenone for treating chronic kidney disease in people with type 2 diabetes [ID3773]

A Single Technology Appraisal

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G.J. Melendez-Torres	Critical appraisal of the company submission, writing and editorial input. Guarantor of the report

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Abbreviations

ACE-i	angiotensin converting enzyme inhibitors
ACR	albumin-to-creatinine ratio
ADA	American Diabetes Association
AEs	adverse events
AF	atrial fibrillation
AKI	acute kidney injury
ARB	angiotensin receptor blocker(s)
BMI	body mass index
BNF	British National Formulary
BNP	B-type natriuretic peptide
BT	background therapy
CABG	coronary artery bypass graft
CE	cost-effectiveness
CEAC	cost-effectiveness acceptability curve
CEC	Clinical Event Committee
CG	clinical guideline
CI	confidence interval
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CRD	Centre for Reviews and Dissemination
CS	company submission
cTn	cardiac troponin
CV	cardiovascular
CVD	cardiovascular disease
CYP3A4	cytochrome P450 3A4
DBP	diastolic blood pressure
DKD	diabetic kidney disease
DPP-4	dipeptidyl peptidase-4 (inhibitors)
DSA	deterministic sensitivity analysis
EASD	European Association for the Study of Diabetes
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EOS	end of study
EQ-5D-5L	EuroQol five dimensions five levels (questionnaire)
EQ VAS	EuroQol Visual Analogue Scale
ERG	Evidence Review Group
ESC	European Society of Cardiology

ESRD	end-stage renal disease
FAS	full analysis set
FTR	full text review
GCP	good clinical practice
GFR	glomerular filtration rate
GLP-1	glucagon-like peptide 1
GP	general practitioner
HCC	half-cycle correction
HEOR	health economics and outcomes research
HF	heart failure
HR	hazard ratio
HTA	health technology assessment
ICER	incremental cost-effectiveness ratio
ID	identification
IQR	interquartile range
IS	ischemic stroke
ITT	intention to treat
IV	intravenous
KDIGO	The Kidney Disease: Improving Global Outcomes
KDQOL-36	Kidney Disease Quality of Life questionnaire (36 questions)
LBBB	left bundle branch block
LS	least squares
LY	life year(s)
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines & Healthcare products Regulatory Agency
MI	myocardial infarction
MR	mineralocorticoid receptor
MRA	mineralocorticoid receptor antagonist
MSM	multi-state model
NA	not applicable
NCT	National Clinical Trial
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NR	not reported
NYHA	New York Heart Association
o.d.	once daily
ONS	Office for National Statistics
OR	odds ratio
PAI	platelet aggregation inhibitor
PAOD	peripheral arterial occlusive disease

PAS	patient access scheme
PCI	percutaneous coronary intervention
PD	premature discontinuation
PH	proportional hazards
PICO	population, intervention, comparator, outcome
PPS	per protocol set
PSA	probabilistic sensitivity analysis
PSS	Personal Social Services
PYs / p-years	patient years
QA	quality assessment
QALY	quality adjusted life year
QoL	quality of life
RAS	renin-angiotensin system
RAAS	renin-angiotensin aldosterone system
RCT	randomised controlled trial
RRT	renal replacement therapy
SAF	safety analysis set
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SGLT-2i	sodium-glucose Cotransporter 2 inhibitor(s)
SLR	systematic literature review
ST-T	ST segment or T-wave
T2D	type 2 diabetes
TA	technology appraisal
TEAE	treatment emergent adverse event(s)
UACR	urinary albumin-to-creatinine ratio
UK	United Kingdom
URL	upper reference limit
VBA	Visual Basic

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 the ERG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

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 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main ERG report.

All issues identified represent the ERG's view, not the opinion of NICE.

1.1. Overview of the ERG's key issues

Table 1: Summary of key issues

Summary of issues	Report sections
Key Issue 1: Uncertainty in appropriate population	Section 2.4.1 and Section 3.2.2.1
Key Issue 2: Missing comparison with SGLT-2i	Section 2.4.3
Key Issue 3: Uncertainty in clinical relevance of trial outcomes	Section 2.4.4 and Section 3.2.3.1 and Section 4.2.6.1
Key Issue 4: Model transitions subject to substantial limitations	Section 4.2.2
Key Issue 5: Several influential model inputs lack clinical plausibility affecting overall face validity of model results	Section 4.2.6 and Section 4.2.7
Key Issue 6: Overall uncertainty in the results of the model is not adequately captured by the company's sensitivity analyses	Section 5.1

Abbreviations: SGLT-2i(s), Sodium/glucose cotransporter-2 inhibitor(s)

The key differences between the company's preferred assumptions and the ERG's preferred assumptions are outlined in Table 2.

Table 2: Key differences between the company's preferred assumptions and ERG's preferred assumptions

	Company's preferred assumption	ERG preferred assumption	Report Sections
Population	Label population	Label population, accounting for CV event history	4.2.3, 4.2.8.4
Comparator	BT only	BT only and SGLT-2 is (though the latter of these is not possible to consider in the company's model)	4.2.4
Risk for CV events and CV deaths	Affected by CKD stage and HR for finerenone	Affected by HR for finerenone only	4.2.6.2, 4.2.6.3
Renal deaths	Including explicitly based on data from the FIDELIO-DKD study	Captured as part of background mortality only	4.2.6.3
Duration of treatment	Based on reported rate in FIDELIO-DKD	Re-calibrated rate accounting for competing risks in the model	4.2.6.4
Utilities	Various, see CS Section B.3.4 for specific details	Edit to utility for CKD1/2, amendment to disutilities applied in 'post-acute' period	4.2.7
Costs	Various, see CS Section B.3.5 for specific details	Removal of death costs, correction of BT costs, inclusion of wastage for finerenone	4.2.8

Abbreviations: BT, background therapy; CKD, chronic kidnety disease; CS, company submission; CV. cardiovascular; ERG, Evidence Review Group; HR, hazard ratio; SGLT-2i(s), Sodium/glucose cotransporter-2 inhibitor(s)

1.2. Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Reducing the rate at which kidney disease progresses
- Reducing the risk of experiencing a cardiovascular event (such as a heart attack or stroke)
- Extending overall survival through avoiding cardiovascular- or kidney-related deaths

Overall, the technology is modelled to affect costs by:

- Drug acquisition costs for finerenone

- Avoiding (or delaying the time to) expensive health states related to kidney disease progression (such as dialysis or a kidney transplant)
- Avoiding (or delaying the time to) events associated with high costs, such as hospitalisations due to cardiovascular events

The modelling assumptions that have the greatest effect on the ICER are:

- How the benefits of finerenone are reflected in the company's model, which may include some possible double counting of effects
- How cardiovascular event history may influence the risk of subsequent events (and costs) over a lifetime horizon
- Several individual model inputs which do not align with clinical expectation (for example, quality of life improving as disease progresses)

1.3. The decision problem: summary of the ERG's key issues

The ERG reviewed the approach of the company to addressing the NICE decision problem for this appraisal, and identified the following key issues for consideration by the committee.

Key Issue 1: Uncertainty in appropriate population

Report sections	Section 2.4.1 and Section 3.2.2.1
Description of issue and why the ERG has identified it as important	The population in the final scope is adults with T2D and CKD. The decision problem is narrower than the population specified in the final scope as it focused on adults with CKD ([redacted]) and T2D aligned with the proposed indication (referred to as the "label population"). Also, the analysis population selected from the FIDELIO-DKD trial data referred to as the "label population" is narrower than that of the decision problem. Data provided by the company in the CS were taken from the FIDELIO-DKD trial and included: • **Full analysis set (FAS):** The FAS included all randomised participants (except those excluded for good clinical practice [GCP] violations). The majority of participants were in CKD Stage 3 and CKD Stage 4; however, a small proportion of participants were in CKD Stage 2 ([redacted]%). It should be noted that the trial inclusion criteria for eGFR levels were not completely aligned with the eGFR staging according to the KDIGO 2012 / NG203 classification for CKD Stage 4; i.e. the lowest eGFR per trial inclusion criteria was 25 mL/min/1.73 m^2 meaning that participants with eGFR <25 mL/min/1.73 m^2 were excluded. Despite this, [redacted]% participants had eGFR <25 ml/min/1.73 m^2 at baseline.

Report sections	Section 2.4.1 and Section 3.2.2.1
	• **"Label population":** The "label population" included participants from the FIDELIO-DKD study with eGFR ≥25 to <60 ml/min/1.73 m^2. While the company stated that it sought marketing authorisation and appraisal by NICE in adults with CKD ([redacted]) and T2D it also stated that, given the minimum eGFR inclusion criterion in the FIDELIO-DKD study and limited data, use in patients with CKD Stage 4 eGFR <25 ml/min/1.73m^2 was likely to be advised with caution. Assuming the SmPC does allow the use of finerenone with caution in patients with eGFR <25 ml/min/1.73 m^2, the analysis population selected from the FIDELIO-DKD trial data referred to as the "label population" is narrower than that of the decision problem in its exclusion of the available data (albeit limited) in participants with eGFR <25 ml/min/1.73 m^2. Thus, the ERG considered that generalisability of data from the FIDELIO-DKD "label population" (for CKD Stage 4) to CKD classification to be a potential issue.
What alternative approach has the ERG suggested?	The appropriate population for decision making needs to be defined such that any guidance produced by NICE could be followed in clinical practice. Ideally, the evidence presented should be aligned with both the licensed indication and CKD staging used in clinical practice whereas currently data presented for the "label population" exclude participants with CKD Stage 4 with eGFR <25 ml/min/1.73 m^2 at baseline. However, the ERG noted that patients with an eGFR <25 ml/min/1.73 m^2 were not intentionally included within the FIDELIO-DKD study, and so all patients with CKD Stage 4 in the FIDELIO-DKD study will not represent all CKD Stage 4 patients in practice. While the company stated that it sought marketing authorisation and appraisal by NICE in adults with CKD ([redacted]) and T2D, it also stated that use in patients with CKD Stage 4 eGFR <25 ml/min/1.73m^2 was likely to be advised with caution given the minimum eGFR inclusion criterion in the FIDELIO-DKD study and limited data. Given that, in the ERG's understanding, the SmPC will allow for use in patients with CKD Stage 4 eGFR <25 ml/min/1.73m^2 albeit under cautionary advisement, the ERG considered that the company could have conducted an analysis that did not exclude participants with eGFR <25 ml/min/1.73 m^2 at baseline to align with the CKD classification.
What is the expected effect on the cost-effectiveness estimates?	The impact on cost-effectiveness estimates is uncertain.
What additional evidence or analyses might help to resolve this key issue?	If the company is seeking reimbursement to align with the EMA indication "… treatment of chronic kidney disease [redacted] which is anticipated to allow for use in patients with eGFR <25 ml/min/1.73 m^2 with caution, it may be helpful to update the model to include the additional [redacted]% of participants with eGFR <25 within the label population, notwithstanding the limitations of this analysis highlighted above.

Abbreviations: CKD, chronic kidney disease; CS, company submission; eGFR, estimated glomerular filtration rate; ERG, Evidence Review Group; NICE, National Institute for Health and Care Excellence, UK, United Kingdom

Key Issue 2: Missing comparison with SGLT-2i

Report sections	Section 2.4.3
Description of issue and why the ERG has identified it as important	The ERG does not agree with the company's assertion that SGLT2 inhibitors (SGLT-2i) are not a relevant comparator in this appraisal as indicated in the final scope.[1] The absence of such an analysis with a comparator listed in the scope and one that is available as standard clinical practice therefore constitutes a key issue. Relatedly, it is unclear how the company views finerenone as relating to SGLT-2i: as an add-on to background therapy (BT) or as an alternative.
What alternative approach has the ERG suggested?	A comparison with an SGLT-2i could occur in two ways: • finerenone + established clinical management including SGLT-2i vs. finerenone + established clinical management excluding SGLT-2i, using FIDELIO-DKD trial data (i.e. finerenone as add-on and SGLT-2i as BT) • finerenone + established clinical management vs. SGLT-2i + established clinical management, using an indirect comparison with FIDELIO-DKD trial (i.e. finerenone and SGLT-2i as alternatives)
What is the expected effect on the cost-effectiveness estimates?	The impact on cost-effectiveness estimates is uncertain.
What additional evidence or analyses might help to resolve this key issue?	The ERG acknowledged that comparability between SGLT-2i trials might be limited due to differences in study populations, and the definition of endpoints, but this would not preclude a formal feasibility assessment and an indirect comparison with acknowledgment of such limitations.

Abbreviations: BT, background therapy; ERG, Evidence Review Group; SGLT-2i(s), Sodium/glucose cotransporter-2 inhibitor(s); vs, versus

1.4. The clinical effectiveness evidence: summary of the ERG's key issues

The ERG reviewed the clinical effectiveness and safety evidence presented in the CS, and identified the following key issues for consideration by the committee.

Key Issue 3: Uncertainty in clinical relevance of trial outcomes

Report sections	Section 2.4.4 and Section 3.2.3.1 and Section 4.2.6.1
Description of issue and why the ERG has identified it as important	The trial showed that in the label population there was a statistically significant improvement on the composite outcome for finerenone vs. placebo. However, this was only reproduced for one of the disaggregated outcomes, sustained decrease ≥40% in eGFR from baseline. Given that such a change in eGFR could occur from any current level of eGFR up to 60 and that there was no statistically significant improvement in progression to kidney failure or ESRD, the clinical relevance of any improvements remain unclear.
What alternative approach has the ERG suggested?	No alternative approach is proposed by the ERG other than to seek clinical expert opinion to determine the clinical relevance.

Report sections	Section 2.4.4 and Section 3.2.3.1 and Section 4.2.6.1
What is the expected effect on the cost-effectiveness estimates?	The impact on cost-effectiveness estimates is uncertain.
What additional evidence or analyses might help to resolve this key issue?	The ERG would recommend further consideration of clinical expert opinion.

Abbreviations: eGFR, estimated glomerular filtration rate; ERG, Evidence Review Group; ESRD, end stage renal disease; vs, versus

1.5. The cost effectiveness evidence: summary of the ERG's key issues

The ERG reviewed the economic model and cost-effectiveness evidence presented in the CS and identified the following key issues for consideration by the committee.

Key Issue 4: Model transitions subject to substantial limitations

Report sections	Section 4.2.2
Description of issue and why the ERG has identified it as important	The model has a number of limitations with respect to how it reflects the patient journey over the model's lifetime horizon. These include the fact that nearly all transitions are time-invariant, and that the CV event risks are not based on risk equations (instead, these are simply linked to CKD stage). Because of these limitations of the model, the ERG was unable to produce its preferred base-case analysis accounting for several important limitations it expects would have a potentially important impact on the ICER.
What alternative approach has the ERG suggested?	The ERG has suggested that an alternative modelling approach incorporating time-varying risks (such as a multi-state model) and/or risk equations (such as a study identified by the company within its SLR by Schlackow *et al.,* (2017)[2] could have been undertaken. The ERG also highlighted the economic model in the NICE guideline: Type 2 diabetes in adults: management - SGLT2 inhibitors for chronic kidney disease (update). Owing to the limited timeframe over which the ERG was able to conduct its critique of the CS, the economic analysis conducted for the NICE guideline was not investigated in depth, but the ERG expects elements of the NICE guideline model may have provided a more suitable means of quantifying the overall progression of CKD (including, for example, risk equations for CV events).
What is the expected effect on the cost-effectiveness estimates?	The effect of addressing some of these limitations on the ICER is unclear, and theoretically could cause the ICER to either increase or decrease.
What additional evidence or analyses might help to resolve this key issue?	To address this key issue, the company would need to make substantial revisions to its submitted model in order to capture some of the elements that are either missing or overly simplified in the current model.

Abbreviations: CKD, chronic kidney disease; CV, cardiovascular; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; SLR, systematic literature review.

Key Issue 5: Several influential model inputs lack clinical plausibility affecting overall face validity of model results

Report sections	Section 4.2.6 and Section 4.2.7
Description of issue and why the ERG has identified it as important	Several different components of the company's model lack face validity from a clinical perspective, which put into question the plausibility of the model results. These include a utility value for CKD stage 3 that is higher than for CKD stage 1 / 2, CV risk for CKD stage 3 that is lower than for CKD stage 1 / 2, and transition probabilities that seem to bias against finerenone with no clear rationale.
What alternative approach has the ERG suggested?	The ERG has proposed several scenarios to simply, but arbitrarily, address some of the face validity issues inherent within the company's model.
What is the expected effect on the cost-effectiveness estimates?	The impact on the company's ICER varies, but generally caused the ICER to increase. Were some analyses re-run (such as the utility analysis, combining CKD1/2 with CKD3, for example), the impact on the ICER could vary in either direction.
What additional evidence or analyses might help to resolve this key issue?	Further clinical input would be useful to further understand areas where the model appears to lack face validity, and potentially inform suggestions to perform additional (alternative) analyses to populate the model. Examples of this include combining health states to estimate more robust utility values and/or risks of CV events with logical bounds of uncertainty.

Abbreviations: CKD, chronic kidney disease; CV, cardiovascular; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; SLR, systematic literature review.

Key Issue 6: Overall uncertainty in the results of the model is not adequately captured by the company's sensitivity analyses

Report sections	Section 5.1
Description of issue and why the ERG has identified it as important	The company's exploration of uncertainty in the model is technically flawed in several ways, including unrealistic bounds of uncertainty in individual parameters factored into deterministic and probabilistic analyses, as well as a limited set of scenario analyses which have direct relevant to the decision problem.
What alternative approach has the ERG suggested?	The ERG has explored and presenting a large range of scenario analyses in an attempt to further investigate areas of uncertainty in the estimates of cost effectiveness.
What is the expected effect on the cost-effectiveness estimates?	The ERG's exploration of uncertainty demonstrated a much larger range of ICERs, most of which caused the ICER to increase slightly. However, a handful of scenarios (and particularly scenarios considered in combination) could cause the ICER to increase by a large amount.
What additional evidence or analyses might help to resolve this key issue?	Ideally, the company would re-program its sensitivity analyses in accordance with standard guidelines, parameterise uncertainty most appropriate based on plausible bounds, and present a more representative range of scenarios which adequately investigate key model settings and assumptions.

Abbreviations: CKD, chronic kidney disease; CV, cardiovascular; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; SLR, systematic literature review.

1.6. Other key issues: summary of the ERG's views

No other key issues were identified.

1.7. Summary of ERG's preferred assumptions and resulting ICER

A summary of ERG's preferred assumptions and resulting ICER is provided in Table 3.

Table 3: Summary of ERG's preferred assumptions and ICER

Scenario #*	Preferred assumption	Incremental cost	Incremental QALYs	ICER (change from ERG-corrected company base case)
NA	**Company's original base-case**	[redacted]	**0.10**	**£17,552**
NA	**ERG-corrected company's base-case**	[redacted]	**0.11**	**£17,882 (+£330)**
#1	Set risk of CV events to be independent of CKD stage	[redacted]	0.05	£18,309 (+£427)
#4	Amend application of renal deaths	[redacted]	0.11	£17,929 (+£47)
#7	Set risk of CV death to be independent of CKD stage	[redacted]	0.10	£17,001 (−£881)
#8	Assume 45.9% of patients enter post-CV event sub-model	[redacted]	0.09	£22,490 (+4,608)
#9	Remove all death costs	[redacted]	0.11	£17,931 (+£49)
#10	Edit BT cost to ERG's calculations	[redacted]	0.11	£17,777 (+£105)
#11	Include one additional pack of finerenone to reflect wastage	[redacted]	0.11	[redacted]
#14	Assume utility for CKD1/2 is 0.80	[redacted]	0.11	£18,167 (+285)
#15	Assume post-acute disutility is half of acute disutility	[redacted]	0.11	£18,236 (+£354)
NA	**ERG base case**	[redacted]	**0.08**	**£23,706 (+£5,824)**

Abbreviations: BT, background therapy; CKD, chronic kidney disease; CV, cardiovascular; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

Note: *Scenario # refers to the numbering programmed into the company's model, reported here for completeness. ICERs are expressed as cost per QALY gained. Some changes to incremental QALY gain affect decimal places not reported in this table.

Modelling errors identified and corrected by the ERG are described in Section 6.1. For further details of the exploratory and sensitivity analyses done by the ERG, see Section 6.2 and Section 6.3, respectively.

2. INTRODUCTION AND BACKGROUND

2.1. Introduction

In this report, the Evidence Review Group (ERG) provides a review of the evidence submitted by Bayer in support of finerenone for treating chronic kidney disease (CKD) in people with type 2 diabetes (T2D).

2.2. Critique of the company's description of the underlying health problem

The company's description of the underlying health problem, CKD in people with T2D, is summarised in Section B.1.3 of the CS.

CKD is defined as abnormalities of kidney structure or function; i.e. persistently elevated urine albumin excretion (≥30 mg/g [3 mg/mmol] creatinine), persistently reduced estimated glomerular filtration rate [eGFR] (eGFR <60 ml/min per 1.73 m^2), or both), for greater than three months, in accordance with current KDIGO guidelines.[3] With estimated prevalence of 9.1%, and the cause of 1.2 million deaths worldwide in 2017, CKD represents a significant burden on health care systems globally. As well as being a major direct cause of morbidity and mortality (12th leading cause of death globally), the main risk associated with CKD is cardiovascular (CV) morbidity and mortality. There are multiple possible causes and risk factors for chronic kidney disease (CKD) and its progression, including hypertension, diabetes mellitus, cardiovascular disease (CVD), glomerular disease, and current or previous history of acute kidney injury (AKI). Also, there is an age-related decline in renal function. The burden of CKD is therefore likely to rise as a consequence of population growth, ageing populations and increasing prevalence of Type II diabetes mellitus (T2D).

The CS referenced the CKD classification system based on cause, estimated glomerular filtration rate (eGFR) (six categories), and proteinuria (three categories) developed by Kidney Disease: Improving Global Outcomes (KDIGO).[3] This classification is used within the UK and referred to within the current NICE Clinical Guideline for CKD assessment and management (NG203).[4]

Table 4. Prognosis of CKD by GFR and albuminuria category developed by KDIGO 2012

				Persistent albuminuria categories. Description and range		
				A1	**A2**	**A3**
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	<30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
GFR categories (ml/min/1.73 m²) Description and range	G1	Normal or high	≥90			
	G2	Mildly decreased	60–89			
	G3a	Mildly to moderate decreased	45–59			
	G3b	Moderately to severely decreased	30–44			
	G4	Severely decreased	15–29			
	G5	Kidney failure	<15			

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; NICE, National Institute for Health and Care Excellence

Low risk if no other markers of kidney disease, no CKD

Moderately increased risk

High risk

Very high risk

Source: NICE Guideline NG203[4]; KDIGO, 2012[3]

Diabetes is a growing issue globally, with an estimated 4.8 million people in the UK with the disease, 90% of which have type 2 diabetes.[5] This emphasises the importance of effectively managing these patients' diabetes and associated conditions such as CKD. Diabetes is the leading cause of end stage renal disease (ESRD) with one in three type 2 diabetes patients developing chronic kidney disease (CKD) in their lifetime. In addition, 11% of deaths in those with type 2 diabetes can be attributed to CKD.[6] Patients suffering from CKD caused by type 2 diabetes also have increased rates of cardiovascular morbidity and mortality although the mechanisms behind this association are poorly understood.[7] Of those with diabetes, those from lower socioeconomic backgrounds are more likely to develop CKD and are more likely to die earlier. In addition, those from Black and ethnic minority backgrounds are less likely to receive a kidney transplant. Women are more likely to be diagnosed with CKD, although men are more likely to receive dialysis.[8]

CKD in diabetes is caused when blood glucose levels are poorly managed in combination with the high blood pressure associated with the disease, damaging the small blood vessels within the kidneys. When these conditions are sustained over a long period of time the healing process becomes dysregulated leading to fibrosis of the blood vessels, further contributing to CKD development.

While in its early stages CKD often goes unnoticed by patients, the impact on quality of life increases as the disease progresses. The most substantial decrement to patients' quality of life comes when they reach ESRD, at which point most people will require dialysis in order to compensate for their failing kidneys. It is notable, however, that very few diabetic CKD patients reach ESRD and therefore most do not need renal replacement therapy. Dialysis is both highly burdensome for patients and extremely expensive for the NHS and though some patients may receive a kidney transplant, this can lead to long-term complications and is also expensive. As a result of both the quality of life and budget impact of ESRD, early identification and treatment to prevent patients reaching the later stages of CKD is key to management of the disease.

2.3. Critique of the company's overview of current service provision

Current management of CKD in T2D is reliant on early detection in order to begin treatment and prevent further deterioration, thus avoiding end stage renal disease (ESRD) and reducing the risk of CV events. In its early stages, kidney disease has few symptoms; it is therefore important that diabetic patients at risk of CKD are monitored regularly. Monitoring takes the form of blood tests for urea and electrolyte levels, including creatinine which is a good indicator of kidney

function. In addition, HbA1C will be measured to establish how well the patient has managed their blood sugar in the past three months. Urine will also be assessed for proteinuria in order to monitor kidney damage caused by CKD. If these tests indicate that a patient has developed diabetic nephropathy, they will be referred to a nephrologist for further tests.

The CS proposed treatment pathway was broadly based on guidelines issued by NICE. However, the ERG considered that although the company had reflected the recent updates to guidance in respect of SGLT-2i, their potential use of these in clinical practice was understated, especially given recent clinical practice guidance from the UK Kidney Association.[9]

Key interventions in early-stage CKD management include advice and lifestyle changes to diet, exercise, alcohol intake and cessation of smoking typically alongside pharmacological strategies to reduce the rate of progression of CKD by optimisation of blood pressure control, lipid levels (using statins), and glycaemic control (using anti-diabetics).

Angiotensin-converting enzyme inhibitors (ACE-is) and angiotensin receptor blockers (ARBs), are typically used to control blood pressure and constitute the current standard of care according to many CKD / T2D guidelines (e.g. KDIGO,[10] the American Diabetes Association (ADA), [11] NICE[4,12] and joint guidelines from the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD)).[13] ACE-is and ARBs are recommended to manage blood pressure in order to prevent progression of CKD, as well as managing proteinuria.

In the CS the company highlighted emerging evidence for the effectiveness of sodium-glucose cotransporter-2 inhibitors (SGLT-2i) e.g. canagliflozin and dapagliflozin and referenced international guidelines[10,11,13] which recommend the use of SGLT-2i in addition to RAS blockers for patients with T2D with albuminuria >300 mg/g (>30 mg/mmol) if their eGFR is >30 mL/min/1.73 m^2. The company noted the absence of a recommendation for the use of SGLT-2i in people with CKD and T2D in NICE clinical guideline CG182[12] and while it noted that SGLT-2i were “considered” in the recent guideline update (NG203)[4] it made no reference to the recommendation for SGLT-2i use included within that. The company correctly highlighted that NICE was reviewing the evidence on SGLT-2i in people with CKD and T2D (NG10246).[14]

While the ERG acknowledged the various guideline updates were in process during the development of the CS, it noted that the guideline update (NG203)[4] had included a recommendation in respect of SGLT-2i use in adults with CKD and T2D, to offer an SGLT-2i in

addition to an ARB or an ACE-i (titrated to the highest dose that they can tolerate), if: albumin-to-creatinine ratio (ACR) was over 30 mg/mmol and criteria per the marketing authorisation (including relevant eGFR thresholds) were met. Although the final guideline was published in August 2021, this information was available in the draft guideline that was in consultation in January 2021 so could have been anticipated by the company. In addition, the ERG noted that in the draft guideline currently in consultation (NG10246)[15] the existing recommendation in respect of SGLT-2i use had not substantively changed and an additional recommendation had been added to consider the use of SGLT-2i in addition to an ARB or an ACE-i (titrated to the highest dose that patients can tolerate), if: albumin-to-creatinine ratio (ACR) was between 3 and 30 mg/mmol; and criteria per the marketing authorisation (including relevant eGFR thresholds) were met (Table 5).

Table 5. NICE Clinical Guideline Recommendations: NG203 → NG10246

NG203		**NG10246 Draft consultation Recommendation**	
Recommendation		**Recommendation**	
1.6.7	For adults with CKD and type 2 diabetes, offer an SGLT2 inhibitor, in addition to an ARB or an ACE inhibitor ~~at an optimised dose~~ if: • ACR is more than 30 mg/mmol, and • they meet the criteria in the marketing authorisation (including relevant eGFR thresholds). Monitor for volume depletion and eGFR decline. In ~~August~~ 2021, not all SGLT-2is were licensed for this indication	1.6.1	For adults with type 2 diabetes and CKD, offer an SGLT-2i, in addition to an ARB or an ACE inhibitor ***(titrated to the highest dose that they can tolerate)***, if: • ACR is over 30 mg/mmol and • they meet the criteria in the marketing authorisation (including relevant eGFR thresholds). Monitor for volume depletion and eGFR decline. In ***September*** 2021, not all SGLT-2is were licensed for this
		1.6.2	***For adults with type 2 diabetes and CKD, consider an SGLT-2i, in addition to an ARB or an ACE inhibitor (titrated to the highest dose that they can tolerate), if:*** • ***ACR is between 3 and 30 mg/mmol and*** • ***they meet the criteria in the marketing authorisation (including relevant eGFR thresholds).*** ***Monitor for volume depletion and eGFR decline.*** ***In September 2021, not all SGLT-2is were licensed for this***

Abbreviations: ACE, angiotensin converting enzyme; ACR, albumin to creatinine ratio; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; SGLT2,

Source: NICE NG203 (2021)[4]; NG10246 Draft Consultation (2021)[15]

As discussed in Section B.1.3 (Document B, pp.28-29), the three factors contributing to CKD in diabetic patients are metabolic, haemodynamic and inflammatory/fibrotic. The current standard of care described above addresses metabolic and haemodynamic factors but fails to target the inflammatory factors. The company envisage that finerenone will be used in conjunction with existing treatments to target the inflammatory/fibrotic processes in those with Stage 3/4 CKD with albuminuria and type two diabetes.

In the event that patients do progress beyond Stage 4 of CKD, they may require renal replacement therapy in the form of dialysis. However, clinical advice sourced by the ERG suggested that the patients in question rarely progress to needing dialysis. For the small proportion of patients that do require dialysis, kidney transplant may also be considered if appropriate. Both dialysis and transplant have substantial implications on a patient's quality of life and can be extremely costly to the NHS. The company's model captures long-term CKD progression including the need for renal replacement therapy, as discussed in Section 4.

2.4. Critique of company's definition of decision problem

A summary of the company's critique of the decision problem is provided in Table 6 and the subsections that follow.

Table 6: Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
Population	Adults with type 2 diabetes and CKD	[redacted]	The proposed indication submitted to EMA is: [redacted]	The population addressed in the decision problem is narrower than the population defined in the NICE scope but aligned with the planned marketing authorisation, see Section 2.4.1.
Intervention	Finerenone	Finerenone	N/A	In line with NICE scope
Comparator(s)	• Established clinical management without finerenone, alone or in combination with ACE-i, ARB or direct renin inhibitors • SGLT-2is	The comparator to finerenone is standard of care established in clinical practice which is ACE-i/ARB. Finerenone is an add-on therapy to ACE-i/ARB.	Bayer do not consider that SGLT-2i should be listed as comparators. When considering the most clinically relevant comparator for inclusion within an appraisal of the clinical and cost effectiveness of finerenone, Bayer refers to the NICE methods guide.[16] Section 6.2.2 of the 'Guide to the methods of technology appraisal 2013'[16] states that the committee must consider the following five factors, when selecting the most appropriate comparator(s): • Established NHS practice in England • The natural history of the condition without suitable treatment • Existing NICE guidance • Cost-effectiveness • The licensing status of the comparator Additionally, Section 6.2.3. states that the above five factors are not considered equally; rather, the committee will normally be guided by established practice in the NHS.	The comparators addressed in the decision problem were not aligned with the NICE scope, and indeed no evidence or economic case was presented by the company to compare finerenone with SGLT-2i, see Section 2.4.2

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
			When considering SGLT-2i as a comparator to finerenone, the five factors of Section 6.2.2. have not been met. The NICE guideline for the assessment and management of CKD that was "live" during the development of this submission (CG182) makes no reference to SGLT-2i as part of the treatment pathway. The place of SGLT-2i in CG update 2021 is considered but this CG states that "*NICE are reviewing the evidence on SGLT-2is in people with CKD and type 2 diabetes*" and may update recommendations as a result of this (consultation scheduled September 2021 with publication November 2021). Most importantly, sales data estimate the market share (by volume) of SGLT-2i at less than [redacted]% as compared against oral and parenteral hypoglycaemics. The guiding principle for comparator selection of Section 6.2.3, has not been met. SGLT-2i do not represent part of established practice in the NHS. As such, comparison should not be made either against the class or any particular SGLT-2i; and, importantly, consultee feedback on the draft scope also confirmed that SGLT-2is should not be considered a comparator. The mode of action of the two classes of drugs are different; finerenone is a drug designed to work at the molecular level on the kidney to address inflammation and fibrosis.	
Outcomes	The outcome measures to be considered include: • cardiovascular outcomes	The outcomes evaluated include: • CKD progression	N/A	In line with NICE scope. Refer to Section 2.4.4

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
	• disease progression • mortality • adverse effects of treatment • health-related quality of life	• CV events – non-fatal MI, non-fatal stroke and hospitalisation for heart failure • Mortality • Subsequent CV events • Sustained decrease of eGFR ≥40% from the baseline • New onset of an atrial fibrillation/atrial flutter • Health-related quality of life • Adverse events – hyperkalaemia		
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	Costs were considered from an NHS and Personal Social Services perspective over a lifelong time horizon. The cost effectiveness of finerenone is expressed in terms of incremental cost per quality-adjusted life year.	N/A	Mostly in line with NICE scope, with concerns regarding model structure including use of time invariant risks for CKD progression and CV event occurrence, mortality, and utility values. See Section 4.2.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
Subgroups	None specified	N/A	N/A	N/A
Other considerations including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	Some equity and equality issues with the scoped population discussed.	N/A	The company noted some considerations in terms of equity and equality which are noted in Section 2.4.5

Abbreviations: ACE-i, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; EMA, European Medicines Agency; ERG, Evidence Review Group; MI, myocardial infarction; N/A, not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; SGLT-2i, sodium-glucose co-transporter-2 inhibitors

2.4.1. Population

The population in the final scope is adults with T2D and CKD.

The decision problem is narrower than the population specified in the final scope as it focused on [redacted] aligned with the proposed indication (referred to as the "label population"). Also, the analysis population selected from the FIDELIO-DKD trial data referred to as the "label population" is narrower than that of the decision problem.

Evidence in the CS was from the FIDELIO-DKD trial. The FIDELIO-DKD trial was conducted cross [redacted]study centres across 48 countries. In the UK, [redacted]clinical trial centres randomised a total of [redacted]patients (Section 3.2.2.1 and CS, Document B, Section B.2.3). Patients enrolled in the FIDELIO-DKD study were adults with T2D and a diagnosis of CKD based on either: (1) persistently (≥2 out of 3 morning void samples taken on consecutive days assessed by the central laboratory) moderately elevated ("high") albuminuria (ACR ≥30 to <300 mg/g or ≥3.4 to <33.9 mg/mmol) and an eGFR ≥25 to <60 ml/min/1.73 m^2 and presence of diabetic retinopathy in the medical history OR (2) persistent (≥2 out of 3 morning void samples taken on consecutive days assessed by the central laboratory), severely elevated ("very high") albuminuria (ACR ≥300 to ≤5,000 mg/g or ≥33.9 to ≤565 mg/mmol) and an eGFR ≥25 to <75 ml/min/1.73 m^2.

Data from the FIDELIO-DKD trial presented in the CS included:

- Full analysis set (FAS): The FAS included all randomised participants (except those excluded for good clinical practice [GCP] violations). The majority of participants were in CKD Stage 3 and CKD Stage 4; however, a small proportion of participants were in CKD Stage 2 ([redacted]%). It should be noted that the trial inclusion criteria for eGFR levels were not completely aligned with the eGFR staging according to the KDIGO 2012 / NICE NG203 classification for CKD Stage 4; i.e. the lowest eGFR per trial inclusion criteria was 25 mL/min/1.73 m^2 meaning that participants with eGFR <25 mL/min/1.73 m^2 were excluded. Despite this, [redacted]% participants had eGFR <25 ml/min/1.73 m^2 at baseline.

- "Label population": The "label population" included participants from the FIDELIO-DKD study with eGFR ≥25 to <60 ml/min/1.73 m^2. While the company stated that it sought marketing authorisation and appraisal by NICE in adults with CKD ([redacted]) and T2D it also stated that, given the minimum eGFR inclusion criterion in the FIDELIO-DKD study

and limited data, use in patients with CKD Stage 4 eGFR <25 ml/min/1.73m^2 was likely to be advised with caution. Assuming the SmPC does allow the use of finerenone with caution in patients with eGFR <25 ml/min/1.73 m^2, the analysis population selected from the FIDELIO-DKD trial data referred to as the "label population" is narrower than that of the decision problem in its exclusion of the available data (albeit limited) in participants with eGFR <25 ml/min/1.73 m^2. Thus, the ERG considered that generalisability of data from the FIDELIO-DKD "label population" (for CKD Stage 4) to CKD classification to be a potential issue.

2.4.2. Intervention

The intervention was consistent with the NICE scope: finerenone. Finerenone is a novel, non-steroidal and selective mineralocorticoid receptor (MR) antagonist. The steroidal hormones, aldosterone and cortisol, are natural ligands of the MR, which is expressed extensively in the heart, kidneys and blood vessels. Overactivation of the MR contributes to organ damage found in CKD, heart failure and hypertension, through mediation of pro-inflammatory and pro-fibrotic effects, as well as via sodium retention and endothelial dysfunction. It is considered that targeting MR overactivation as a key driver of CKD progression remains largely unaddressed by currently approved therapies in patients with CKD and T2D.

The indicative NHS list price is [redacted] per [redacted] supply. The company's health economic analysis was based on the indicative NHS list price for finerenone.

Table 7. Prognosis of CKD by GFR and albuminuria category KDIGO 2012 and NICE NG203

				Persistent albuminuria categories. Description and range		
				A1	**A2**	**A3**
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	<30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
GFR categories (ml/min/1.73 m²) Description and range	G1	Normal or high	≥90			
	G2	Mildly decreased	75-89			
			60–74			
	G3a	Mildly to moderate decreased	45–59			
	G3b	Moderately to severely decreased	30–44			
	G4	Severely decreased	25–29			
			15–24			
	G5	Kidney failure	<15			

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; NICE, National Institute for Health and Care Excellence

FIDELIO DKD FAS ≥25 to <75 ml/min/1.73 m² eGFR (inclusion criteria)*

FIDELIO DKD label population ≥25 to <60 ml/min/1.73 m² eGFR (inclusion criteria)

NICE Scope

* Note that the above diagram reflects trial inclusion criteria (approximately [redacted]% participants had <25 ml/min/1.73 m² eGFR at baseline)

Source: NICE Guideline NG203[4]; KDIGO, 2012[3]

2.4.3. Comparators

The final NICE scope[1] lists two comparators: (1) established clinical management without finerenone, alone or in combination with ACE inhibitors, ARB, or direct renin inhibitors; and (2) SGLT-2is. The company has included the former but not the latter.

2.4.3.1. Established clinical management without finerenone, alone or in combination with ACE inhibitors, ARB, or direct renin inhibitors

Standard treatment of CKD due to T2D has been medicines for hyperglycaemia (metformin, sulfonylureas, insulin) and cardiovascular disease (antihypertensives, ACE-i or ARB). Recently, glucagon-like peptide 1 (GLP-1) receptor agonists and SGLT-2is have been added to the list of medications for use in adults with CKD and T2D.

In respect of ACE-i and ARB, the company has presented evidence from the FIDELIO-DKD[17] trial which compares finerenone + standard of care with placebo + standard of care. In the FIDELIO-DKD trial, 1,942 participants received ACE-i ([redacted] participants in the label population) and 3,725 participants received ARB ([redacted] participants in the label population). Other baseline medications received by participants at baseline included: diuretics, statins, potassium lowering agents, glucose lowering therapy, insulin, GLP-1 receptor agonist and SGLT-2i.

2.4.3.2. SGLT-2i

The company argued in the CS that SGLT-2i are as yet not part of established clinical practice in the NHS and therefore should not be considered as comparators in the appraisal (CS, Document B, pp.27-28).

While the ERG noted that NICE guidance in respect of SGLT-2i use was only recent (published August 2021) with an update in respect of SGLT-2i in progress (due for publication November 2021), the proposed recommendation in people with CKD and T2D with severe ACR has not substantively changed and an additional recommendation to consider use in people with CKD and T2D with moderately increased ACR has been added (Section 2.3).

The company argued in the CS that SGLT-2i should not be considered standard of care as the evidence had not yet translated into widespread changes in established clinical practice in the UK. While the ERG acknowledged that SGLT-2i use in this population was not yet fully established, it noted that clinical guidelines do allow for their use in adults with CKD and T2D

and, in fact, estimated market share (by volume) reported by the company in the CS reflected some current use in clinical practice ([redacted]%). In addition, the ERG noted that the guidelines committee had indicated that the recommendations would: "*lead to a significant change in practice, since SGLT-2i will be prescribed more widely*",[15] which was aligned with advice received from the ERG's clinical expert which indicated that SGLT-2i would be a relevant comparator in the scoped population and use is likely to increase

The company also highlighted in the CS that SGLT-2i were not suitable for use in all patients with CKD and T2D and highlighted a number of safety updates from the MHRA about their use Section B.1.3 (Document B, p.28). Clinical advice to the ERG suggested the following patients in whom SGLT-2i may not be used based on the risk of adverse events; for example, in people: with increased risk of diabetic ketoacidosis; with active foot disease; or, at risk of Fournier's gangrene.

The ERG would also maintain that variation in mechanism of action is not reason for the lack of comparison between finerenone and SGLT-2i: the main issue is whether patients who might currently receive a SGLT-2i in addition to established clinical management in current practice might instead be given finerenone in addition to established clinical management.

It is the ERG's understanding that there are in fact two possible scenarios for the use of finerenone in clinical practice: (1) in addition to SGLT-2i where SGLT-2i are background therapy and (2) instead of SGLT-2i and we comment in respect of both below:

- **Finerenone + SGLT-2i background**

  The ERG noted that 259 participants received a SGLT-2i at baseline in the FIDELIO-DKD trial (124 in the finerenone arm and 135 in the placebo arm).

  In Appendix E of the CS the company presented subgroup analysis on the primary outcome. The ERG noted that in the subgroup of participants receiving SGLT-2i, finerenone had no statistically significant effect on the primary outcome compared with those participants not receiving SGLT-2i in which a reduction in the primary outcome was observed, although the sample size is small (Table 8). The company noted in Appendix E of the CS that "*because of the low number of clinical endpoint events in the small subgroups of patients taking SGLT-2is or GLP-1 receptor agonists, as evidenced by the wide confidence intervals seen for these subgroups, no meaningful conclusions can be drawn from subgroup time-to-event efficacy endpoint analyses.*" The ERG noted that while the

company provide comment on subgroup analysis for secondary outcomes it is not specifically clear which subgroups the company describes as part of 'these subgroups'. It is therefore not possible to comment further on the impact of SGLT-2i use at baseline in respect of the other FIDELIO-DKD outcomes.

Table 8. Primary composite renal outcome according to prespecified subgroup SGLT-2i at baseline

SGLT-2i at baseline	Finerenone	Placebo	Finerenone vs placebo	
	n/N (n/100 PYs)	n/N (n/100 PYs)	HR (95% CI)	p value
No	490/2709 (7.73)	590/2706 (9.39)	0.82 (0.72, 0.92)	0.2114
Yes	14/124 (4.66)	10/135 (3.07)	1.38 (0.61, 3.10)	

Abbreviations: CI, confidence interval; HR, hazard ratio; PYs, patient years; SGLT-2i, sodium-glucose cotransporter 2 inhibitors; vs, versus

- **Finerenone instead of SGLT-2i**

  No evidence was presented in the CS comparing finerenone with SGLT-2i (as class or any particular SGLT-2i). Given the absence of direct trial evidence, comparison between finerenone and SGLT-2i would have required an indirect comparison. The ERG noted a systematic literature review had been conducted as part of the NICE guidelines review. The ERG acknowledged that comparability between SGLT-2i trials might be limited due to differences in study populations, and the definition of endpoints, but this would not preclude a formal feasibility assessment and conduct of an indirect comparison with acknowledgment of such limitations.

In summary, the ERG does not agree with the company's assertion that SGLT-2i are not a relevant comparator in this appraisal as indicated in the final scope.[1] The absence of such an analysis with a comparator listed in the scope and one that is part of standard clinical practice therefore constitutes a key issue.

2.4.4. Outcomes

Outcomes included in the final NICE scope include:

- cardiovascular outcomes;
- disease progression;
- mortality;

- adverse effects of treatment;
- health-related quality of life.

The CS presents clinical data relating to all of the scoped outcomes. The primary outcome, assessed in a time-to-event analysis, was a composite of kidney failure, a sustained decrease of at least 40% in the eGFR from baseline over a period of at least four weeks, or death from renal causes. Kidney failure was defined as end-stage kidney disease or an eGFR of less than 15 ml/min/1.73 m^2; end-stage kidney disease was defined as the initiation of long-term dialysis (for ≥90 days) or kidney transplantation. All eGFR outcome events required confirmation with a second consecutive central laboratory measurement at least four weeks after the initial measurement.[17]

The key secondary outcome, assessed in a time-to-event analysis, was a composite of death from cardiovascular (CV) causes, non-fatal myocardial infarction, non-fatal stroke, or hospitalisation for heart failure. Other secondary outcomes (in order of sequential hierarchical testing) were death from any cause, hospitalisation for any cause, the change in the urinary albumin-to-creatinine ratio from baseline to Month 4, and a composite of kidney failure, a sustained decrease of at least 57% in the eGFR from baseline (equivalent to a doubling of the serum creatinine level) maintained for at least four weeks, or death from renal causes (secondary composite kidney outcome).

Adverse events that occurred during the treatment period were defined as those that started or worsened during finerenone or placebo intake or up to three days after any temporary or permanent interruption.

The company's health economic model included data relating to disease progression based on transition probabilities obtained from patient level data; CV events (including new onset of atrial fibrillation / atrial flutter); mortality (CV death; renal death; and non-CV or non-renal death); development of hyperkalemia, and health-related quality of life.

2.4.5. Other relevant factors

The company claimed finerenone is an innovative medicine in the treatment of CKD in T2D because: "*it offers an additional therapeutic approach on top of current standard of care medicine. It has a distinctive mode of action and properties compared to currently available*

standard of care treatments, i.e. ACE-is and ARBs (and other background therapy)." (CS, Document B, Section B.2.12).

The company claimed that there are aspects of innovation that are not captured within the quality adjusted life year (QALY) calculation, namely delay progression to kidney failure and the need for dialysis offering benefits to both patients and their caregivers (CS, Document B, Section B.2.12).

The company did not submit a Patient Access Scheme (PAS).

End of life criteria are not applicable for this appraisal (Section 7).

In Section B.1.4 of the CS (Document B), the company stated that it considered there may be equality issues associated with this appraisal when considering race and socioeconomic status. The company highlighted that CKD disproportionately affects patients from lower socio-economic groups and those from black, Asian and ethnic minority backgrounds, particularly emphasising those of South Asian and Black ethnicities. These inequalities are primarily driven by a greater prevalence of risk factors such as diabetes and hypertension in these populations. In addition, treatment differs between both groups and the general population as they are less likely to receive peritoneal dialysis, or to receive a kidney transplant. In addition, the CS identified inequality of outcomes with both groups progressing faster towards kidney failure and those from lower socioeconomic groups dying earlier than the overall population. The company also mentioned some more specific groups disproportionately affected by CKD including those living in socially deprived areas and those in rural areas and highlighted the high rates of severe mental illness in those with CKD. The company claimed that finerenone will reduce these health inequalities by improving outcomes for the relevant groups and highlighted that 37% of participants in the FIDELIO-DKD study were non-white, illustrating that the results are relevant to a diverse population.

3. CLINICAL EFFECTIVENESS

3.1. Critique of the methods of review(s)

The company conducted a systematic review to identify evidence on the efficacy and safety of interventions for the treatment of CKD in people with T2D. Table 9 provides the critique of the methods of the review including searching, inclusion criteria, data extraction, quality assessment and evidence synthesis.

Table 9: Summary of ERG's critique of the methods implemented by the company to identify evidence relevant to the decision problem

Systematic review step	Section of CS in which methods are reported	ERG assessment of robustness of methods
Searches	Appendix D, Section D 1.1	The searches appear broadly appropriate and likely to have captured the available evidence, however, the ERG notes that no specific searches for adverse events were completed.
Inclusion criteria	Appendix D, Section D 1.1	The population criterion allowed for the inclusion of studies with population described as CKD, DKD or patients with diabetic nephropathy. In other cases, only studies reporting results for patients with eGFR and UACR criteria similar to criteria defined in FIDELIO/FIGARO were included. Where CKD was not explicitly mentioned, only included studies with a similar eGFR and UACR to those in FIDELIO/FIGARO, though this is a very broad population. The intervention criterion specified interventions belonging to the following classes: MRAs, DPP-4 inhibitors, SGLT-2i, and GLP-1 agonists were eligible for inclusion. However, during the full-text review interventions were restricted to finerenone. Given the comparators listed in scope and the absence of direct evidence comparing finerenone with SGLT-2i, the ERG considered that the company should reasonably have conducted a feasibility assessment for an indirect treatment comparison with the studies included in the review. A broad range of outcomes were specified in the PICO. Outcomes specified were broader with those specified scope. Study design was limited to RCT which may have excluded certain evidence, for example case reports which could provide further evidence of adverse events.
Screening	Appendix D, Section D1.2	Both the title and abstract screening, and the full-text review were carried out independently by two

Systematic review step	Section of CS in which methods are reported	ERG assessment of robustness of methods
		reviewers. Any disagreements were resolved by a third reviewer.
Data extraction	Not reported	It was unclear to the ERG whether data extraction was performed independently by two reviewers as not details were reported. The approach should follow the recommendations of the Cochrane Handbook which states that: “as a minimum, information that involves subjective interpretation and information that is critical to the interpretation of results (e.g. outcome data) should be extracted independently by at least two people”.
Tool for quality assessment of included study or studies	Appendix D, Section D3	An appropriate tool was used to conduct quality appraisal. The tool was adapted from the CRD tool for systematic reviews. It is not clear whether the risk of bias assessment followed best practice. The Cochrane Handbook recommends that the assessment should be performed independently by at least two people.
Evidence synthesis	Not reported	A total of four studies reported in seven publications evaluating finerenone were identified. Of these, three studies (reported in five publications) were subsequently excluded as they were Phase 2 dose-finding studies (ARTS, ARTS-DN, ARTS-DN Japan). No evidence synthesis or meta-analysis was conducted by the company as they deemed only one study (reported in two publications) to be relevant to the submission. The ERG agreed that meta-analysis was not possible given the existence of only one relevant RCT. The ERG agreed that the comparison of finerenone + standard of care with placebo + standard of care was appropriate as representative of standard of care in the UK according to NICE, though SGLT-2i should have been included in a comparison. It may have been possible to construct an indirect comparison of finerenone with SGLT-2i using RCTs identified in the review; however, these were excluded at full text review. No feasibility assessment or indirect comparison was performed (see Section 3.3).

Abbreviations: CKD, chronic kidney disease; CRD, Centre for Reviews and Dissemination; CS, Company submission; DKD, diabetic kidney disease; DPP-r, dipeptidyl peptidase 4 (inhibitors); eGFR, estimated glomerular filtration rate; ERG, Evidence Review Group; GLP-1, glucagon-like peptide-1 (agonists); MRAs, mineralocorticoid receptor antagonists; NICE, National Institute for Health and Care Excellence; PICO, population, intervention, comparator, outcomes; RCT, randomised controlled trials; SGLT-2i, sodium-glucose cotransporter 2 inhibitor(s); UACR, urine albumin-to-creatinine ratio

3.2. Critique of trials of the technology of interest, the company's analysis and interpretation

3.2.1. Studies included in/ excluded from the submission

The clinical evidence in this submission is based on results from FIDELIO-DKD, a pivotal Phase 3 randomised controlled trial (RCT) in adult patients with CKD and T2D, who were on optimised background therapy including a maximum tolerated labelled dose of either an angiotensin-converting enzyme inhibitor (ACE-i) or an angiotensin receptor blocker (ARB).

Table 10. FIDELIO-DKD: publications

Study	NCT	Publications
FIDELIO-DKD	NCT02540993	Bakris 2019;[18] Bakris 2020[17]
		Additional abstracts reporting results from FIDELIO-DKD identified by the ERG:[a] Filippatos 2021 (new-onset AFF and cardiorenal effects by history of AFF)[19] Rossing 2021 (subgroup by GLP-1 receptor agaonist treatment)[20]

Abbreviations: AFF, atrial fibrillation and atrial flutter; ERG, Evidence Review Group

Notes: a Abstracts identified by the ERG when critiquing the evidence in the CS (publication date outside of the date parameters of the company's literature search hence not identified in the company's systematic literature review)

3.2.2. Description and critique of the design of the studies

3.2.2.1. Study design and methods

Trial design

FIDELIO-DKD was a randomised, double-blind, placebo-controlled, parallel-group, multicentre, event-driven trial. The study took place across [redacted] study centres across 48 countries in Europe, Middle East, Africa, North America, Central and South America, Australia, New Zealand and Asia. In the UK, [redacted] clinical trial centres randomised a total of [redacted] patients (Document B, Section B.2.3). Within the label population, [redacted] patients were from the UK (n=[redacted] finerenone + standard of care and n=[redacted] placebo + standard of care) (Document B, Section B.2.3).

The trial consisted of run-in, screening, and double-blind treatment periods. The run-in period (4 to 16 weeks) allowed background medical therapies to be adjusted, including adjustment of ACE inhibitor or ARB therapy to a maximum labelled dose that did not cause unacceptable side effects. At the end of the run-in period, patients were reassessed for eligibility during a

screening visit with subsequent randomisation within two weeks. Eligible patients were then randomly assigned in a 1:1 ratio to receive:

- oral finerenone (10 mg or 20 mg once daily) plus background therapy (BT) or
- placebo, in addition to BT.

Treatment assignment was stratified by: region (North America, Latin America, Europe, Asia, Other), eGFR category at screening (25–<45, 45–<60, and ≥60 mL/min/1.73 m^2), and category of albuminuria at screening (very high albuminuria [UACR ≥300 mg/g] or high albuminuria [UACR ≥30 to <300 mg/g]).

Eligibility criteria

Eligibility criteria for the FIDELIO-DKD criteria are summarised in Table 7 of the CS (Document B). Key inclusion and exclusion criteria are summarised in Table 11.

Table 11. FIDELIO-DKD study: Key eligibility criteria

Inclusion criteria:
• Men or women ≥18 years of age with: – T2DM as defined by the American Diabetes Association in the 2010 Standards of Medical Care in Diabetes, and – Diagnosis of CKD with the following criteria at run-in and screening visits – persistent ***albuminuria*** (≥2 out of three morning void samples taken on consecutive days assessed by central laboratory) and eGFR criteria at the run-in and screening visits of either: ▪ persistently moderately elevated "high" albuminuria (defined as UACR ≥30 to <300 mg/g [≥3.4 to <33.9 mg/mmol]) AND an eGFR ≥25 to <60 ml/min/1.73m^2 AND presence of diabetic retinopathy OR ▪ persistently severely elevated "very high" albuminuria (defined as UACR ≥300 to <5,000 mg/g [≥33.9 to <565 mg/mmol]) AND an eGFR ≥25 to <75 ml/min/1.73m^2 • Prior treatment with an ACE-i or ARB as follows: – For ≥4 weeks prior to the run-in visit, treated with either an ACE-i or an ARB or both – Starting with the run-in visit, treated with only an ACE-i or ARB – For ≥4 weeks prior to the screening visit, treated with the maximum tolerated labelled dose (but not below the minimal labelled dose) of only an ACE-i or an ARB (not both) preferably without any adjustments to dose • Serum potassium ≤4.8 mmol/L at both the run-in visit and the screening visit. • For women of child-bearing potential, a negative pregnancy test at screening visit and agreement to use adequate contraception (≥2 effective methods of birth control, of which ≥1 is a physical barrier). • Ability to understand and follow study-related instructions. • Written informed consent before any study-specific criteria.
Exclusion criteria:
• Any history of or current: – Confirmed significant non-diabetic renal disease, including clinically relevant renal artery stenosis – Uncontrolled arterial hypertension (ie, mean sitting SBP ≥170 mmHg, sitting DBP ≥110 mmHg at run in visit, or mean sitting SBP ≥160 mmHg, sitting DBP ≥100 mmHg at screening)

- Clinical diagnosis of chronic HFrEF and persistent symptoms (NYHA class II – IV) at run in visit (class 1A recommendation for MRAs)
- Dialysis for acute renal failure within 12 weeks of run-in visit.
- Stroke, transient ischaemic cerebral attack, acute coronary syndrome, or hospitalisation for worsening heart failure, in the 30 days before the screening visit.
- Renal allograft in place or scheduled within next 12 months
- HbA1c > 12% at the run-in or screening visit.
- A mean SBP of <90 mmHg at the run-in or screening visit.
- Addison's disease
- Hepatic insufficiency classified as Child-Pugh C.
- Known hypersensitivity to the study treatment (active substance or excipients).

- Disallowed medications:
  - Concomitant therapy with eplerenone, spironolactone, any renin inhibitor, or potassium-sparing diuretic which cannot be discontinued ≥4 weeks prior to the screening visit.
  - Concomitant therapy with both ACEi and ARBs which cannot be discontinued for the purpose of the study.
  - Concomitant therapy with potent cytochrome P450 isoenzyme 3A4 (CYP3A4) inhibitors or inducers (to be stopped ≥7 days before randomisation).
- Any other condition or therapy, which would make the patient unsuitable for the study and would not allow participation for the full planned study period (e.g., active malignancy or other condition limiting life expectancy to <12 months).
- Pregnant or breast-feeding or intention to become pregnant during the study.
- Previous (≤30 days prior to randomisation) or concomitant participation in another clinical study with investigational medicinal product(s), except for participation in the run-in and screening period of FIGARO-DKD.
- A close affiliation with the investigational site, e.g. a close relative of the investigator.

Abbreviations: ACE-i, Angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1C, haemoglobin A1c; HFrEF, heart failure with reduced ejection fraction; MRA, Mineralocorticoid Receptor Antagonists; NYHA, New York Heart Association; SBP, systolic blood pressure; UACR, Urine Albumin-to-Creatinine Ratio

Notes: eGFR, calculated with the use of the Chronic Kidney Disease Epidemiology Collaboration formula, with adjustment for race in Black patients [21]

Interventions

The starting dose of finerenone was determined by the estimated glomerular filtration rate [eGFR] at the screening visit: eGFR 25–< 60 mL/min/1.73 m^2: finerenone 10 mg / day or matching placebo; eGFR ≥60 mL/min/1.73 m^2: finerenone 20 mg / day or matching placebo. An increase in the dose from 10 to 20 mg once daily was encouraged after one month, provided the serum potassium level was 4.8 mmol per litre or less and the eGFR was stable; a decrease in the dose from 20 to 10 mg once daily was allowed any time after the initiation of finerenone or placebo. Patients in the placebo group underwent sham adjustment of the dose. After randomisation, trial visits were conducted at Month 1, Month 4, then every four months until trial completion. Finerenone or placebo was withheld if potassium concentrations exceeded 5.5 mmol per litre and restarted when potassium levels fell to 5.0 mmol per litre or less. Restarts after interruptions of >7 days were at the lower (10 mg) dose. Study drug administration in

respect of missing tablets, up-titration and down-titration of dose was provided in the CS (Document B, Table 8).

Concomitant medication

Patients maintained their usual diet throughout the study and were not given any specific advice on dietary potassium restrictions. Use of potassium supplements was permitted during the study – investigators were advised to closely monitor potassium levels, to adjust potassium supplement dosing based on potassium values, and to discontinue potassium supplements once potassium was within the normal range. Potassium-lowering agents were also permitted during the study.

Information on new concomitant medication initiated after participants started the study drug, showed comparable results for the two treatment arms ([redacted]); refer to Table 12 for new concomitant medication initiated after start of study drug by type.

Table 12. Percentage new concomitant medication initiated after start of study drug (FAS)

	Finerenone	Placebo
New non-anti-diabetic medications	[redacted]%	[redacted]%
Diuretics	42.8%	45.4%
Calcium channel blockers	35.3%	41.5%
Loop diuretics	[redacted]%	[redacted]%
Statins	29.4%	30.3%
Alpha-blocking agents	28.5%	31.0%
Beta-blockers	27.1%	30.1%
Potassium lowering agents	10.8%	6.5%
Potassium supplements	[redacted]	[redacted]
New anti-diabetic medications	**63.3%**	**64.8%**
Insulins and analogues	47.1%	48.7%
Biguanides	18.2%	17.4%
Dipeptidyl peptidase-4	16.7%	16.7%
Glucagon-like peptide 1 receptor agonists	9.2%	9.3%
Sodium–glucose cotransporter 2 inhibitors	6.6%	7.6%

Source: CS, Document B, Section B.2.3, p.44

Analysis sets

The analysis sets from the FIDELIO-DKD study are provided in Table 13. Participants in the key subgroup were required to have eGFR ≥25 to <60 at baseline (measured as mL/min/1.73m^2). This population is termed the 'label population' in the CS, and this terminology is maintained

throughout the ERG's report for consistency. While the label population is defined as those in the FIDELIO-DKD study with a baseline eGFR between 25 and 60, the company explained within its submission that this group of patients *"corresponds to CKD 3 and CKD 4, and albuminuria."* (CS Section B.3.3.1).

Table 13. Main analysis sets in FIDELIO-DKD

Analysis set	Definition	FIDELIO-DKD population		Label population	
		Finerenone o.d. + BT	Placebo o.d. + BT	Finerenone o.d. + BT	Placebo o.d. + BT
Randomised patients		**N=2,866**	**N=2,868**	[redacted]	[redacted]
FAS	All randomised patients except those excluded for GCP violations.	N=2,833 (100%)	N=2,841 (100%)	[redacted]	[redacted]
	Patients excluded for GCP violations	*n=33*	*N=27*	[redacted]	[redacted]
SAF	All patients in the FAS who received at least one dose of study medication.	N=2,827 (99.8%)	N=2,831 (99.6%)	[redacted]	[redacted]
	Excluded from SAF as did not receive study medication	*6 (0.2%)*	*10 (0.4%)*	[redacted]	[redacted]
PPS	All patients in the FAS without any protocol deviations	*N=2,391 (84.4%)*	*N=2,451 (86.3%)*	[redacted]	[redacted]
	Excluded from PPS (mainly due to reduced compliance)	*442 (15.6%)*	*417 (13.7%)*	[redacted]	[redacted]

Abbreviations: BT, background therapy; CS, company submission; FAS, full analysis set; GCP, good clinical practice; N, number of participants; o.d., once daily; PPS, per protocol set; SAF, safety analysis set

Source: CS, Document B, Section B.2.4 and Table 11

Endpoints

Clinical endpoints in the FIDELIO-DKD study were described in Table 9 of the CS (Document B) (see also Table 14, below). The primary outcome was the composite of time to first occurrence of kidney failure, a sustained decrease of eGFR ≥40% from baseline over at least four weeks, or renal death. Key secondary endpoints included time to occurrence of CV mortality and morbidity which was a composite of first occurrence of CV death, non-fatal myocardial infarction (MI), non-fatal stroke, or hospitalisation for heart failure; time to all-cause mortality; time to all-cause hospitalization; change in UACR from baseline to four months; a composite of kidney failure or sustained decrease in eGFR ≥57% from baseline over at least four weeks or renal death. Other endpoints included individual components of the primary and secondary outcomes; new diagnosis of atrial fibrillation or atrial flutter; health-related quality of life (as measured by Kidney Disease Quality of Life (KDQOL-36) and European Quality of Life (EuroQol) – 5 Dimension (EQ-

5D-5L)), and safety. Exploratory efficacy outcomes included the composite endpoint of time to CV death, kidney failure, eGFR decrease of ≥57% sustained over at least four weeks or renal death; change in UACR from baseline; and change in eGFR from baseline.

Table 14. Outcomes measured in FIDELIO-DKD

Outcome	FIDELIO-DKD	Label population	Subgroup SGLT-2i at baseline +/-
Primary endpoint: composite of kidney failure[a]; a sustained decrease in **eGFR ≥40% from baseline over at least 4 weeks[b]; or, renal death[c]**	■	■	■
Key secondary endpoint: Time in days from randomisation to first occurrence of CV mortality and morbidity. Composite of CV death[d] or non-fatal MI[e] or non-fatal stroke[f] or hospitalisation for heart failure[g]	■	■	
Other secondary endpoints			
Time in days from randomisation to all-cause mortality[h]	■	■	
Time in days from randomisation to all-cause hospitalisation	■	■	
Change in UACR from baseline to 4 months	■	■	
Composite of kidney failure[a] or sustained decrease in eGFR ≥57% from baseline over at least 4 weeks[b] or renal death[c]	■	■	
Other endpoints			
Individual components of the primary and secondary outcomes:			
Renal:			
Kidney failure[a]	■	■	
Sustained decrease in eGFR ≥40% from baseline over at least 4 weeks[b]	■	■	
Sustained decrease in eGFR ≥57% from baseline over at least 4 weeks[b]	■	■	
Renal death[c]	■	■	
Cardiovascular:			
CV death[d]	■	■	
Non-fatal MI[e]	■	■	
Non-fatal stroke[f]	■	■	
Hospitalisation for heart failure[g]	■	■	
New diagnosis of atrial fibrillation and atrial flutter[i]	■		
Health-related quality of life			
Kidney Disease Quality of Life (KDQOL-3***6***)	■	■	
European Quality of Life 5 Dimension (EQ-5D)-5L	■	■	
Safety	■		

■ outcome data reported in the CS

Abbreviations: AE, adverse event; AKI, Acute Kidney Injury; BNP, B-type natriuretic peptide; CABG, coronary artery bypass grafting; CEC, clinical endpoint committee; CKD, chronic kidney disease; cTn, cardiac troponin; CV, cardiovascular, ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; EOS, end of study; EQ-5D-5L, European quality of life – 5 dimension – 5l levels questionnaire; EQ VAS, EQ Visual Analogue scale; ESRD, end-stage renal disease; HF, heart failure; HRqol, Health-related quality of life; KDQOL, Kidney Disease quality of life; LBBB, left bundle branch block; MedDRA, Medical Dictionary for Regulatory Activities; MI, myocardial infarction; PCI, percutaneous coronary intervention; PD, premature discontinuation; RRT, renal replacement therapy; ST-T, ST segment or T-wave; TEAE, treatment emergent adverse event; URL, upper reference limit

Notes:

a Kidney failure was defined as: ESRD including 1) initiation of chronic dialysis [haemo- or peritoneal dialysis] for ≥ 30 days and did not recover at 90 days or 2) renal transplantation. Acute kidney injury (AKI) events leading to dialysis and death, which occurred whilst on dialysis were also considered an ESRD event; sustained eGFR[b] < 15 mL/min/1.73 m^2. eGFR confirmed by a second measurement at the earliest 4 weeks after the initial measurement. The eGFR threshold is consistent with the definition of kidney failure from Kidney Disease: Improving Global Outcomes[21] and was chosen to include an objective component to the endpoint because the decision to initiate dialysis therapy or kidney transplantation may be affected by factors other than eGFR.

b Sustained decrease ≥40% or ≥57% (as determined by endpoint) in eGFR compared to baseline over ≥4 weeks was defined by evidence of ≥2 consecutive central laboratory assessments of eGFR. The confirmatory sample for eGFR assessment confirming the sustained decrease had to be collected ≥4 weeks after the initial eGFR measurement showing a decrease in eGFR by ≥40%. The baseline eGFR value was the eGFR from Visit 1 (unless this value was missing, in which case the last value measured prior to randomisation was used as the baseline value). The date of onset of sustained decrease in eGFR ≥40% compared with baseline was the date of the initial sample exceeding the threshold.

c Renal death was determined if: (1) the patient died; (2) RRT had not been initiated despite being clinically indicated; and (3) there was no other likely cause of death. If a patient was initially denied RRT for a specific reason (e.g. metastatic cancer, shock or sepsis) then another more proximal cause of death was identified.

d Events that were classified as CV death included the following: (1) death due to acute MI, (2) sudden cardiac death, (3) undetermined death; (4) death due to HF; (5) death due to stroke; (6) death due to CV procedures; or (7) death due to other CV causes

e Acute MI was defined based on detection of rise and/or fall in cardiac biomarkers (preferably cTn) with at ≥1 value above the 99th percentile of the upper reference limit [URL] or ≥1 value exceeding the local reference limit for non-highly sensitive methods), together with evidence of myocardial ischaemia, including ≥1 of the following: symptoms of ischaemia; ECG changes indicative of new ischaemia (new ST-T changes or new LBBB); development of pathological Q waves in the ECG; imaging evidence of new loss of viable myocardium or new regional wall motion abnormality; identification of an intracoronary thrombus by angiography. PCI-related MI was arbitrarily defined by elevation of cTn values (>5 x 99th percentile URL) in patients with normal baseline values (≤99th percentile URL) or a rise of cTn values >20% if the baseline values were elevated and were stable or falling. In addition, either (i) symptoms suggestive of myocardial ischaemia, or (ii) new ischaemic ECG changes, or (iii) angiographic findings consistent with a procedural complication, or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality, were required. CABG-related MI was arbitrarily defined by elevation of cardiac biomarker values (>10 x 99th percentile URL) in patients with normal baseline cTn values (≤99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality, were required.

f Stroke was defined as an acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of haemorrhage or infarction, with symptom duration of ≥24 hours. Episodes lasting <24 hours could be considered a stroke if there was an intervention to abort the stroke (e.g., thrombolytic therapy), diagnostic confirmation of the stroke, or the patient died prior to reaching the 24-hour duration. Subdural hematomas were considered intracranial haemorrhagic events and not strokes.

g Hospitalisation due to HF was an event meeting ALL of the following criteria: the patient was admitted to hospital with a primary diagnosis of HF; the patient's length of hospital stay was ≥24 hours; on presentation, the patient exhibited documented new symptoms or worsening HF symptoms; the patient had objective evidence of worsening HF, consisting of ≥2 physical examination findings or one physical examination finding and ≥1 laboratory criterion; the patient received initiation or intensification of HF-specific treatment

h Causes of death were classified into three categories: cardiovascular (CV) death (see Note d for definition); renal death (see Note c for definition) or non-CV and non-renal death - all deaths not due to a CV or renal cause. These were categorised as infection, malignancy or other specific causes.

i Any new diagnosis of atrial fibrillation or atrial flutter. This endpoint was independently adjudicated by the CEC

j AE assessment occurred at every visit. AEs that started or worsened after the first dose of study drug up to 3 days after any temporary or permanent interruption of study drug were considered as TEAEs. Adverse events were coded by MedDRA Version 23.0

Source: CS, Document B, Table 9

Statistical analysis

FIDELIO-DKD was an event-driven trial was designed to have 90% power to detect a 20% lower risk of a primary outcome event with finerenone than with placebo, on the basis of 1,068 patients with a primary outcome event. Efficacy analyses were performed in the full analysis set (all randomly assigned patients without critical Good Clinical Practice violations). In time-to-event analyses, the superiority of finerenone plus BT over placebo plus BT was tested by means of a stratified log-rank test; stratification factors were geographic region (North America, Latin America, Europe, Asia, or other), eGFR category (25 to <45, 45 to <60, or ≥60 ml/min/1.73 m^2) at screening, and albuminuria category (moderately or severely elevated) at screening. Treatment effects are expressed as hazard ratios with corresponding confidence intervals from stratified Cox proportional-hazards models. Events were counted from randomisation to the end-of-trial visit, and data on participants without an event were censored at the date of their last contact with complete information on all components of the respective outcome.

To account for multiple testing, the weighted Bonferroni–Holm procedure was used for the primary outcome and the key secondary outcome, followed by a hierarchical testing procedure of additional secondary outcomes. Because of the formal interim analysis, significance levels for the multiple-testing procedure in the final analysis were adjusted from 1.6667%, 3.3333%, and 5% to 1.5762%, 3.2827%, and 4.9674%, respectively.

Safety analyses were performed in the safety analysis set (all randomly assigned patients without critical Good Clinical Practice violations who received at least one dose of finerenone or placebo). Additional details on efficacy and safety analyses are provided in the trial protocol and the statistical analysis plan.

3.2.2.2. Baseline characteristics

The company presented data for the overall population and the label population in Table 10 of the CS (CS, Document B, Table 10).

The label population (n=4,860/5,674; 85.7% of full analysis set (FAS)) generally resembled characteristics of the overall population (Table 15). The label population was predominately male ([redacted]%) and white ([redacted]%), with a mean age of [redacted]years in both treatment groups. Mean eGFR was slightly lower at [redacted]mL/min/1.73 m^2 and by definition of the subpopulation, all patients had eGFR 25 to <60 ml/min/1.73m^2: [redacted]% participants had eGFR 45 to <60 mL/min/1.73 m^2 and [redacted]% eGFR 25 to <45 mL/min/1.73 m^2; the

majority of patients ([redacted]%) had very high albuminuria (≥300 mg/g [33.9 mg/mmol]) at baseline. At baseline, [redacted]([redacted]%) participants were taking ARBs and [redacted]([redacted]%) ACE-is, as requested by the protocol, and almost all patients ([redacted]%) were on glucose-lowering medication. Approximately [redacted] ([redacted]%) were using insulin, while metformin was the most frequently used glucose-lowering oral drug at baseline. Glucagon-like peptide 1 agonists were used by [redacted]% of patients, while [redacted]% were using SGLT-2is. At baseline, nearly all patients ([redacted]%) had arterial hypertension as concomitant disease, and [redacted]% had diabetic retinopathy. Less than half ([redacted]%) had CV disease (CVD) in the medical history: [redacted]% had coronary artery disease, [redacted]% myocardial infarction, [redacted]% ischemic stroke, and [redacted]% peripheral artery disease. Only [redacted]% of all patients suffered from heart failure at baseline, although people with reduced ejection fraction with New York Heart Association Class II–IV at run-in and screening were not eligible for inclusion per protocol.

Table 15. Baseline demographic and disease characteristics for overall FIDELIO-DKD study population and 'label' population

	FIDELIO-DKD population		Label population	
	Finerenone (N=2,833)	Placebo (N=2,841)	Finerenone (N=[redacted])	Placebo (N=[redacted])
Age (yr)	65.4±8.9	65.7±9.2	[redacted]	[redacted]
Male, n (%)	1,953 (68.9)	2,030 (71.5)	[redacted]	[redacted]
Race, n (%) †				
White	1,777 (62.7)	1,815 (63.9)	[redacted]	[redacted]
Black / African American	140 (4.9)	124 (4.4)	[redacted]	[redacted]
Asian	717 (25.3)	723 (25.4)	[redacted]	[redacted]
Other	199 (7.0)	179 (6.3)	[redacted]	[redacted]
Geographic region, n (%)				
Europe	1,182 (41.7)	1,176 (41.4)	[redacted]	[redacted]
North America	467 (16.5)	477 (16.8)	[redacted]	[redacted]
Latin America	295 (10.4)	298 (10.5)	[redacted]	[redacted]
Asia	790 (27.9)	789 (27.8)	[redacted]	[redacted]
Other	99 (3.5)	101 (3.6)	[redacted]	[redacted]
Duration of diabetes (yr)	16.6±8.8	16.6±8.8	[redacted]	[redacted]
Glycated haemoglobin (%)	7.7±1.3	7.7±1.4	[redacted]	[redacted]
Systolic blood pressure (mmHg)	138.1±14.3	138.0±14.4	[redacted]	[redacted]
eGFR			[redacted]	[redacted]
Mean	44.4±12.5	44.3±12.6	[redacted]	[redacted]
Distribution, n (%)				

	FIDELIO-DKD population		Label population	
	Finerenone (N=2,833)	Placebo (N=2,841)	Finerenone (N=[redacted])	Placebo (N=[redacted])
≥60 ml/min/1.73m^2	318 (11.2)	338 (11.9)	[redacted]	[redacted]
45 to <60 ml/min/1.73m^2	972 (34.3)	928 (32.7)	[redacted]	[redacted]
25 to <45 ml/min/1.73m^2	1476 (52.1)	1505 (53.0)	[redacted]	[redacted]
<25 ml/min/1.73m^2	66 (2.3)	69 (2.4)	[redacted]	[redacted]
Missing data	1 (<0.1)	1 (<0.1)	[redacted]	[redacted]
UACR ‡				
Median (IQR)	833 (441-1628)	867 (453-1645)	[redacted]	[redacted]
Distribution, n (%)			[redacted]	[redacted]
<30	11 (0.4)	12 (0.4)	[redacted]	[redacted]
30 to <300	350 (12.4)	335 (11.8)	[redacted]	[redacted]
≥300	2470 (87.2)	2493 (87.8)	[redacted]	[redacted]
Missing data	2 (<0.1)	1 (<0.1)	[redacted]	[redacted]
Serum potassium (mmol/litre)	4.37±0.46	4.38±0.46	[redacted]	[redacted]
Medical history			[redacted]	[redacted]
Hypertension, n (%)	2,737 (96.6)	2,768 (97.4)	[redacted]	[redacted]
Diabetic retinopathy, n (%)	1,312 (46.3)	1,351 (47.6)	[redacted]	[redacted]
Diabetic neuropathy, n (%)	738 (26.1)	716 (25.2)	[redacted]	[redacted]
History of CV disease, n (%)	1,303 (46.0)	1,302 (45.8)	[redacted]	[redacted]
Coronary artery disease	842 (29.7)	860 (30.3)	[redacted]	[redacted]
Myocardial infarction	378 (13.3)	388 (13.7)	[redacted]	[redacted]
PAOD	470 (16.6)	453 (15.9)	[redacted]	[redacted]
Ischaemic stroke	329 (11.6)	360 (12.7)	[redacted]	[redacted]
Heart failure, n (%)	195 (6.9)	241 (8,5)	[redacted]	[redacted]
Baseline medications, n (%)				
ACE inhibitor §	950 (33.5)	992 (34.9)	[redacted]	[redacted]
ARB §	1,879 (66.3)	1,846 (65.0)	[redacted]	[redacted]
Diuretic	1,577 (55.7)	1,637 (57.6)	[redacted]	[redacted]
Statin	2,105 (74.3)	2,110 (74.3)	[redacted]	[redacted]
Potassium-lowering agent ¶	70 (2.5)	66 (2.3)	[redacted]	[redacted]
Glucose-lowering therapy	2,747 (97.0)	2,777 (97.7)	[redacted]	[redacted]
Insulin	1,843 (65.1)	1,794 (63.1)	[redacted]	[redacted]
GLP-1 receptor agonist	189 (6.7)	205 (7.2)	[redacted]	[redacted]
SGLT-2i	124 (4.4)	135 (4.8)	[redacted]	[redacted]

Abbreviations: ACE=angiotensin-converting enzyme; ARB=angiotensin receptor blocker; CV=cardiovascular; eGFR=estimated glomerular filtration rate; GLP-1=glucagon-like peptide 1; IQR=interquartile range; mmHg=millimetres of mercury; PAOD=peripheral arterial occlusive disease; SD=standard deviation; SGLT2=sodium–glucose cotransporter 2; UACR=urinary albumin-to-creatinine ratio

Notes:

* Plus–minus values indicate means ±SD. Patients in the finerenone group received 10 or 20 mg once daily. Percentages may not total 100 because of rounding.

† Race was reported by the patients.

‡ The ratio was calculated with albumin measured in milligrams and creatinine measured in grams.

§ A total of 14 patients were not treated with either an ACE inhibitor or an angiotensin-receptor blocker at baseline; 7 patients received treatment with both an ACE inhibitor and an angiotensin-receptor blocker

¶ These agents included sodium polystyrene sulfonate, calcium polystyrene sulfonate, and potassium-binding agents.

Considering the FAS and label populations, the ERG agreed with the company's assertion that the finerenone plus BT and placebo plus BT arms were generally well balanced for baseline characteristics and reasonably representative of the target population.

3.2.2.3. Critical appraisal of the design of the studies

The ERG reviewed the company's quality assessment for the FIDELIO-DKD trial using quality assessment criteria adapted from the Centre for Reviews and Dissemination. The ERG considered the FIDELIO-DKD trial to be a well-conducted RCT and agreed with the company's judgement that the risk of bias was low.

3.2.3. Description and critique of the results of the studies

3.2.3.1. Clinical effectiveness results

The main findings for the FIDELIO-DKD study are presented in the CS (Section B.2.6) and reproduced below for the full analysis set (FAS) and the label population, Table 16 and Table 17, respectively.

Primary outcome: Composite of onset of kidney failure, a sustained decrease of eGFR ≥40% from baseline over at least 4 weeks, or renal death

In the full analysis set (FAS), the incidence of the primary composite outcome of kidney failure, a sustained decrease of at least 40% in the eGFR from baseline, or death from renal causes was significantly lower in the finerenone plus BT group than in the placebo plus BT group, occurring in 504 patients (17.8%) and 600 patients (21.1%), respectively (hazard ratio, 0.82; 95% confidence interval [CI], 0.73 to 0.93; p=0.001). Incidences for the primary outcome components were consistently lower with finerenone plus BT than with placebo plus BT but [redacted](p=[redacted]) (Table 16).

Similarly, in the label population the incidence of the primary composite outcome of kidney failure, a sustained decrease of at least 40% in the eGFR from baseline, or death from renal causes was significantly lower in the finerenone plus BT group than in the placebo plus BT group, occurring in [redacted]patients ([redacted]%) and [redacted]patients ([redacted]%), respectively (hazard ratio, [redacted]; 95% confidence interval [CI], [redacted]; p=[redacted]). The [redacted]observed on the composite outcome for

finerenone plus BT vs. placebo plus BT was also only reproduced for one of the disaggregated outcomes, [redacted](p=[redacted]) (Table 17).

In both the FAS and the label populations, the [redacted]observed on the composite outcome for finerenone vs. placebo was also only reproduced for one of the disaggregated outcomes, [redacted](Table 16 and Table 17, respectively). Given that such a change in eGFR could occur from any current level of eGFR up to 60 ml/min/1.73m^2 in the label population and up to 75 ml/min/1.73m^2 in the trial inclusion criteria and that there was [redacted], it is questionable whether the trial showed a clinically important difference in outcome with respect to 'average' eGFR change between groups. This is therefore a key issue.

Key secondary outcome: Composite of onset of death from cardiovascular causes, non-fatal myocardial infarction, non-fatal stroke, or hospitalisation for heart failure

In the FAS, participants in the finerenone plus BT group also had a significantly lower risk of a key secondary outcome event (death from cardiovascular causes, non-fatal myocardial infarction, non-fatal stroke, or hospitalisation for heart failure), which occurred in 367 patients (13.0%) compared with 420 patients (14.8%) in the placebo plus BT group (HR, 0.86; 95% CI, 0.75 to 0.99; p=0.03). Incidence of each component was lower with finerenone plus BT than with placebo plus BT except for non-fatal stroke, which had a similar incidence in the two groups; however, the statistically significant improvement observed on the composite outcome for finerenone plus BT vs. placebo plus BT was not reproduced for any of the disaggregated outcomes (Table 16). The company reported in the CS that [redacted](HR [redacted], 95% CI [redacted]; p=[redacted]) (refer to CS, Document B, Figure 7).

In the label population, participants in the finerenone plus BT group also had a significantly lower risk of a key secondary outcome event (death from cardiovascular causes, non-fatal myocardial infarction, non-fatal stroke, or hospitalisation for heart failure), which occurred in [redacted]patients ([redacted]%) in the finerenone plus BT group and [redacted]patients ([redacted]%) in the placebo plus BT group (hazard ratio [redacted]; 95% CI, [redacted]; p=[redacted]). Incidence of each component was lower with finerenone plus BT than with placebo plus BT except for [redacted], which had a similar incidence in the two groups and [redacted](Table 17).

Other secondary endpoints

All-cause mortality:

Causes of death were classified into three categories; CV death; renal death; or, non-CV and non-renal death.

In the FAS, death from any cause was lower with finerenone compared to placebo (219 [7.7%] vs 244 [8.6%], respectively) (HR of 0.90, [95% CI 0.75; 1.07], p=[redacted]). The incidence of CV deaths and fatal non-CV or non-renal events was [redacted] with finerenone plus BT than with placebo plus BT [redacted] (Table 16).

Similarly in the label population, death from any cause was lower with finerenone compared to placebo ([redacted] [redacted]%] vs [redacted] [redacted]%], respectively) (HR of [redacted], [95% CI [redacted]], p=[redacted]). The incidence of CV deaths and fatal non-CV or non-renal events were [redacted] with finerenone plus BT than with placebo plus BT [redacted] (Table 17).

Data for CV deaths were used in the economic model. While based on relatively small event numbers, the ERG interpreted this finding to suggest that the cardioprotective effects of finerenone are potentially more pronounced in the patient population not captured within the label population (FAS) (given that removing patients with CKD Stage 1/2 and those patients with eGFR < 25 ml/min/1.73m^2 led to [redacted] the risk of CV death [i.e., the HR increased from 0.86 to [redacted], meaning the risk reduction fell from 14% to [redacted]%]) (Table 16 and Table 17).

Data for renal deaths were used in the economic model. In the FIDELIO-DKD study, there were two renal deaths recorded on the finerenone arm, and two on placebo arm.[17] No HR was reported. From the information provided in the CS, the ERG inferred that the [redacted] (Table 16 [FAS] and Table 17 [label population]).

All-cause hospitalisation:

In the FAS, all-cause hospitalisation consisted of CV hospitalisation, hospitalisation for heart failure, and 'other hospitalisation'. Treatment with finerenone plus BT resulted in a relative risk reduction of [redacted]% compared with placebo plus BT (HR=0.95 [95% CI 0.88; 1.02], p=[redacted]). (Table 16). [redacted] (CS, Document B, Table 22). Results in the label population were similar: treatment with finerenone plus BT resulted in a relative risk reduction of

[redacted]% compared with placebo plus BT (HR=[redacted][95% CI [redacted]], p=[redacted]) (Table 17). [redacted](CS, Document B, Table 23).

Change in UACR from baseline to Month 4:

Finerenone plus BT was associated with a 31% greater reduction in the **urinary albumin-to-creatinine ratio (UACR) from baseline to Month 4** than placebo plus BT (ratio of least-squares mean change from baseline [finerenone plus BT vs. placebo plus BT], 0.69; 95% CI, 0.66 to 0.71) (Table 16), and a lower mean urinary albumin-to-creatinine ratio with finerenone plus BT than with placebo plus BT was maintained thereafter (CS, Document B, Figure 13). [redacted] (Table 17).

Secondary renal composite endpoint: Composite of kidney failure or sustained decrease of ≥57% in the eGFR from baseline, or death from renal causes:

In the FAS, a total of 252 patients (8.9%) who received finerenone plus BT and 326 patients (11.5%) who received placebo plus BT had a **secondary composite kidney outcome event (kidney failure, a sustained decrease of ≥57% in the eGFR from baseline, or death from renal causes)** (hazard ratio, 0.76; 95% CI, 0.65 to 0.90; p=[redacted]) (Table 16). [redacted] (Table 17). As for the primary composite kidney outcome, the[redacted]observed on the composite outcome for finerenone plus BT vs. placebo plus BT [redacted](Table 16 and Table 17, respectively).

Other secondary endpoints

New diagnosis of atrial fibrillation or atrial flutter:

In the FAS, a new diagnosis of atrial fibrillation or atrial flutter occurred less frequently in the finerenone arm (for 82 of 2,593 patients with no known history of atrial fibrillation or flutter, 3.2%) than in the placebo arm (for 117 of 2,620 patients, 4.5%) (odds ratio 0.698, p=0.0146) (Table 16). No data were reported for this outcome for the label population in the CS.

Health-related quality of life:

The Fidelio-DKD trial evaluated quality of life (QoL) using two instruments: the kidney disease quality of life-36 questionnaire (KDQOL-36) and EuroQoL five-dimension five-level (EQ-5D-5L) results were summarised in the CS for the FAS and label populations.

KDQOL-36 data were reported for the FAS and label populations (CS, Document B, Table 28 and Table 30, respectively). Estimates of the treatment differences between finerenone and placebo were calculated for each of the KDQOL-36 domain scores using a mixed model. [redacted]

EQ-5D-5L data were reported for the FAS and label populations (CS, Document B, Table 29 and Table 31, respectively). [redacted] were also seen by the results of EQ-5D-5L summary scores and VAS. Estimates of the treatment differences for changes from baseline to Months 12, 24 and 36 were calculated using a mixed model. EQ-5D-VAS results [redacted].

Table 16. Efficacy result summary (FAS population)

Outcome		Finerenone o.d. + BT N=2,833 (100%)	Placebo o.d. + BT N=2,841 (100%)	Finerenone +BT vs placebo + BT	
				HR (95% CI)	P value
Primary efficacy endpoint					
Primary composite outcome (kidney failure + sustained decrease of at least 40% in eGFR[a] from baseline over a period of ≥4 weeks + renal death)	**Crude incidence n (%)**	**504 (17.8)**	**600 (21.1)**	**0.82 (0.73-0.93)**	**0.001***
	Incidence rate / 100 PYs (95% CI)	**7.59** [redacted]	**9.08** [redacted]		
Key secondary endpoint					
Key secondary composite outcome (CV death + non-fatal MI + non-fatal stroke + hospitalisation for HF)	**Crude incidence n (%)**	**367 (13.0)**	**420 (14.8)**	**0.86 (0.75-0.99)**	**0.03***
	Incidence rate / 100 PYs (95% CI)	**5.11** [redacted]	**5.92** [redacted]		
Other secondary endpoints (in order of sequential hierarchical testing)					
Death from any cause[b]	**Crude incidence n (%)**	**219 (7.7)**	**244 (8.6)**	**0.90 (0.75-1.07)**	[redacted]
	Incidence rate / 100 PYs (95% CI)	**2.90** [redacted]	**3.23** [redacted]		
Fatal non-CV / non-renal[c]	Crude incidence n (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Incidence rate / 100 PYs (95% CI)	[redacted]	[redacted]		
Hospitalisation from any cause	**Crude incidence n (%)**	**1,263 (44.6)**	**1,321 (46.5)**	**0.95 (0.88-1.02)**	[redacted]
	Incidence rate / 100 PYs (95% CI)	**22.56** [redacted]	**23.87** [redacted]		
Change in UACR from baseline to 4 months[d]	**N**	[redacted]	[redacted]	**NA**	**NA**
	LS mean (95% CI)	[redacted]	[redacted]		
Secondary composite kidney outcome (kidney failure or sustained	**Crude incidence n (%)**	**252 (8.9)**	**326 (11.5)**	**0.76 (0.65-0.90)**	**0.001***

Outcome		Finerenone o.d. + BT N=2,833 (100%)	Placebo o.d. + BT N=2,841 (100%)	Finerenone +BT vs placebo + BT	
				HR (95% CI)	P value
decrease in eGFR[a] ≥57% from baseline over at least 4 weeks or renal death)	**Incidence rate / 100 PYs (95% CI)**	**3.64** [redacted]	**4.74** [redacted]		
Other endpoints					
Individual components of the primary and secondary outcomes					
Renal components:					
Kidney failure	Crude incidence n (%)	208 (7.3)	235 (8.3)	0.87 (0.72-1.05)	[redacted]
	Incidence rate / 100 PYs (95% CI)	2.99 [redacted]	3.39 [redacted]		
End stage renal disease	Crude incidence n (%)	119 (4.2)	139 (4.9)	0.86 (0.67-1.1)	[redacted]
	Incidence rate / 100 PYs (95% CI)	1.60 [redacted]	1.87 [redacted]		
Sustained decrease in eGFR[a] <15ml /min/ 1.73 m^2	Crude incidence n (%)	167 (5.9)	199 (7.0)	0.82 (0.67-1.01)	[redacted]
	Incidence rate / 100 PYs (95% CI)	2.40 [redacted]	2.87 [redacted]		
Sustained decrease ≥40% in eGFR[a] from baseline	Crude incidence n (%)	479 (16.9)	577 (20.3)	0.81 (0.72-0.92)	[redacted]
	Incidence rate / 100 PYs (95% CI)	7.21 [redacted]	8.73 [redacted]		
Sustained decrease ≥57% in eGFR[a] from baseline	Crude incidence n (%)	167 (5.9)	245 (8.6)	0.68 (0.55-0.82)	[redacted]
	Incidence rate / 100 PYs (95% CI)	2.41 [redacted]	3.54 [redacted]		
Renal death	Crude incidence n (%)	2 (<0.1)	2 (<0.1)	-	-
	Incidence rate / 100 PYs (95% CI)	-	-		
Cardiovascular components:					
CV death	Crude incidence n (%)	128 (4.5)	150 (5.3)	0.86 (0.68-1.08)	[redacted]
	Incidence rate / 100 PYs (95% CI)	1.69 [redacted]	1.99 [redacted]		
Non-fatal MI	Crude incidence n (%)	70 (2.5)	87 (3.1)	0.80 (0.58-1.09)	[redacted]
	Incidence rate / 100 PYs (95% CI)	0.94 [redacted]	1.17 [redacted]		
Non-fatal stroke	Crude incidence n (%)	90 (3.2)	87 (3.1)	1.03 (0.76-1.38)	[redacted]
	Incidence rate / 100 PYs (95% CI)	1.21 [redacted]	1.18 [redacted]		

Outcome		Finerenone o.d. + BT N=2,833 (100%)	Placebo o.d. + BT N=2,841 (100%)	Finerenone +BT vs placebo + BT	
				HR (95% CI)	P value
Hospitalisation for HF	Crude incidence n (%)	139 (4.9)	162 (5.7)	0.86 (0.68-1.08)	[redacted]
	Incidence rate / 100 PYs (95% CI)	1.89 [redacted]	2.21 [redacted]		
New diagnosis of atrial fibrillation or atrial flutter	Crude incidence n/N[e] (%)	82/2,593 (3.2)	117/2,620 (4.5)	OR 0.698 (NR)	0.0146*

Abbreviations: BT, background therapy; CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; FAS, full analysis set; HF, heart failure; HR, hazard ratio; MI, myocardial infarction; NA, not applicable; NR, not reported; o.d., once daily; OR, odds ratio; PYs, patient years; UACR, urinary albumin to creatinine ratio

Notes:

Refer to Table 14 for definitions used in endpoints

* indicates statistical significance

a For eGFR-based endpoints, consecutive central laboratory measurements of eGFR were necessary. Estimations of GFR were calculated based on the CKD-EPI formula

b Causes of death were classified into three categories: (1) cardiovascular (CV) death (see key secondary endpoint for definition),; (2) renal death (see primary endpoint for definition) or (3) non-CV and non-renal death - all deaths not due to a CV or renal cause. These were categorised as infection, malignancy or other specific causes.

c Non-CV and non-renal death - all deaths not due to a CV or renal cause. These were categorised as infection, malignancy or other specific causes

d Month 4 (closest): is the visit closest to day 120 within a time window of 120 ± 30 days after randomisation. If no measurements were available in this time window, the patient was excluded from this analysis

e n is the number of participants with a new diagnosis of atrial fibrillation or atrial flutter of the total number (N) of participants with no known history of atrial fibrillation or flutter

Table 17. Efficacy result summary (Label population: patients with eGFR ≤25 to <60 and albuminuria at baseline [FAS])

Outcome		Finerenone o.d. + BT N=[redacted] (100%)	Placebo o.d. + BT N=[redacted] (100%)	Finerenone + BT vs placebo + BT	
				HR (95% CI)	P value
Primary efficacy endpoint					
Primary composite outcome (kidney failure + sustained decrease of at least 40% in eGFR[a] from baseline over a period of ≥4 weeks + renal death)	**Crude incidence n (%)**	[redacted]	[redacted]	[redacted]	[redacted]
	Incidence rate / 100 PYs (95% CI)	[redacted]	[redacted]		
Key secondary endpoint					

Outcome		Finerenone o.d. + BT N=[redacted] (100%)	Placebo o.d. + BT N=[redacted] (100%)	Finerenone + BT vs placebo + BT	
				HR (95% CI)	P value
Key secondary composite outcome (CV death + non-fatal MI + non-fatal stroke + hospitalisation for HF)	**Crude incidence n (%)**	[redacted]	[redacted]	[redacted]	[redacted]
	Incidence rate / 100 PYs (95% CI)	[redacted]	[redacted]		
Other secondary endpoints (in order of sequential hierarchical testing)					
Death from any cause[b]	**Crude incidence n (%)**	[redacted]	[redacted]	[redacted]	[redacted]
	Incidence rate / 100 PYs (95% CI)	[redacted]	[redacted]		
Fatal non-CV / non-renal[c]	Crude incidence n (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Incidence rate / 100 PYs (95% CI)	[redacted]	[redacted]		
Hospitalisation from any cause	**Crude incidence n (%)**	[redacted]	[redacted]	[redacted]	[redacted]
	Incidence rate / 100 PYs (95% CI)	[redacted]	[redacted]		
Change in UACR from baseline to 4 months[d]	**N**	[redacted]	[redacted]	**NA**	**NA**
	LS mean (95% CI)	[redacted]	[redacted]		
Secondary composite kidney outcome (kidney failure or sustained decrease in eGFR[a] ≥57% from baseline over at least 4 weeks or renal death)	**Crude incidence n (%)**	[redacted]	[redacted]	[redacted]	[redacted]
	Incidence rate / 100 PYs (95% CI)	[redacted]	[redacted]		
Other endpoints					
Individual components of the composite primary and secondary outcomes					
Renal components:					
Kidney failure	Crude incidence n (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Incidence rate / 100 PYs (95% CI)	[redacted]	[redacted]		
End stage renal disease	Crude incidence n (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Incidence rate / 100 PYs (95% CI)	[redacted]	[redacted]		
	Crude incidence n (%)	[redacted]	[redacted]	[redacted]	[redacted]

Outcome		Finerenone o.d. + BT N=[redacted] (100%)	Placebo o.d. + BT N=[redacted] (100%)	Finerenone + BT vs placebo + BT	
				HR (95% CI)	P value
Sustained decrease in eGFR[a] <15ml /min/ 1.73m^2	Incidence rate / 100 PYs (95% CI)	[redacted]	[redacted]		
Sustained decrease ≥ 40% in eGFR[a] from baseline	Crude incidence n (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Incidence rate / 100 PYs (95% CI)	[redacted]	[redacted]		
Sustained decrease ≥ 57% in eGFR[a] from baseline	Crude incidence n (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Incidence rate / 100 PYs (95% CI)	[redacted]	[redacted]		
Renal death	Crude incidence n (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Incidence rate / 100 PYs (95% CI)	[redacted]	[redacted]		
Cardiovascular components:					
CV death	Crude incidence n (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Incidence rate / 100 PYs (95% CI)	[redacted]	[redacted]		
Non-fatal MI	Crude incidence n (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Incidence rate / 100 PYs (95% CI)	[redacted]	[redacted]		
Non-fatal stroke	Crude incidence n (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Incidence rate / 100 PYs (95% CI)	[redacted]	[redacted]		
Hospitalisation for HF	Crude incidence n (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Incidence rate / 100 PYs (95% CI)	[redacted]	[redacted]		
New diagnosis of atrial fibrillation or atrial flutter	Crude incidence n/N[e] (%)	NR	NR	NR	NR

Abbreviations: BT, background therapy; CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; FAS, full analysis set; HF, heart failure; HR, hazard ratio; MI, myocardial infarction; NA, not applicable; NR, not reported; o.d., once daily; PYs, patient years; UACR, urinary albumin to creatinine ratio

Notes:

Refer to Table 14 for definitions used in endpoints

* indicates statistical significance

a For eGFR-based endpoints, consecutive central laboratory measurements of eGFR were necessary. Estimations of GFR were calculated based on the CKD-EPI formula

b Causes of death were classified into three categories: (1) cardiovascular (CV) death (see Table 14 for definition); (2) renal death (see Table 14 for definition) or (3) non-CV and non-renal death - all deaths not due to a CV or renal cause, these were categorised as infection, malignancy or other specific causes.

c Non-CV and non-renal death - all deaths not due to a CV or renal cause (refer to Table 14 for definition), these were categorised as infection, malignancy or other specific causes

d Month 4 (closest): is the visit closest to day 120 within a time window of 120 ± 30 days after randomisation. If no measurements were available in this time window, the patient was excluded from this analysis

e n is the number of participants with a new diagnosis of atrial fibrillation or atrial flutter of the total number (N) of participants with no known history of atrial fibrillation or flutter

3.2.3.2. Subgroup analyses

The company noted 44 pre-specified subgroups, of which the key groups were:

- Region (North America, Latin America, Europe, Asia, Others)
- eGFR category at screening (eGFR 25 to <45, 45 to <60, ≥60 mL/min/1.73 m^2)
- Type of albuminuria at screening (high albuminuria, very high albuminuria).
- History of CV disease (present [i.e. coronary artery disease, MI, ischaemic stroke, peripheral arterial occlusive disease or carotid endarterectomy recorded on the medical history electronic case report form page], absent)
- Sex (male, female)
- Race (white, black, Asian, other)
- Age at run-in visit (<65, ≥65 years)
- eGFR category at baseline (eGFR <25, 25 to <45, 45 to <60 and ≥60 mL/min/1.73 m^2)
- Type of albuminuria at baseline (normalbuminuria [UACR <30 mg/g], high albuminuria, very high albuminuria)
- Baseline serum potassium value (≤ median and > median in the FAS)
- UACR at baseline (≤ median and > median in the FAS)
- Systolic blood pressure at baseline (≤ median and > median in the FAS)
- Baseline BMI (<30, ≥30 kg/m^2)
- Haemoglobin A1C (≤7.5% / >7.5%)
- SGLT-2 inhibitors treatment at baseline (yes, no)
- GLP-1 agonists treatment at baseline (yes, no).

Appendix E of the CS indicates that subgroup analyses of both the primary and secondary endpoints returned consistent results across a range of demographic and baseline characteristics groups. Specifically, Appendix E states that estimates for the primary renal

composite outcome from the subgroup analyses were in line with those reported for the overall population. In those subgroups where secondary outcomes are reported within Appendix E, [redacted].

Although no subgroups were specified in the NICE final scope, subgroup analysis by SGLT-2i treatment at baseline (yes/no) was of particular interest as discussed in Section 2.4.3. The ERG noted that in the subgroup of participants receiving SGLT-2i, finerenone had no effect on the primary outcome compared with those participants not receiving SGLT-2i in which a reduction in the primary outcome was observed (Table 18). The company noted in Appendix E of the CS that "*because of the low number of clinical endpoint events in the small subgroups of patients taking SGLT-2is …, as evidenced by the wide confidence intervals seen for these subgroups, no meaningful conclusions can be drawn from subgroup time-to-event efficacy endpoint analyses.*" The company did not report results for secondary outcomes for the subgroup and as such it was not possible to comment further on the impact of SGLT-2i use at baseline.

Table 18. Primary composite renal outcome according to prespecified subgroup SGLT-2i at baseline

SGLT-2i at baseline	Finerenone + BT	Placebo + BT		
	n/N (n/100 p-yrs)	n/N (n/100 p-yrs)	HR (95% CI)	p value
No	490/2709 (7.73)	590/2706 (9.39)	0.82 (0.72, 0.92)	0.2114
Yes	14/124 (4.66)	10/135 (3.07)	1.38 (0.61, 3.10)	

Abbreviations: BT, background therapy; CI, confidence interval; HR, hazard ratio; p-yrs, patient years

Source: CS, Appendix E

3.2.3.3. Adverse effects

Adverse events (AE) data were taken from the FIDELIO-DKD study. The safety analysis set (SAF) comprised all participants randomised without critical GCP violations who had received at least one dose of finerenone or placebo (n=5,658: n=2,827 finereone and n=2,831 placebo). No safety data were provided for the label population in the CS.

The incidence of adverse events (AEs) and of treatment-emergent adverse events (TEAEs) that occurred during the treatment period was similar in the finerenone plus BT and placebo plus BT groups (Table 19). The incidence of TEAEs that led to permanent study treatment discontinuation was higher in the finerenone plus BT arm than for placebo plus BT (7.3 vs 5.9%), the difference mainly driven by hyperkalaemia events (2.3% and 0.9%, respectively). Serious TEAE occurred in

31.9% of the patients in the finerenone plus BT group and 34.3% of those in the placebo group (Table 19). The incidence of serious drug-related TEAEs and of serious TEAEs leading to discontinuation of study drug were similar in both arms (Table 19).

Table 19. Overall summary of the number of participants with AEs (SAF)

	Finerenone o.d. + BT N=2827 (100%)	**Placebo o.d. + BT N=2831 (100%)**
Any AE	[redacted]	[redacted]
Any TEAE*	**2468 (87.3%)**	**2478 (87.5%)**
Drug-related TEAE	646 (22.9%)	449 (15.9%)
TEAE leading to discontinuation of study drug	207 (7.3%)	168 (5.9%)
Any Serious TEAE	**902 (31.9%)**	**971 (34.3%)**
Serious drug-related TEAE	48 (1.7%)	34 (1.2%)
Serious TEAE leading to discontinuation of study drug	75 (2.7%)	78 (2.8%)
TEAE resulting in death (excluding efficacy outcome events)	[redacted]	[redacted]

Abbreviations: AE, adverse event; BT, background therapy; o.d., once daily; SAF, safety analysis set; TEAE, treatment-emergent adverse event

Notes: * AEs that occurred during the treatment period, defined as those that started or worsened during finerenone or placebo intake or up to 3 days after any temporary or permanent interruption. A causal relationship between any adverse event and administration of finerenone or placebo was based on the opinion of the reporting investigator

Of the commonly reported treatment-emergent adverse events (TEAEs) (≥5% of participants), hyperkalaemia (15.8% finerenone + BT vs. 7.8% placebo + BT) and decreased GFR (6.3% vs. 4.7%) were more frequently reported in the finerenone plus BT arm than in the placebo plus BT arm. The following commonly reported TEAEs were more frequently reported in the placebo plus BT arm than in the finerenone plus BT arm: peripheral oedema (10.7% placebo + BT vs. 6.6% finerenone + BT), hypertension (9.6% placebo + BT vs. 7.5% finerenone + BT), hypoglycaemia (6.9% placebo + BT vs. 5.3% finerenone + BT), pneumonia (6.4% placebo + BT vs. 4.5% finerenone + BT), and constipation (5.8% placebo + BT vs. 4.6% finerenone + BT). Refer to Table 33 of the CS (Document B) for summary of frequent AEs occurring in ≥5% of participants.

The occurrence of drug-related TEAEs were higher in the finerenone plus BT arm (22.9%) compared with the placebo plus BT arm (15.9%). This was mostly driven by the higher number of patients reported with study drug-related hyperkalaemia / blood potassium increased TEAEs (11.8 vs 4.8% for finerenone plus BT vs placebo plus BT, respectively). No fatal drug-related TEAEs were reported. A lower incidence of treatment-emergent serious adverse events

(TESAEs) was observed in the finerenone plus BT arm compared with the placebo plus BT arm of the study (31.9 vs 34.3%). The most frequent TESAEs in both treatment arms were [redacted]([redacted]% finerenone + BT vs [redacted]% placebo + BT) and [redacted] ([redacted]vs [redacted]%). Drug-related TESAEs were low in both groups (overall 1.7 vs 1.2%, finerenone + BT vs placebo + BT, respectively), the most common of these being [redacted]([redacted]vs [redacted]%, finerenone + BT vs placebo + BT, respectively) and [redacted]([redacted]vs [redacted]%, finerenone + BT vs placebo + BT, respectively).

AEs of interest included disease risk factors not specifically measured by efficacy outcomes, and those potentially related to the mode of action of MR antagonism (e.g. hyperkalaemia, hypotension, hyponatraemia). Overall hyperkalemia-related AEs were twice as frequent with finerenone plus BT as with placebo plus BT (18.3% and 9.0%, respectively), and the frequency of hyperkalemia leading to discontinuation of the trial regimen was also higher with finerenone plus BT (2.3% and 0.9, finerenone + BT vs placebo + BT, respectively). No fatal hyperkalemia events were reported. The company reported in the CS that most treatment-emergent hyperkalaemia events were [redacted]. The company noted hyperkalemia to be an inherent risk associated with the population due to their underlying disease (as serum potassium tends to increase with decreasing eGFR) and background standard of care therapy (ACE-i/ARB), and also noted that hyperkalaemia is associated with the mode of action of finerenone and mineralocorticoid receptor antagonism.

Table 20. Incidence of hyperkalemia (FIDELIO-DKD)

Characteristic[a]	Finerenone o.d. + BT	Placebo o.d. + BT
Potassium binder use at baseline	70 (2.5%)	66 (2.3%)
Potassium binder use through the trial	307 (10.8%)	184 (6.5%)
Investigator-reported hyperkalemia	516 (18.3%)	255 (9%)
Serious hyperkalemia	44 (1.6%)	12 (0.4%)
Hospitalisation owing to hyperkalemia	40 (1.4%)	8 (0.3%)
Discontinuation owing to hyperkalemia	65 (2.3%)	25 (0.9%)
Development of end-stage kidney disease[b]	119 (4.2%)	139 (4.9%)

Abbreviations: BT, background therapy; o.d., once daily

Notes:

a Numbers as reported based on the trial outcome definitions; see Bakris et al[17] for details.

b Presented to contrast magnitude of small absolute benefit against the similar or higher absolute risk of hyperkalemia events.

Source: CS, Document B, Section B.2.10, p.101) (cells highlighted in grey); Waitzman et al. 2021 (comment identified by the ERG from a keyword search, unable to verify for CSR presented for information)[22]

Hypokalaemia was less common among patients who received finerenone than among those who received placebo (1.0% and 2.2%, respectively). Worsening renal function and acute kidney injury-related AEs and SAEs were balanced between the two groups (CS, Document B, Table 34). Finerenone had modest effects on blood pressure: the changes in mean systolic blood pressure from baseline to Month 1 and to Month 12 were −3.0 and −2.1 mmHg, respectively, with finerenone and −0.1 and 0.9 mmHg, respectively, with placebo. [redacted].

The incidence of TEAEs that led to permanent study treatment discontinuation was higher in the finerenone arm than for placebo (7.3 vs 5.9%), the difference mainly driven by hyperkalaemia events (2.3% and 0.9%, respectively).

Overall, the data indicated that finerenone plus BT was well-tolerated in patients with advanced CKD and T2D. The main risk observed with finerenone in FIDELIO-DKD was hyperkalaemia.

3.2.4. Ongoing studies

In the CS the company provided details of one other Phase 3 trial of finerenone in CKD and T2D: FIGARO (NCT02545049). FIGARO is a randomised, double-blind, placebo-controlled, parallel-group, multicentre, event-driven trial designed to evaluate the efficacy and safety of finerenone in reducing cardiovascular morbidity and mortality in addition to standard of care. Aside of the difference in primary and secondary endpoints, the FIGARO study allowed for the inclusion of participants with earlier stage CKD. The company noted that full data were not yet available from this study. From scrutiny of the NCT record, the ERG noted the recent full-text publication of FIGARO data: Pitt et al. (2021);[23] however, given the date parameters of the company's systematic literature review the ERG does not consider this to be an oversight.

3.3. Critique of the indirect comparison and/or multiple treatment comparison

No indirect comparisons or multiple treatment comparisons were conducted.

No comparison of finerenone with SGLT-2i (as class or any particular SGLT-2i) was presented in the CS. Given the absence of direct trial evidence, comparison between finerenone and SGLT-2i would have required an indirect comparison. The ERG noted a systematic literature review had been conducted as part of the NICE guidelines review. The ERG acknowledged that comparability between SGLT-2i trials might be limited due to differences in study populations,

and the definition of endpoints, but this would not preclude a formal feasibility assessment and conduct of an indirect comparison with acknowledgment of such limitations.

When considering the estimand for any subsequent comparison, it is important to identify if finerenone is positioned as an add-on to background therapy that would include SGLT-2i, or as an alternative to SGLT-2i. This is an area of clinical ambiguity that remains. The ERG describes the role of SGLT-2i thusly as either 'background therapy' or as 'alternative'. This distinction is also important given that SGLT-2i were not proscribed in FIDELIO-DKD.

In the event that SGLT-2i are considered background therapy, there is possibly little need for an indirect comparison, as previous trials' background therapy would not have included SGLT-2i and indeed SGLT-2i are not unto themselves a comparator to finerenone. However, in this case, the relevant analysis is to consider the subgroup of FIDELIO-DKD that received SGLT-2i at baseline, inspect the resultant subgroup for similarity on baseline characteristics, undertake any matching or reweighting necessary, and present this analysis as potentially more representative of the current and future UK clinical practice. An obvious weakness for this analysis would be the small sample size as compared to the wider trial.

If that SGLT-2i are considered an alternative, a similar analysis would need to be undertaken for FIDELIO-DKD *excluding* patients receiving SGLT-2i at baseline. Resultant treatment effects could then be used in an indirect treatment comparison. An important challenge to this approach is that composite endpoints are systematically different between trials, meaning that those endpoints that are likely to be best evidenced in individual trials may not be directly comparable. However, it is possible, if not likely, that a feasibility assessment would identify enough overlap on reported outcomes (including components of composite outcomes) to generate meaningful and usable estimates of the effectiveness of finerenone as compared to SGLT-2i. Relevant trials that could inform such an assessment as included in the NICE guideline review are reported in Table 21, the majority of which were identified in the company's SLR (abstract or full text).

Table 21. Summary of available evidence SGLT-2i and finerenone

Trial, author, year, sample size	Population	Baseline eGFR and ACR (mean/median/n%)	Intervention	Comparator	Outcome
Finerenone vs placebo					
FIDELIO-DKD (Bakris 2020)[17] n=5,674	Patients with type 2 diabetes, and CKD with: eGFR **≥**25-<75 ml/min per 1.73 m^2 + ACR (A3 ≥***3***3.9–≤565 mg/mmol) eGFR 25 <60 ml/min per 1.73 m^2 + history of diabetic ***retion***opathy + ACR (A2 and A3 ≥3.4-33.9 mg/mmol)	Mean eGFR: 44.3 (±12.6) Median ACR 852 (IQR 446-1,634) mg/g	Finerenone + standard care Patients with an eGFR of 25 to less than 60 ml/min per 1.73 m^2 at the screening visit received an initial dose of 10 mg once daily, and those with an eGFR of 60 ml/min per 1.73 m^2 or more at the screening visit received an initial dose of 20 mg once daily	Placebo + standard care	Renal composite – kidney failure (end stage kidney disease or eGFR **<**15 ml/min/1.73 m^2), sustained decrease of at least 40% in eGFR from baseline, or renal death Cardiovascular composite – CV death, non-fatal MI, non-fatal stroke, hospitalization for heart failure All-cause mortality All-cause hospitalisation Change in ACR from baseline to Month 4 Renal composite – sustained decrease of at least 57% in eGFR from baseline maintained for at least 4 weeks or death from renal causes ***New diagnosis of atrial fibrillation or flutter***

Trial, author, year, sample size	Population	Baseline eGFR and ACR (mean/median/n%)	Intervention	Comparator	Outcome
					Safety HRQoL Individual components of the primary and secondary outcomes
FIDELIO-DKD label population (Bakris 2020)[17] n=4,860	Patients with type 2 diabetes, and CKD with: eGFR ≥25-<60 ml/min per 1.73 m^2 + albuminuria at baseline (ACR ≥3.4 ***to*** **≤**565 mg/mmol)	Mean eGFR [redacted] (finerenone) and [redacted](placebo) Median ACR [redacted] (finerenone) [redacted](placebo)	[redacted]	[redacted]	[redacted]
SGLT-2i vs placebo (as reported in the evidence report for the NICE guideline review)[14]					
Subgroup of VERTIS CV (Cherney 2021)[24] n=1807	Adults with Type 2 Diabetes and CKD with eGFR 30-60 or ACR A2 and A3	CKD stage 3 subgroup: Mean eGFR 48.9 ml/min/1.73 m^2 Median ACR 3.5 mg/mmol	Ertugliflozin 5 or 15 mg + existing therapy at study entry	Placebo + existing therapy at study entry	Renal composite - doubling of baseline serum creatinine, kidney dialysis/transplant or renal death eGFR >2 years Percentage change from baseline ACR at last available data point
Subgroup of CANVAS (Neuen 2019)[25] N=2039	Adults with Type 2 Diabetes and CKD with eGFR 30-60 or ACR A2 and A3	Subgroup eGFR 30-60: Mean eGFR 49.1 ml/min/1.73 m^2 Median ACR 2.4 mg/mmol	Canagliflozin 100 mg	Placebo	Renal composite – 40% decrease in eGFR or doubling of baseline serum creatinine, kidney dialysis/transplant or renal death

Trial, author, year, sample size	Population	Baseline eGFR and ACR (mean/median/n%)	Intervention	Comparator	Outcome
					CV composite – CV death, nonfatal MI, nonfatal stroke CV death Fatal/non-fatal MI Fatal/non-fatal stroke Hospitalisation for heart failure eGFR >2 years Amputation Fracture Acute Kidney Injury
CREDENCE (Perkovic 2019)[26] (n=4401)	Adults with Type 2 Diabetes CKD and eGFR 30-90 and ACR A3	Mean eGFR 56.2 ml/min/1.73 m^2 Mean ACR 104.8 mg/mmol	Canagliflozin 100 mg	Placebo	Renal composite - doubling of baseline serum creatinine, kidney dialysis/transplant or renal death CV composite All-cause mortality CV death Hospitalisation for heart failure End stage kidney disease Doubling serum creatinine Dialysis Diabetic ketoacidosis Amputation

Trial, author, year, sample size	Population	Baseline eGFR and ACR (mean/median/n%)	Intervention	Comparator	Outcome
					Fracture Acute Kidney Injury eGFR 6 months
Subgroup of DAPA-CKD (Wheeler 2021)[27] N=4304	Adults with Type 2 Diabetes and CKD with eGFR 25-75	Mean eGFR 43.8 ml/min/1.73 m^2 Median ACR 114.64 mg/mmol	Dapagliflozin (10 mg)	Placebo	All-cause mortality Cardiovascular death End stage kidney disease eGFR reduction >50% Diabetic ketoacidosis Fracture Hypoglycaemia
Subgroup of DECLARETIMI (Wiviott 2019)[28] N=1265	Adults with Type 2 Diabetes and CKD with eGFR	Mean eGFR 51.4 ml/min/1.73 m^2 ACR not measured at baseline for all patients	Dapagliflozin (10 mg)	Placebo	eGFR 6 months CV composite (as above) eGFR >2 years
DELIGHT (Pollock 2019)[29] N=293	Adults with Type 2 Diabetes and CKD with eGFR 20-80 or ACR A3	Mean eGFR 49.0 ml/min/1.73 m^2 Median ACR 29.8 mg/mmol	Dapagliflozin (10 mg)	Placebo	Percentage change from baseline ACR 6 months Diabetic ketoacidosis Amputation Fracture Hypoglycaemia Genitourinary infection
DERIVE (Fioretto 2018)[30] N=321	Adults with Type 2 Diabetes and CKD with eGFR 45-60	Mean eGFR 53.5ml/min/1.73 m^2 Median ACR 2.97 mg/mmol	Dapagliflozin (10 mg)	Placebo	eGFR 6 months Diabetic ketoacidosis Fracture Hypoglycaemia

Trial, author, year, sample size	Population	Baseline eGFR and ACR (mean/median/n%)	Intervention	Comparator	Outcome
					Genitourinary infection
Subgroup of EMPA-REG (Wanner 2018)[31] (N=2250)	Adults with Type 2 Diabetes and CKD with eGFR 30-60 or ACR A1&A2, A3	Subgroup eGFR 30-60: Mean eGFR 54.4 ml/min/1.73 m^2 A1 = 37.7% A2 = 27.35% A3 = 34.3	Empagliflozin 10 mg	Placebo	CV composite (as above) All-cause mortality CV death Hospitalisation for heart failure Fatal/non-fatal MI Fatal/non-fatal stroke
VERTIS RENAL (Grunberger 2018)[32] n=467	Adults with Type 2 Diabetes and CKD with eGFR 30-60	Mean eGFR 46.6 ml/min/1.73 m^2 ACR not reported at baseline	Ertugliflozin 5 mg and 15 mg	Placebo	eGFR 6 months Hypoglycaemia Genitourinary infection
YALE 2013/14[33,34] n=269	Adults with Type 2 Diabetes and CKD with eGFR 30-50	eGFR 39.9 ml/min/1.73 m2 Mean ACR 30.6 mg/mmol	Canagliflozin 100/300 mg	Placebo	eGFR 6 months Genitourinary infection

Abbreviations: ACR, albumin creatinine ratio; CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; IQR, interquartile range; MI, myocardial infarction; SLR, systematic literature review

Notes:

a Check performed by ERG on primary references cited

The ERG did not undertake a formal feasibility assessment as the ERG did not have access to the relevant individual patient data from FIDELIO; in addition, due to time constraints, the ERG was unable to consider each possible trial e.g. as part of a systematic review and meta-analysis.

3.3.1.1. Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

Not applicable.

3.3.1.2. Critique of the indirect comparison and/or multiple treatment comparison

Not applicable.

3.4. Additional work on clinical effectiveness undertaken by the ERG

No additional work on clinical effectiveness was undertaken by the ERG.

3.5. Conclusions of the clinical effectiveness section

The ERG considered that the company had identified all relevant clinical evidence for this appraisal with respect to the comparison with one of the scoped comparators: established clinical management without finerenone, alone or in combination with angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers or direct renin inhibitors. All key outcomes from the NICE final scope[1] were covered in the CS. Requisite information regarding the methodology and outcomes for clinical effectiveness was available in the CS and clarification responses provided by the company, and was generally reasonably described.

The company submission focuses on an analysis from one trial: the FIDELIO-DKD trial. FIDELIO-DKD is a good quality randomised controlled trial. The ERG has no concerns with the trials design and the trial methods. While the company focuses on a subgroup of the trial population, the subgroup makes up 85% of the trial population. FIDELIO-DKD compared finerenone with BT against placebo with BT. The population in the CS was limited to focus on the proposed label population, specifically patients who met other inclusion criteria but with eGFR ≥25 to <60 (reflecting Stage 3 to “fitter” Stage 4 patients [it is anticipated that eGFR <25 will not be included in the licence due to lack of clinical data; however, this is not yet clear]). Thus, the population in the CS is not the same as the population specified in the NICE final scope. When considered in the context of the decision problem, it is unclear how the label population generalises to the scoped population. This generalisability is a key issue.

In the label population, finerenone showed [redacted] benefits on the primary outcome (composite of onset of kidney failure, a sustained decrease of eGFR ≥40% from baseline over at least four weeks, or renal death) and key secondary outcome (composite of onset of death from cardiovascular causes, non-fatal myocardial infarction, non-fatal stroke, or hospitalisation for heart failure), [redacted]. It is important to note that when the primary outcome was disaggregated, [redacted], sustained decrease ≥ 40% in eGFR from baseline. Moreover, the definition of outcomes, specifically the use of sustained decrease in eGFR of ≥40%, precludes a clear view of the clinical relevance of effects demonstrated.

A final key issue arose in the consideration of SGLT-2i as a comparator intervention in the CS. The company asserted that SGLT-2i were not relevant comparators and thus did not seek to undertake an indirect treatment comparisons. The company also claimed that established clinical management plus ACE-i or ARB was the only relevant comparator in the submission due to the fact that SGLT-2i were not established clinical practice. The ERG noted that despite only recent introduction into clinical guidelines, SGLT-2i would almost certainly represent an appropriate comparator for people with CKD and T2D, and noted that while beyond the scope of this report, a feasibility assessment would likely have suggested an opportunity for an indirect comparison of finerenone with SGLT-2i.

4. COST-EFFECTIVENESS

4.1. ERG comment on company's review of cost-effectiveness evidence

This section evaluates the review of cost effectiveness analysis studies. However, the search section (Section 4.1.1) also contains summaries and critiques of other searches related to cost effectiveness presented in the CS. Therefore, Section 4.1.1 includes searches for the cost effectiveness analysis review, measurement and evaluation of health effects as well as for cost and healthcare resource identification, measurement and valuation.

4.1.1. Searches performed for cost-effectiveness studies

Appendix G of the CS details systematic searches of the literature used to identify cost effectiveness evidence, critique is provided in Table 22. Searches and eligibility criteria were appropriate and therefore it is unlikely that relevant studies were missed.

The ERG noted that the dates of the company's literature searches would have precluded the identification of the recent update of the NICE guidance: Type 2 diabetes in adults: management - SGLT2 inhibitors for chronic kidney disease (update);[14,15] however, it acknowledged that it would not have been possible for the company to identify this economic evaluation in time to inform its own model development. Nevertheless, given the limitations with the company's approach to economic evaluation (refer to Section 4.2), the ERG considered it worth highlighting. Owing to the limited timeframe over which the ERG was able to conduct its critique of the CS, the economic analysis conducted for the NICE guideline was not investigated in depth, but the ERG expects elements of the NICE guideline model may have provided a more suitable means of quantifying the overall progression of CKD (including, for example, risk equations for CV events).

Table 22. Summary of ERG's critique of the methods implemented by the company to identify cost-effectiveness evidence

Systematic review step	Section of CS in which methods are reported	ERG assessment of robustness of methods
Searches	Appendix G, Section G1.1	The searches appear broadly appropriate with minor limitations: the Embase search strategy failed to include key subject headings for identifying cost-effectiveness evidence (e.g. EMTREE subject heading for economic evaluation/). However, the searches included multiple databases and

Systematic review step	Section of CS in which methods are reported	ERG assessment of robustness of methods
		sources, and the ERG is satisfied that all relevant evidence has been identified.
Inclusion criteria	Appendix G, Section G1.1	The inclusion criteria are broad and therefore likely to have captured the available evidence.
Screening	Appendix G, Section G1.1	Titles and abstracts were screened by two independent reviewers and disagreements were resolved by consensus or by a third reviewer. Full texts were also screened by the two reviewers and disagreements resolved in the same way.
Data extraction	No information reported in Appendix G	Data extraction was completed but the approach taken was unclear as no information was reported in the methods section.
QA of included studies	Appendix G, Section G3	The methodological quality of included full text publications was assessed using the Drummond 10-point checklist. This meant 66 of the 68 included studies were critically appraised; two were not quality assessed as they reported cost-benefit analysis and not cost-effectiveness or cost-utility analysis.

Abbreviations: CS, Company Submission; ERG, Evidence Review Group; HRQoL, health-related quality of life; QA, quality assessment

Appendix H of the CS details systematic searches of the literature used to identify health-related quality of life evidence, critique is provided in Table 23. Searches and eligibility criteria were appropriate and therefore it is unlikely that relevant studies were missed.

Table 23. Summary of ERG's critique of the methods implemented by the company to identify health related quality of life

Systematic review step	Section of CS in which methods are reported	ERG assessment of robustness of methods
Searches	Appendix H, Section 1.1	The searches appear broadly appropriate and likely to have captured the available evidence.
Inclusion criteria	Appendix H, Section 1.1	The inclusion/exclusion criteria set out in appendix H are appropriate for the decision problem.
Screening	Appendix H, Section 1.2	Titles and abstracts were screened by two independent reviewers and disagreements were resolved by consensus or by a third reviewer. Full texts were also screened by

Systematic review step	Section of CS in which methods are reported	ERG assessment of robustness of methods
		the two reviewers and disagreements resolved in the same way.
Data extraction	Appendix H, Section H1.3	Data on the publication, study design, population and outcomes were extracted. The extraction was then checked by a second reviewer.
QA of included studies	Appendix H, Section H3.1.1	The company conducted QA using the quality assessment (QA) relevance criteria for the NICE reference case.

Abbreviations: CS, Company Submission; ERG, Evidence Review Group; HRQoL, health-related quality of life; QA, quality assessment

Appendix I of the CS details systematic searches of the literature used to identify cost and healthcare resource measurement and valuation evidence, critique is provided in Table 24. Searches and eligibility criteria were appropriate and therefore it is unlikely that relevant studies were missed.

Table 24. Summary of ERG's critique of the methods implemented by the company to identify healthcare resource use and costs

Systematic review step	Section of CS in which methods are reported	ERG assessment of robustness of methods
Searches	Appendix I, section I1.1	The searches appear broadly appropriate; however, the ERG notes the following limitations: database searches were limited to MEDLINE only, and a validated geographic search filter for the UK was not applied.
Inclusion criteria	Appendix I, section I1.1	The inclusion/exclusion criteria set out in appendix I are appropriate for the decision problem.
Screening	Appendix I, section I1.1	Title and abstract screening was generally only carried out by a single reviewer. A second reviewer was only involved where there was uncertainty. It is unclear how the full texts were screened.
Data extraction	No information reported in Appendix I	Data extraction was completed but the approach taken was unclear as no information was reported in the methods section.
QA of included studies	No information reported in Appendix I	No detail provided. It appears that no critical appraisal of the studies was conducted.

Abbreviations: CS, Company Submission; ERG, Evidence Review Group; HRQoL, health-related quality of life; QA, quality assessment

4.2. Summary and critique of company's submitted economic evaluation by the ERG

4.2.1. NICE reference case checklist

Table 25: NICE reference case checklist

Attribute	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	✓ No comment
Perspective on costs	NHS and PSS	✓ No comment
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	× The economic model only presents a comaprison to background therapy (i.e., no comaprison to SGLT-2is provided), and the ERG has substantial concerns with model transitions
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	✓ Lifetime horizon is suitable for decision making within the context of a potentially life-extending therapy
Synthesis of evidence on health effects	Based on systematic review	✓ All utility data used in the model were obtained from analysis of the FIDELIO-DKD study
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	✓ No comment
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	✓ EQ-5D data collected from patients in the FIDELIO-DKD study
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	✓ Standard EQ-5D valuation used for health-state utility values estimated from the FIDELIO-DKD study
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	✓ No comment
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be	✓ No comment

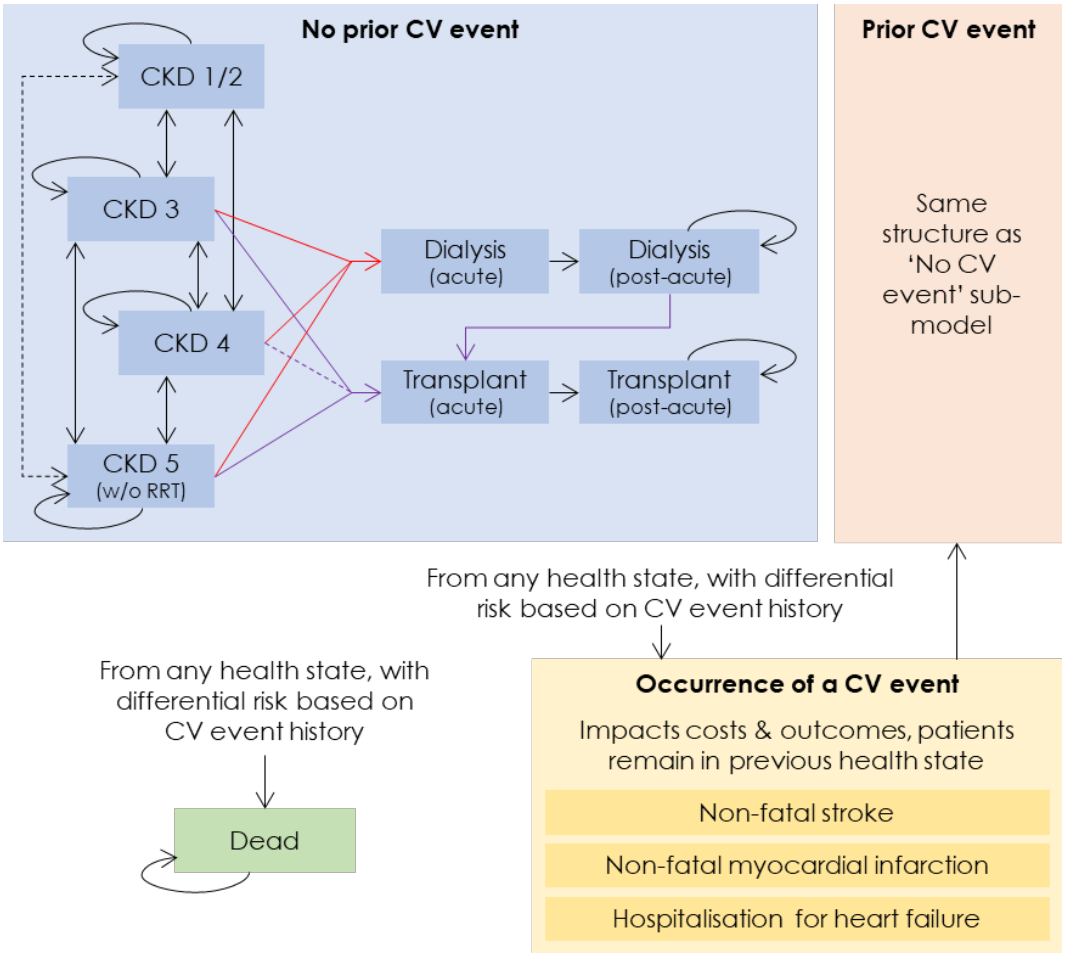
Attribute	Reference case	ERG comment on company's submission
	valued using the prices relevant to the NHS and PSS	
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	✓ No comment

Key: EQ-5D, EuroQol 5 dimension; HRQoL: health-related quality of life; NHS, National Health Service; PSS, Pseronal Social Services; QALY: quality-adjusted life year; TA: technology appraisal

4.2.2. Model structure

The company developed a *de novo*, cohort-level, state-transition Markov model to estimate the cost effectiveness of finerenone + BT versus BT alone in the treatment of adult patients with Stage 3 or 4 CKD with T2DM (limited to data on those patients with an eGFR ≥25 ml/min/1.73m^2, reflecting the anticipated caution in patients with levels below this in the draft SmPC). A schematic of the submitted model was provided in the CS, and a revised version was requested at clarification to illustrate all possible transitions (clarification question B4). However, the ERG identified a number of discrepancies between the company's model structure diagram and the transitions reflected within the company's model, and therefore opted to produce an alternative diagram, shown in Figure 1.

Figure 1: Company's economic model structure



Abbreviations: CV, cardiovascular; RRT, renal replacement therapy; w/o, without.

Note(s): This diagram is a revised version of the original diagram provided by the company in its submission based on a request to confirm which transitions are possible within the model structure. The dashed lines illustrate transitions that are technically permitted within the company's model, but for at least one treatment arm, this transition probability is assigned a value of zero (effectively removing this transition from the model). The red arrows illustrate from which states patients can progress to dialysis. The purple arrows illustrate from which states patients can progress to a kidney transplant.

At baseline, all patients are assumed to have no prior CV event, and so enter the 'No prior CV event' sub-model (the breakdown of patients by CKD stage at baseline is presented in Section 4.2.3). In the FIDELIO-DKD study, patients were excluded if they experienced a number of CV events in the 30 days before screening visit (which included stroke, transient ischaemic cerebral attack, acute coronary syndrome, or hospitalisation for worsening heart failure, see CS Section B.2.3). No exclusion criteria are stipulated for CV events that occurred before this time, and so the ERG considers that it is entirely possible (and indeed expected) that some patients in the FIDELIO-DKD study will have previously experienced at least one CV event. Consequently, the

sub-models inherent within the company's model structure in essence represent CV event history only within the context of the FIDELIO-DKD study, which has important implications for the incorporation of transition probabilities and the risks of events (see Section 4.2.6).

The ERG considers that the overarching model *concept* is suitable to characterise the progressive nature of CKD, along with capturing relevant clinical events (most notably, the occurrence of CV events, initiation of dialysis, and need for kidney transplantation). However, the ERG has substantial concerns regarding the technical implementation of the model, mostly due to a number of simplifying assumptions made. A brief summary of the most critical concerns the ERG has with the model are listed below, with a cross-reference to where each aspect of the model is discussed within greater detail later in the ERG's report:

- Transitions between CKD-based health states are time-invariant and some probabilities appear to lack face validity, which is likely linked to the approach taken to estimate the transition matrices independently by treatment arm (Section 4.2.6.1)
- The risk of a clinically relevant event is also time-invariant within the model (with the exception of the first event being associated with a linear increase in risk as patients age), and these risks are otherwise based only on CKD stage as opposed to a more formal risk equation (Section 4.2.6.2)
- Deaths are estimated separately for those which are CV-related, renal-related, and other-cause related, with the estimation of probabilities of each type of death associated with limitations (Section 4.2.6.3)
- Some utility values are misaligned with the ERG's understanding of the relationship between HRQoL and CKD progression, and the estimation methods suffer from a lack of transparency (Section 4.2.7)

Separately to the considerations specific to the model submitted by the company, the ERG also queried why alternative model structures were not explored by the company to inform its submission. At clarification stage, the ERG asked the company to explain why other modelling approaches were not used to inform its submission, such as specifying risk equations and/or other methods of incorporating a time-varying risk of CV events (clarification question B3). In response, the company explained that the main reason risk equations were not considered was due to the lack of established risk equations in populations with CKD and T2D specifically. The company also explained that applying time-invariant transition probabilities is *"a common*

approach in the modelling of CKD" and cited three previous economic evaluations as supporting evidence.[2,35,36] Taking these in turn:

- Black *et al.*, (2010)[35] developed a cohort model with annual transition and event probabilities estimated from the literature (i.e., the authors of this study did not have access to sufficient individual-level data to estimate time-varying transitions and/or risks)
- Go *et al.*, (2019)[36] estimated the progression of CKD on the basis of the aforementioned study by Black *et al.*, (2010) (i.e., the authors of the Go *et al.* study applied the transition probabilities reported in the study by Black *et al.*)
- Schlackow *et al.*, (2017)[2] state that in the context of their model: *"… the annual risks of* [cardiovascular disease] *and CKD endpoints were estimated using multivariate risk equations with a range of baseline characteristics and time-updated age, time since CKD diagnosis,* [cardiovascular disease] *history (including within-trial events) and CKD status at end of previous year"* (Schlackow *et al.*, 2017, p.1881).[2] Moreover, the transitions cited for CKD status in this study are shown to have been estimated separately for patients aged <65 versus >=65 years in the online supplementary appendix (Table S3)

Based on the explanation provided by the company, and the ERG's understanding of the previous models cited in the company's response, the ERG view remains unchanged – that an alternative modelling approach using time-varying transitions and/or risks is possible to consider within the context of the available individual-level data from the FIDELIO-DKD study. The ERG does not consider the company's choice of model structure (and associated input values, which are described in the remainder of the ERG's report) to form a robust basis for decision making. Nevertheless, in spite of the issues highlighted with the company's model structure, the ERG has proceeded with its critique of the company's model and has explored a range of sensitivity analyses in an attempt to appropriately reflect the inherent uncertainty that has arisen as a direct consequence of the choice of model structure.

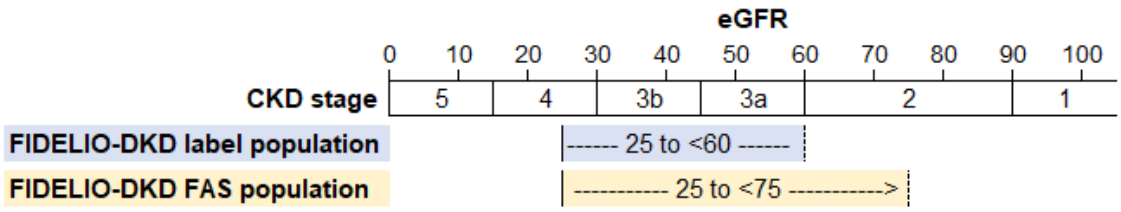
4.2.3. Population

Based on the anticipated marketing authorisation to be granted by the EMA, the company states that finerenone is intended to be indicated for the treatment of adults with CKD ([redacted]) and T2D. Patients enrolled in the FIDELIO-DKD study were required to either have moderately or severely elevated albuminuria (defined as having a urinary albumin-to-creatinine ratio of ≥30-<300 mg/g [moderately elevated] or ≥300-≤5,000 mg/g [severely elevated]).

The company's model base-case analysis is based on a subgroup analysis of approximately 85% of the FIDELIO-DKD study, reflecting the anticipated label population. As described above (Section 2.4.1), patients in this subgroup were required to have 25 ≤ eGFR < 60 at baseline (measured as mL/min/1.73m^2).

In the company's base-case analysis for the label population, all patients enter the model in the CKD3 or CKD4 health states ([redacted] and [redacted], respectively). Figure 2 illustrates the discordance between the cut-offs used in CKD staging versus the FIDELIO-DKD study.

Figure 2: Illustration of relationship between CKD stage and eGFR in the modelled populations



In addition to the label population, the company also presents analyses for the full analysis set (FAS). The FAS population comprises a total of 5,674 patients, versus the label population which considers 4,860 patients (CS Table 11). In the FAS population, the following breakdown of patient by CKD stage is applied within the model:

- **CKD1/2:** [redacted]
- **CKD3:** [redacted]
- **CKD4:** [redacted]

As described in Section 0, patients in FIDELIO-DKD were randomised according to several stratification factors including eGFR category (25-<45, 45-<60, ≥60 mL/min/1.73 m^2), and a number of subgroup analyses were considered including eGFR category. However, the label population was not explicitly pre-specified as a subgroup of interest within the context of the FIDELIO-DKD study, and therefore the study was not designed to specifically evaluate outcomes in this population. The ERG acknowledges however that this subgroup comprises the majority of patients in the study, and that the removal of the 'non-label population' patients does not appear to have led to any major imbalances across treatment groups (based on clinical opinion provided to the ERG).

4.2.4. Interventions and comparators

The intervention reflected in the CS is finerenone, used in combination with background therapy (BT). Finerenone is available in 10mg or 20mg tablets and is administered orally. Finerenone is administered at a starting dose according to eGFR measured at screening visit:

- eGFR ≥25-<60: 10 mg / day ([redacted] of finerenone patients in FIDELIO-DKD [label population])
- eGFR ≥60: 20 mg / day ([redacted] of finerenone patients in FIDELIO-DKD [label population])

It should be noted however that the values above represent the label population from FIDELIO-DKD. In this population, all patients had an eGFR of ≥25-<60, but in the full FIDELIO-DKD study patients could have had an eGFR of greater than 60, less than 25, or a missing value.

The comparator reflected in the company's model is BT alone, described by the company within its submission as *"standard of care established in clinical practice"* (CS Section B.3.2.3) which is assumed to be reflected by the placebo arm of FIDELIO-DKD. Therefore, both treatment arms in the model received BT, and so for simplicity throughout the remainder of the ERG's report the finerenone + BT group is termed the 'finerenone arm', and the placebo + BT group is termed the 'BT alone arm'.

BT comprises a range of different therapies, including ACE-is, ARBs, beta-blockers, diuretics, calcium antagonists, statins, platelet aggregation inhibitors, and glucose-lowering therapies (CS Section B.3.5.1). In the company's model, the distribution of BT was assumed to be represented by the BT used in patients in the FIDELIO-DKD study, assuming no difference in BT use by treatment arm. At clarification stage, the ERG asked the company to confirm the basis on which this assumption was made (clarification question B20). In response, the company explained that the FIDELIO-DKD study was randomised and the distribution of medications was well balanced across the study arms, and so it was considered appropriate to pool BT by arm. The ERG also obtained clinical advice which aligned with the view expressed by the company that BT is likely to be similar by arm, and that the introduction of finerenone is unlikely to affect the type(s) of BT patients would receive in clinical practice.

The final scope issued by NICE included a comparison to SGLT-2 inhibitors, however the company's model does not present this comparison. Accordingly, the remainder of the ERG's

critique of the company's model focuses solely on a comparison to BT alone. Please refer to Section 2.4.3 of the ERG's report for a more detailed discussion of the role of SGLT-2 inhibitors in the management of patients with CKD and T2D.

4.2.5. Perspective, time horizon and discounting

The company's model adopts an NHS and PSS perspective on costs and outcomes, discounted at 3.5% per annum. The model is capable of outputting a range of clinical outcomes, including QALYs and LYs, as well as the number of occurrences of specific clinical events (such as CV events and CV deaths). Overall, the ERG was satisfied that the perspective adopted and discounting applied in company's model are both aligned with the NICE reference case.

The model calculates costs and outcomes over a 'lifetime' horizon, set to [redacted] years in the company's base-case analysis (though this is stated to be 34.4 years in CS, Section B.3.2.2, which the company confirmed at clarification stage was a typographical error, clarification question B5). The value of [redacted] years was based on the mean age of patients in the FIDELIO-DKD study of [redacted] years, meaning that all patients are assumed to have died by the age of 100 years (assuming that the mean age is representative of the cohort). The ERG notes that there is a possibility that for some patients, the lifetime horizon of [redacted] years may be insufficient to capture the full lifetime costs and effects (because of the distribution of age at baseline in the FIDELIO-DKD study). However, the ERG acknowledges that capturing the distribution of age at baseline is unlikely to have a marked effect on cost-effectiveness results. Therefore, the ERG is otherwise satisfied that the choice of time horizon is suitable.

Owing to the selection of a 4-month cycle length, the company included a half-cycle correction (HCC), justified on the basis of the following statement included in the company's submission: *"In order to reduce the difference between real-world and the simulated costs and QALYs, a half-cycle correction is applied in the model"* (CS Secion B.3.2.2). The ERG agrees that an HCC is appropriate in the context of this model, and initially queried the company's choice to apply the HCC to the discounting factor as well as to the health state occupancy at each cycle (clarification question B6). However, the ERG is satisified on the basis of the company's response to this question that the initial application of the HCC is suitable.

4.2.6. Treatment effectiveness and extrapolation

4.2.6.1. Transition probabilities

The company estimated transition probabilities between CKD-based health states using data from the FIDELIO-DKD study. At clarification stage, the company confirmed that the transition probabilities applied in the model were estimated non-parametrically – in other words, that no formal modelling approach was taken, and that the probabilities were estimated on the basis of the observed numbers of patients that resided within each health state across each four-month model cycle (clarification question B7). Also, as part of its response to this question, the company confirmed its approach taken to estimate the specific transition probabilities.

The ERG does not consider this to be the most methodologically robust means of estimating transition probabilities, as it is naïve to a number of issues that arise within the context of estimating transitions in a competing risk setting. These include assumptions related to missing data (the company imputed missing data via last-observation-carried-forward), deaths, drop-outs, and transitions that may have occurred mid-cycle.

The transitions were also determined dependent only on the current stage (i.e., the same transitions are used over time), and the company explained that this *"simplifying assumption was validated with UK clinical experts"* (CS Section 3.3.2). As described earlier within the context of the model structure (see Section 4.2.2), the ERG has concerns that such an approach may oversimplify the estimation of overall disease progression. However, the ERG accepts that the decision to impose time-invariant transition probabilities was made with the intention of simplifying reality.

It is the ERG's view that other approaches could have instead been considered in the context of competing risks. For example, a multi-state modelling (MSM) approach may have instead been suitable, which could also explore the possibility of time-varying transition probabilities. This is especially suitable in the context of a clinical study that recruited over 5,000 patients. An MSM was used to inform decision making as part of HST11[37] (voretigene neparvovec for RPE65-mediated inherited retinal dystrophies) in the context of an RCT of only 29 patients (although the approach taken in this appraisal was subject to criticism in light of the population size).

The company estimated transition probabilities independently by treatment arm (on the basis of the non-parametric approach undertaken). Consequently, the ERG identified a number of

specific aspects of the transition probabilities that appear to lack face validity and/or are subject to uncertainty:

- Patients with CKD1/2 are less likely to progress to CKD4 if treated with finerenone plus BT versus BT ([redacted] versus [redacted]), yet are more likely to progress to CKD3 ([redacted] versus [redacted]) or CKD 5 without RRT ([redacted] versus [redacted])
  - Similar observations apply to other starting health states, primarily affecting relatively uncommon transitions
- As shown in the ERG's model diagram, some transitions are effectively impossible for at least one treatment arm owing to the occurrence of no events to populate such a transition.
  - Examples include:
    - [redacted] to [redacted] for [redacted]
    - [redacted] to [redacted] for [redacted]
    - [redacted] to [redacted] for [redacted]
  - The ERG asked the company to comment on this at clarification stage, at which point the company explained that *"CKD progression is complex when all eGFR fluctuations are to be modelled but we are satisfied that the submitted model reflects clinical practice."*, and that it is *"important that CKD progression is considered based on all possible transitions, not selectively"* (Clarification question B7). The ERG acknowledges the company's point that transitions should be viewed in their totality given the complexity in modelling CKD progression; however, the ERG's view that some transitions appear to lack face validity (when taken in isolation) remains unchanged
- The company assumed that the risk of progression to kidney transplant is the same by treatment arm, and applied the risks in the model on the basis of data from the BT arm only (though no explanation was provided to confirm why a pooled estimate was not used in light of the infrequency of events)

- At clarification stage, the ERG requested that the company provide further information specifically concerning progression to dialysis within the model (clarification question B11)
  - In response, the company provided additional information demonstrating that the number of people who progressed to dialysis was [redacted] in the finerenone arm and [redacted] in the BT arm, and that the majority of progressions to dialysis occurred from patients who were previously in the CKD4 or CKD5 health states in the cycle prior
  - The ERG acknowledges that transitions to dialysis were infrequent over the course of the FIDELIO-DKD study and is otherwise satisfied that the company estimated transitions on the basis of the description provided within its original submission

In summary, the ERG acknowledged and agreed with the company's choice to estimate and apply transition probabilities on the basis of the FIDELIO-DKD study, with the health states specified according to CKD stage. However, the ERG identified a number of issues relating to the choice of analytical approach, which is expected to explain (at least in part) why some of the resultant probabilities appear to lack face validity. Consequently, the ERG questions the reliability of the model for decision making owing to these issues (and other related issues concerning the occurrence of clinically relevant events discussed in the next sub-section).

4.2.6.2. Risk and duration of clinically-relevant events

Outside of health state transitions, the model captures a number of clinically relevant events which are associated with HRQoL and cost impacts. The sub-sections that follow describe how each event is included within the model. The HRQoL and cost impacts are discussed separately, in Sections 4.2.7 and 4.2.8, respectively. For brevity, the values reported in the section refer to the label population only, though each of the risks and HRs referenced change within the company's model if selecting the FAS population.

At clarification stage, the company provided additional explanation concerning the directional effect of each of these HRs (clarification question B8). The company's response to this question is reflected in the ERG's discussion in the sub-sections that follow. It should also be noted that all HRs are applied indefinitely within the company's model for as long as patients continue to receive treatment with finerenone.

First and subsequent CV events

The company's model captures the risk of 'first' and 'subsequent' CV events. As described in Section 4.2.2, the 'first' CV event is defined in relation to study entry as opposed to considering the full event history of a given patient, whereas 'subsequent' CV events are defined as the second, third, fourth, etc. CV events after study entry.

First CV event

The risk of the first CV event was estimated on the basis of recorded CV events that occurred within the FIDELIO-DKD study. The company estimated risks per model cycle (every 4 months) for each CKD-based health state. Finerenone was associated with a HR of [redacted](95% CI: [redacted]) applied to each of these risks (i.e., a reduced risk of a first CV event). A comparison of the risks of CV events by CKD-based health state is presented in Figure 3.

Figure 3: Risk of first CV event in company's model by health state

Abbreviations: CKD, chronic kidney disease; CV, cardiovascular; RRT, renal replacement therapy; w/o, without.

Note(s): Risks assumed to be the same for acute and post-acute dialysis and kidney transplant states. These risks also increase by age, and the values shown in this diagram refer to the risks applied at baseline.

Figure 3 generally shows that as CKD progresses, the risk of a CV event increases. The CS explains that *"only a few patients experienced a CV event after starting dialysis and no CV events were observed in transplanted patients"*, and so *"in the model, it is assumed that the risk of 1st CV event for dialysis patients is the same as for patients CKD 5 without RRT, and for transplanted patients as for CKD 4"* (CS Section B.3.4.1).

As may be inferred from Figure 3, the risk of a CV event in the CKD3 state is lower than the risk of a CV event in CKD1/2. Moreover, the risk of a CV event in the CKD1/2 state is essentially the same as the risk of a CV event in the CKD4 state. This was not immediately clear to the ERG when preparing its clarification questions, but relatedly the ERG noted that a similar issue affects the risk of CV deaths (discussed further in Section 4.2.6.3). At clarification stage, the ERG requested that the company explore an alternative approach to include CV death risks which ensure that risks do not decrease as CKD progresses (clarification question B10). In response, the company provided a scenario wherein the risk of a CV death in CKD3 was set to be equal to the value estimated for CKD1/2, which caused the company's base-case ICER to reduce from £17,552 to £17,394 per QALY gained.

The ERG is concerned that the combination of the company's approach to estimate transition probabilities by arm (as described in Section 4.2.6.1) and the approach to include the effect of finerenone on CV events carries the risk of double counting the potential *"cardioprotective effects of finerenone"* (CS Section B.2.6). This is because the risk of a CV event is captured within the model both as a function of CKD stage (for which, generally speaking, more advanced CKD is associated with a higher risk of a CV event) and an HR attributable to the use of finerenone specifically, yet the HR was estimated across the entirety of the FIDELIO-DKD study period. Therefore, as finerenone is modelled to affect both the rate of CKD progression and the risk of a CV event (which is also linked to CKD progression), the ERG suspects that the reduction in CV events modelled is likely to be an overestimate.

A further concern the ERG has with respect to the application of HRs for the effect of finerenone on CV events is that the same impact is assumed regardless of health state occupancy – in other words, the reduction in the risk of a CV event is the same relative decrement for patients in the CKD1/2 state versus patients currently on dialysis. Owing to the lack of data available to robustly estimate the potential *"cardioprotective effect"* of finerenone in patients that are on dialysis or have had a transplant, the ERG is unclear whether the difference in CV risk for finerenone versus BT would persist once patients progress to these health states.

Another important consideration of CV events within the company's model is that relative effects are applied to obtain the risk for the finerenone arm, whereas transitions are based on observed data for the finerenone group. The company explains within its submission that for CKD progression, *"it was necessary to use patient level data from FIDELIO-DKD trial to obtain transition probabilities reflecting the change of CKD stages and the impact of finerenone"*;

however, for other health outcomes *"it was possible to model clinical benefits of finerenone by using relative measures obtained within the trial applied to the absolute estimates for BT"* (CS Section 3.3.2). The ERG is unclear why the patient-level data for both arms were not used to capture CV events by treatment arm, as it may have been possible to estimate risks in a more formal statistical analysis (e.g., via a regression model which could have included treatment arm as a covariate).

In addition to the risk of the first CV event being based on CKD progression, the company's model also reflects additional risk for the first CV event based on age. To do this, the company cites a study by Wilson *et al.*, (2012)[38] wherein an HR reflecting the increase in risk as patients age is reported (HR=1.03, 95% CI: 1.03-1.04). The company considers this increase in risk to apply after 4 years, though no rationale for this timepoint is provided in the CS. However, the ERG expects that the selection of four years is likely based on the duration of follow-up available from the FIDELIO-DKD study. The ERG considers the approach taken to uplift the risk of a CV event by age to be crude, though acknowledges that within the confines of the company's model structure this likely represents a suitable means of capturing the impact of age on CV event risk.

Subsequent CV events

After the first CV event, patients enter the 'Post CV event' sub-model and are then at risk of one or more subsequent CV events. However, unlike the first CV event, subsequent CV event risk is independent of CKD stage and is applied at a fixed probability of [redacted] per 4-month model cycle. Owing to the difference in risk for a subsequent CV event versus the first CV event, over the course of the model time horizon most CV events estimated by the model are ultimately subsequent CV events, as shown in Figure 4 (which demonstrates the cumulative proportion of CV events modelled over the course of the time horizon according to whether they were first or subsequent events).

Figure 4: Cumulative proportion of CV events by type over the model time horizon

Abbreviations: CV, cardiovascular.

Note(s): This diagram was produced based on the company's submitted model.

From Figure 4, it can be inferred that within the timeframe of the FIDELIO-DKD study (up to 4 years), approximately 70% of the CV events predicted by the model were primary events, and the remaining 30% were secondary CV events. However, by the end of the model time horizon, approximately 41% of all modelled CV events were primary events, and 59% were secondary CV events. The ERG highlights this important aspect of the company's model to illustrate the influence the estimated risk of subsequent CV events has on the modelled ICER. In addition, similar to how the company modelled the relative risk of the first CV event for finerneone versus BT, finerenone was associated with a HR of [redacted](95% CI: [redacted]) applied to the risk of a subsequent CV event.

In summary, the ERG has a number of concerns with the company's application of CV events within its model, and has therefore opted to explore a range of sensitivity analyses to further investigate how alternative assumptions may influence the estimated ICER.

Hyperkalaemia

The company included development of hyperkalaemia (increase in blood potassium) within its model based on its expected impact on HRQoL and costs, as well as an increase in risk associated with finerenone observed in the FIDELIO-DKD study. Hyperkalaemia events were separated according to whether or not they led to hospitalisation (with hospitalised patients

incurring higher costs, but no difference in HRQoL). In the FIDELIO-DKD study, hyperkalaemia was the most frequently observed TEAE with finerenone, occurring in 15.8% of patients in the safety population randomised to finerenone, versus 7.8% of the BT alone arm (CS, Document B, Table 33).

To capture the risk of hyperkalaemia in the model, the company estimated per-cycle risks (i.e., the probability per four-month model cycle) separately according to whether or not patients had history of a CV event. The modelled risks were as follows:

- Hyperkalaemia leading to hospitalisation without CV event history: [redacted]
- Hyperkalaemia leading to hospitalisation with CV event history: [redacted]
- Hyperkalaemia not leading to hospitalisation without CV event history: [redacted]
- Hyperkalaemia not leading to hospitalisation with CV event history: [redacted]

Based on these risks, it can be seen that the company's model assumes: (a) that the risk of being hospitalised is lower than the risk of not being hospitalised, and (b) that the risk of hyperkalaemia is higher for patients with CV event history than those without. In addition, finerenone is associated with a HR for non-hospitalised events of [redacted](95% CI: [redacted]), and for hospitalised events of [redacted](95% CI: [redacted]).

To explore the occurrence of hyperkalaemia per arm within the company's model, the ERG set the cost for hospitalised and non-hospitalised events to £1, and extracted the total undiscounted costs modelled over a lifetime horizon. This yielded a cost of £0.93 for the finerenone arm, versus £0.60 for the BT arm. From this, the ERG inferred that over the lifetime horizon of the model, an average of 0.93 hyp***er***kalaemia events occur for finerenone patients, versus 0.60 for the BT arm. The ERG considered this cost to likely over-estimate the impact of hyperkalaemia, given that extrapolated risks are based on short-term estimates from the FIDELIO-DKD study. Furthermore, it can be inferred from this comparison that the increased risk of hyperkalaemia experienced by the finerenone arm is, to an extent, offset in the longer term as a consequence of the BT arm being subject to a higher risk of CV events.

The HRQoL and cost implications of hyperkalaemia are described separately later in this report. However, for calculating the duration over which the utility impact occurs, the company

assumed that the disutility associated with hyperkalaemia applies over 4 months (i.e., a full model cycle).

Acknowledging the concerns highlighted above, the ERG notes that hyperkalaemia has a limited impact on costs and outcomes, and so has not considered alternative approaches as part of its report.

Sustained decrease in eGFR ≥ 40% from baseline (over at least 4 weeks)

The company included sustained decrease in eGFR ≥ 40% from baseline (over a period of at least 4 weeks) as a clinically relevant event within its model based on its expected impact on HRQoL, that this event is one component of the primary composite endpoint of the FIDELIO-DKD study, and that a statistically significant reduction in risk associated with finerenone observed in the FIDELIO-DKD study.

The ERG accepted that this is an important event from a clinical perspective but noted that this is challenging to appropriately reflect within the context of a cohort-level model in which patients are categorised by health states based on CKD stage. For example, patients could experience this event if they reside within the CKD1/2 state even though at baseline all patients in the label population had a maximum eGFR of 60 (i.e., patients could experience the sustained decrease in eGFR from baseline event even if they are objectively in a health state with a higher eGFR versus baseline by virtue of the definition of the label population). In addition, as for the previous clinical events, finerenone was associated with an HR of [redacted](95% CI: [redacted]) for this outcome, versus BT alone. However, the risk of this event was considered independent of CV event history.

Similar to the inclusion of hyperkalaemia, the ERG notes that sustained decrease in eGFR ≥40% from baseline has a limited impact on costs and outcomes. However, removing this event from the model entirely causes the base-case ICER to increase from £17,551 to £18,001, driven solely by the impact on the incremental QALY gain since this event is associated with no cost (see Section 4.2.8 for further details on modelled costs).

New onset of atrial fibrillation or atrial flutter

The company included new onset of atrial fibrillation or atrial flutter within its model based on its expected impact on HRQoL and costs, as well as a statistically significant reduction in risk associated with finerenone observed in the FIDELIO-DKD study. As reported in CS Section B.2.6, the odds ratio for this outcome in FIDELIO-DKD was 0.698 (p=0.0146).

The four-monthly risk for patients with history of a CV event was [redacted], versus [redacted] for patients without history of a CV event. In addition, finerenone was associated with an HR of [redacted] (95% CI: [redacted]) for this outcome, versus BT alone, though no description of the methods used to derive these estimates is provided within the CS. The ERG could not validate the estimation of the HR for this outcome measure, for either population, nor could it assess the assumption of PH for this outcome. This event has a small impact on modelled costs and outcomes, and so while the ERG has some concerns with the approach taken, alternative scenarios were not considered further within the company's model.

4.2.6.3. Mortality

In the company's model, patients can die from three causes:

- Cardiovascular (CV) death
- Renal death
- Other-cause death

CV and renal deaths were estimated based on data from the FIDELIO-DKD study, whereas other-cause deaths were based on a range of different sources. The company also estimated the difference in the risk of death for each type of death vis the specification of hazard ratios (HRs). The estimation of mortality risks is described in the relevant sub-sections below. As was the case for the risk and duration of clinically relevant events, the values presented in the section below refer to the label population only.

CV deaths

The company explains that the average risk of a CV death per model cycle was estimated based on data from the BT arm of the FIDELIO-DKD study, though limited information was presented concerning the analytical approach taken to estimate these risks. The risks are presented in CS Table 49. The ERG observes that the risks of CV death used in the model suggest a generally increasing risk as disease progresses, which is aligned with published literature (also acknowledged by the company within its submission).[39] However, the risk of CV death for CKD1/2 patients is higher than the risk of CV death for CKD3 patients ([redacted] versus [redacted]).

At clarification, the ERG asked the company to provide a scenario wherein the risk of CV death does not reduce as CKD progresses, and to comment on this aspect of the model in the context of the scenario requested (clarification question B10). In response, the company manually overwrote the value for CKD3 to assume it was equal to the value for CKD1/2 and considered that the requested scenario was *"reasonable and show that the base case model is conservative"* (clarification question B10), which caused the base-case ICER to reduce from £17,552 to £17,394.

The ERG does not agree that the base-case analysis is conservative. It is the ERG's opinion that the estimate of CV death in the CKD1/2 stage is likely based on few patients and few event numbers, and so of the two values, the estimate for CKD3 is likely the more robust of the two. If the value for CKD1/2 is replaced by the value for CKD3, the company's base-case ICER *increases* from £17,552 to £17,745. The ERG considers this latter approach more suitable to inform the model compared with the company's base-case analysis (which does not exhibit face-validity) or the company's scenario analysis (which takes the less robust of the two estimated values).

Due to a paucity of evidence for transplanted patients, the company assumed that the risk of CV death for transplanted patients was the same as those with CKD4 (based on UK clinical expert opinion). Published literature suggests that CV disease is a leading cause of death in renal transplanted patients, and so the ERG agrees with the company's decision to apply a non-zero risk of CV death for transplanted patients.[40,41] While the risk of CV death should be included for transplanted patients, the ERG notes that the risk attributed to this state is based entirely on assumption. Nevertheless, when the base-case value was doubled or halved, the impact on the ICER was negligible (increasing by £20 when the risk was halved and decreasing by £35 when doubled). Therefore, while the ERG has reservations with respect to the most appropriate risk of CV death for renal transplanted patients, given the impact on the ICER (based on relatively few patients modelled to undergo renal transplant) the company's base-case value was considered suitable to inform decision making.

The company's model includes a differential risk of CV death for patients treated with finerenone (for as long as the treatment effect of finerenone is assumed to apply, discussed further in Section 4.2.6.4). The relative effect of finerenone is included within the model via the specification of an HR which applies to each CV death risk. The HR was [redacted]), as reported in CS Table 52, meaning that finerenone was estimated to be associated with a

[redacted]. The ERG acknowledges that the study was not powered to detect a difference in CV mortality between arms, and so to explore the potential *"cardioprotective effects of finerenone"* (CS Section B.2.6), a composite outcome (occurrence of CV death, non-fatal MI, non-fatal stroke, or hospitalisation for heart failure) was considered in the FIDELIO-DKD study.

The ERG highlighted that the HR applied within the model for the label population ([redacted], 95% CI: [redacted], CS Table 52) differs from the HR presented in the context of the composite secondary outcome measure for the FAS population (0.86, 95% CI: 0.68-1.08, CS Table 18 and reported in the forest plot from the main study publication by Bakris *et al.*, 2020).[17] While based on relatively small event numbers, the ERG interprets this finding to suggest that the cardioprotective effects of finerenone are potentially more pronounced in the patient population not captured within the label population (given that removing patients with CKD stage 1/2 led to [redacted]the risk of CV death [i.e., the HR increased from [redacted]to [redacted], meaning the risk reduction fell from [redacted]to [redacted]]).

Renal deaths

The CS stated that *"In the model, according to the definition from the trial, renal death was possible only in the case of patients with eGFR<15 (before RRT)."* (CS Section B.3.3.6). This means that by using the definition of renal death from the FIDELIO-DKD study to populate the company's model, renal death could not occur in any health state other than 'CKD5 without RRT'. The estimated risk of renal death from this state, for the BT arm, was [redacted] per 4-month cycle.

At clarification stage, the ERG asked the company to provide a scenario wherein renal deaths were completely omitted from the model (clarification question B10). After running this scenario, the company's base-case ICER reduced from £17,552 to £17,550 per QALY gained. The ERG acknowledges the small impact this change has on the ICER, but is concerned that omitting renal deaths from the model makes very little difference to the estimated cost effectiveness.

In the FIDELIO-DKD study, there were two renal deaths recorded on the finerenone arm, and two on the BT arm (as reported in the forest plot presented by Bakris *et al.*, 2020).[17] In the forest plot presented by Bakris *et al.*, an HR is not presented, and based on CS Tables 20 and 21 the ERG infers that the four recorded deaths in the FAS population [redacted]. However, the company presented an HR for renal deaths within the context of the cost-effectiveness model for the label population of [redacted](95% CI: [redacted]), suggesting that finerenone is

associated with a [redacted]. The ERG is unclear how this HR was estimated based on information presented for the FIDELIO-DKD study within the CS, especially given the recorded number of deaths in the FAS population precluding the estimation of a robust HR for this outcome.

The ERG does not consider there to be sufficient evidence to support any impact of finerenone on the occurrence of renal deaths, either in terms of an increased or decreased risk, versus BT alone. In addition, renal deaths have a very small impact on cost-effectiveness results based on exploratory analyses conducted by the ERG – setting the HR to unity caused the ICER to increase by 25 pence. Therefore, based on the information presented above, the ERG preferred to assume no difference in renal deaths between treatment arms.

Other-cause deaths

In addition to CV and renal deaths, the company's model also considers death from other causes. A range of sources are combined to estimate mortality risks to inform the model, centred on background mortality rates from the Office for National Statistics (ONS, 2016-18).[42] The company explains however that as CV and renal deaths are captured separately within the model, it is necessary to remove these deaths from the background mortality data to avoid double counting.

To illustrate the approach taken by the company to remove CV and renal deaths from background mortality, consider the following example for a 60-year-old female:

- The annual risk of death is 0.50%
- For females aged between 60-64 years:
  - The proportion of deaths attributable to CV disease is estimated to be 16.7%
  - The proportion of deaths attributable to renal disease is estimated to be 0.2%
- Therefore, the estimated annual risk of death from other causes in the company's model for a 60-year-old female was estimated to be $0.50\% * (1 - 16.7\% - 0.2\%) = 0.41\%$

The ERG acknowledges the intention of this approach to remove deaths that carry the risk of double counting. However, the ERG notes that because renal deaths could only occur in patients in the 'CKD5 without RRT' health state, it is likely that removing renal deaths from other-cause mortality is likely to have led to an overall under-estimate of the number of renal

deaths captured by the company's model (particularly noting the small impact removing renal deaths had on the ICER, as described earlier in this sub-section). The ERG therefore expects it would be more suitable to not remove the double counting of renal deaths from other-cause mortality and remove the estimated risk of renal deaths from the FIDELIO-DKD study from the model (given that the values are estimated based on very few events).

The company's model includes HRs reflecting the expected increased in risk of death from other causes linked to CKD stage, based on a study by Darlington *et al.*, (2021)[43] and the UK Renal Registry Annual Report 2018.[44]

- Darlington *et al.*, (2021) present the findings of a review of CV morbidity, CV mortality or all-cause mortality. The authors performed an analysis of 323 studies to establish the link between several baseline comorbidities, CKD stage, and *all-cause* mortality. For patients with T2D, the following HRs were estimated by the company based on this study:
  - **CKD1/2 (1.14):** Average of 1.00 and 1.27 reported in Table 2 from Darlington *et al.*, (2021)
  - **CKD3 (1.33):** Weighted average of 1.23 and 1.40 reported in Table 2 from Darlington *et al.*, (2021). Weights based on FIDELIO-DKD study (data not reported)
  - **CKD4 (6.42):** As reported in Table 2 from Darlington *et al.*, (2021)
  - **CKD5 w/o RRT (9.49):** As reported in Table 2 from Darlington *et al.*, (2021). Assumed that HR for all CKD5 patients sufficient to represent increased risk in CKD5 w/o RRT
- The UK Renal Registry collects and reports data annually on approximately 70,000 kidney patients on RRT in the UK. The CS cites findings from the 2018 report. More specifically, the company cites data from this report to inform the estimated increase in the risk of death from other causes (i.e., not CV or renal death) for patients on dialysis or after receiving a kidney transplant, versus the general population. The following HRs were estimated by the company based on this report:
  - **Dialysis, acute and post-acute (10.04):** The ERG could not identify or replicate this value based on information presented in this report or the CS

- **Transplant, acute and post-acute (1.55):** The ERG could not identify or replicate this value based on information presented in this report or the CS

The ERG is concerned that the increased risk for death from other causes has been linked to CKD progression, though the studies used to inform the estimated HRs are seemingly based on *all-cause* mortality, not *other-cause* mortality (adjusted to remove the impact of CV and renal deaths). In other words, it is the ERG's understanding that CV and renal deaths are likely to increase as CKD progresses, but it is unclear how much the risk of death may increase for other causes, especially accounting for the fact that age and sex effects are already captured within the specification of background mortality rates based on life tables. Furthermore, the ERG was not able to validate the two HRs attributed to a report from the UK Renal Registry. Consequently, the ERG has major concerns with the application of mortality within the company's model and considers the estimation of mortality estimates within the company's model to be an area of substantial uncertainty.

4.2.6.4. Duration of treatment with finerenone

Based on the ERG's understanding of the anticipated use of finerenone in NHS practice, treatment is expected to be continued indefinitely unless patients discontinue early for any of the following reasons:

- Withdrawal of consent/ patient choice
- Increase in serum potassium to greater than 5.5mmol/L
- Unacceptable toxicity
- Death

In the FIDELIO-DKD study, over the course of four years, [redacted] of patients on the finerenone arm discontinued treatment. In the CS, treatment discontinuation with finerenone is referred to as *"non-persistence"*, however throughout the ERG's report this is referred to as (permanent) treatment discontinuation for consistency with terminology used in previous appraisals conducted by NICE.

In total, the company considers three different approaches to considering discontinuation of finerenone within the model:

1. Discontinuation is not modelled (apart from discontinuation upon death)

2. Disconsolation is considered in terms of costs, with no impact assumed on efficacy
3. Disconsolation is considered in terms of both costs and efficacy, with patients assumed to incur the corresponding costs and effects of the BT arm

The latter of these three options is considered in the base-case analysis, which the ERG considers to be the most appropriate of the three scenarios (and so the remaining two scenarios are not considered further). The ERG acknowledges the company view that the HRs for the potential *"cardioprotective effects"* of finerenone already account for discontinuation (as they are based on an ITT analysis); however, in light of the previous discussion concerning the potential for double counting of these benefits (see Section 4.2.6.2), the ERG is unable to confirm whether or not it is true that the company's base-case approach is conservative in terms of the modelled waning of treatment effect of finerenone in the context of the full model.

In the company's base-case analysis, it is assumed that if patients discontinue finerenone they will continue their BT, which the ERG considers a reasonable approach. In the company's model, [redacted] of patients are assumed to discontinue treatment with finerenone per 4-month model cycle. A comparison of the rate of discontinuation observed in the FIDELIO-DKD study versus the company's model is presented in Figure 5. Based on this plot, it appears as though discontinuation is approximately reasonably well with an exponential model, though by 4 years there are more patients modelled to have discontinued finerenone ([redacted]) versus the observed proportion in the FIDELIO-DKD study ([redacted]).

Figure 5: Rate of discontinuation in FIDELIO-DKD study

Note(s): This diagram was prepared using information provided in the company's model and the company's response to clarification question B9.

The ERG considers it likely that the company's approach to incorporate treatment discontinuation has led to an overestimation of discontinuation given that the company's estimation of the constant risk is naïve to how the model deals with deaths. In other words, discontinuations due to death will be double counted in the company's model because the reasons for discontinuation were not explicitly separated as part of the estimation of the constant rate of discontinuation. The ERG therefore re-calibrated the constant risk of discontinuation to ensure alignment of the estimated proportion still on treatment by 4 years within its corrected base-case analysis.

4.2.7. Health-related quality of life

4.2.7.1. Methodology

Health-related quality of life (HRQoL) data were obtained via the EQ-5D-5L, collected in FIDELIO-DKD. The periodic completion of EQ-5D questionnaires throughout the trial enabled the calculation of utilities for the different health states considered in the model and various health events. Utility values were mapped from the -5L onto the -3L value set using the standard methods of van Hout *et al* (2012),[45] in line with NICE recommendations.

As is often the case in clinical trials, EQ-5D data from FIDELIO-DKD were collected with varying frequency over the duration of follow-up. The CS explained that the FIDELIO-DKD trial was not designed nor powered to make conclusions based on HRQoL, but due to the collection of EQ-5D questionnaires within the study, utility analyses could be conducted. The company considered that utilities derived directly from the FIDELIO-DKD trial for use within the cost-effectiveness model would be preferred over those reported in the literature or derived from other sources. The ERG agrees that use of EQ-5D data from the trial is generally preferred versus other non-trial sources.

To obtain utility values for use within the model, the company performed multivariate regression analyses to estimate utility decrements for various health outcomes and events. These decrements were applied to a mean baseline utility to obtain the utility values for the different health states (see Section 4.2.2 for a summary of the company's model structure)

Within the CS, the utility values presented did not align with those used in the cost-effectiveness model, which was highlighted by the ERG at clarification. The company confirmed that the values used in the model were correct, with those presented in the CS having been taken from an alternative multivariate regression considered by the company; the correct multivariate regression results were provided for clarity (clarification question B15).

At clarification, the ERG asked the company to provide details on the selection methodology used to determine which variables were included within the multivariate regression (clarification question B14). The company confirmed that *"the selection of the variables was made prior to any results being available from FIDELIO-DKD and pre-specified in the HEOR SAP",* but that *"more variables were considered in the multivariate analysis than were needed for the CE model".* The company also provided a list of the variables that were considered within the analysis, however this did not fully align with Table 40 of the CS (highlighted in the company's response) or the results presented in Section B.3.4 of the CS. Further to this, Table 40 of the CS does not clarify what variables were selected for inclusion in the multivariate analysis as it only states which variables were and were not included in the model. Therefore, there is a lack of clarity concerning which variables were used when calculating the parameter estimates, and whether those that were given at clarification were considered in the analysis before being excluded when they were deemed irrelevant, or whether they were simply omitted from the CS as they were not included in the model. It is therefore still unclear to the ERG what selection method the company used for the variables included in the multivariate analysis.

Within the cost-effectiveness model, differences in utility are captured by combining the following three elements:

- Health state utilities based on CKD stage
- Clinically relevant events (CV events, adverse reactions, and other [relevant] health events)
- Age-adjustments

In the company base-case, health state utilities and utility decrements are taken from the trial data; utilities taken from the literature were used to inform sensitivity analyses to explore the impact of the limitations of the FIDELIO-DKD EQ-5D data.

4.2.7.2. Health state utilities based on CKD stage

The company used baseline EQ-5D data, pooled by treatment arm, to estimate the utility of CKD1/2 patients that had not experienced a CV event; the company confirmed at clarification that "*the whole trial population (FAS) was considered for the EQ-5D analysis to attempt to overcome bias due to low number of events and provide utility estimates based on the most complete data"*. Despite this, only approximately 11.6% of patients were CKD 1/2 at baseline, leading to uncertainty in the CKD1/2 health state utility. The ERG considers that without extending the utility analysis to include the full FAS population, it would likely be challenging to estimate a plausible utility for the CKD1/2 state using data from the FIDELIO-DKD study alone.

Utility decrements associated with CKD stages 3, 4, and 5 (as reported in CS Table 57) were then applied to the CKD1/2 baseline utility to obtain utility values for the respective health states without CV events, as confirmed by the company at clarification. These decrements were calculated using multivariate regression analyses in which all EQ-5D were utilised, with CKD1/2 used as the reference group.

Patients with CKD3 were estimated to have an *increase* in utility of 0.001 when compared to CKD1/2; the ERG highlighted this as clinically implausible at clarification, however the company were unable to explain this, commenting only that this was an "*apparent anomaly in the data*". It is likely that this result is due to the small number of patients with CKD1/2 in the FIDELIO-DKD trial, yet the ERG does not consider the resultant utility values to be suitable to populate the model as a result of this flaw in logic.

Once CKD has progressed to a more severe stage, patients can transition to '*Acute Transplant'* or to '*Acute Dialysis'*, and subsequently to the respective post-acute health states. These health states are associated with utility decrements, as calculated in the multivariate regression analysis performed by the company. The utility values for the acute and post-acute health states are implemented separately within the company's model, yet the values for the dialysis states are identical (reflecting the expectation that utility for dialysis is not expected to be a function of the time on dialysis).

Summary

Overall, the ERG agrees with the approach to specify health state utility values based on CKD stage, but is concerned with the face validity of the resultant values.

4.2.7.3. Clinically relevant events

CV events – non-fatal stroke, non-fatal MI, hospitalisation for HF

Within the model structure, patients can transition from *No CV event* to *CV event* for each CKD based health state. To account for the impact of CV events, the company included *prior MI*, *prior stroke*, and *hospitalisation due to HF* in the multivariate analysis to obtain utility decrements. Although individual decrements were obtained from the multivariate regression, a weighted average is used in model. It is unclear to the ERG why the company did not consider combining the three types of CV events for use within the regression analysis as a sensitivity analysis; using a single variable would have utilised more data, leading to less uncertain utility decrements.

The same weighted average utility decrement is used for both the acute and post-acute phases of CV events, due to "*counterintuitive results… observed in the multivariate analysis when the acute and post-acute phases were analysed separately"* (CS Section B.3.4.7). This means that in the model, the utility decrement associated with the post-acute phase following a CV event is applied in the cycle that the event occurred and for all subsequent cycles, regardless of the amount of time that has passed since the CV event was experienced. The ERG believes this approach to be illogical, as the impact of experiencing a CV event will change over time (likely decreasing as patients recover from their CV event). Further to this, different types of CV events may have different recovery times, and so using a weighted average in the model may not fully capture the different lasting effects that MI, stroke, and hospitalisation due to HF have on utility.

When acute CV events were initially considered in the multivariate analysis by the company, they were determined based on the prior 4 months (i.e., where the CV event was experienced within the last 4 months before a given visit). In its original report, the ERG assumed that this was still used to classify prior CV events when acute and post-acute were combined in the analysis. It was therefore unclear to the ERG whether all CV events were captured in the analysis, as it was not specified how much time passes between each visit – for example, if the time difference is larger than 4 months between one visit and the next, would patients be included as having experienced a CV event? If this was not the case, then using the same utility decrement for the post-acute phase as the acute phase of CV events and applying this indefinitely within the model would not align with the methodology used in the multivariate analysis. However, at the factual accuracy check stage, the company confirmed that grouping CV events by the acute versus post-acute periods was not considered in the multivariate analysis, and so the ERG does not consider this issue further.

It is also unclear to the ERG how frequent visits were in the trial, and how they align with cycle number – again, for example, could multiple CV events occur between visits or between cycles? As provided in Table 55 of the CS, EQ-5D questionnaires were taken at *Visit 5, 8, 11, 14, premature discontinuation* and *End of Study*, meaning multiple visits occurred between the EQ-5D questionnaires. It is unclear whether the company considered the impact that multiple CV events would have on the utility decrements calculated in the multivariate analysis.

Finally, patients that had experienced a CV event within 30 days of trial start date were excluded, but prior CV events in the multivariate analysis were determined based on events that occurred within the trial; the ERG, therefore, note that some patients entering the trial will have perhaps experienced a CV event in the past (i.e., more than 30 days before the trial start date), and therefore should be reflected in the analysis as ‘post-acute CV event’ rather than ‘no CV event’.

While the ERG accepts that there may have been issues in identifying utility impacts for the acute and post-acute periods, the ERG raises issue with the expectation that patients experience the same decrement in utility in the acute period immediately following a CV event as they do for the rest of their lifetime and is concerned with the implicit assumption that all patients enter the study with no CV event history. The ERG has therefore explored a range of alternative scenarios within its exploratory analyses (see Section 6.2).

Adverse reactions – hyperkalaemia

In the company's model, the only adverse reaction included is hyperkalaemia. This is due to it being known by the company that "*finerenone is associated with a higher risk of hyperkalaemia*". In the multivariate analysis, the company considered both hyperkalaemia and hyperkalaemia leading to hospitalization; the utility decrement obtained when considering hyperkalaemia leading to hospitalization was lower than the utility decrement obtained when considering hyperkalaemia in general ([redacted] vs [redacted], respectively), and so the company consider the utility decrement used in the model (which was re-assessed based on all occurrences of hyperkalaemia) to be conservative, as stated in the company's clarification response. The ERG does not agree with this statement, however, as the utility decrement taken from the literature (-0.030), which is used in a scenario analysis, is considerably larger than the utility decrements calculated in the multivariate regression analyses explored by the company.

Other health events – subsequent CV even*t, atrial fibrillation/atrial flutter, sustained decrease of eGFR ≥40% from baseline*

There are three key health events considered in the model: subsequent CV event, atrial fibrillation/atrial flutter, and sustained decrease of eGFR ≥40% from baseline.

In the model, the same disutility is used for subsequent CV events as is used for the first CV event (i.e., a weighted average of MI, stroke, and hospitalisation due to HF). The ERG considers this to be a limitation, as the utility decrement is weighted based on what proportion of all CV events that were MI's, strokes, and hospitalisations due to HF, rather than being based on the distribution of first or subsequent CV events separately. However, the ERG recognizes that these data are likely not available to the extent to robustly inform the model, so in the absence of alternative data this approach is left unchanged.

In the CS, the utility decrement associated with the *new onset of atrial fibrillation/atrial flutter* (as estimated in the multivariate analysis) was determined to be unrealistic, as a health event should not lead to an increase in QoL; therefore, the company assigned a value of zero in the model. Due to the variable *new onset of atrial fibrillation/atrial flutter* being set to zero, the ERG asked the company to clarify whether the variable was excluded from the multivariate analysis to calculate the parameter estimates for the other variables. The company confirmed that this was not the case, but that running the analysis describe by the ERG generated the same parameter estimates for the other variables used in the model. The ERG notes that the parameter estimates are equal 3 d.p., and though while this is not analogous to the values being

equal, it is likely that changing the values would have a minimal effect on results. However, the values of the new analysis presented by the company at clarification were compared to those presented in Table 57 of the CS, and not the values used in the cost-effectiveness model (which the ERG also queried at clarification, with the company confirming the values in the model were correct, and those in its original submission were incorrect). Therefore, the ERG is still unclear whether there truly is an impact with omitting this variable from the 'correct' utility analysis.

Also at clarification, the company confirmed that the difference in parameter estimates between the dossier and the model (as discussed above) was due to a difference in the multivariate analysis performed; the results presented in the dossier were obtained with the inclusion of the variable *hyperkalaemia leading to hospitalization*, whereas the values used in the model were calculated based on hyperkalaemia in general being included in the multivariate analysis. This subtle difference in how hyperkalaemia is defined caused differences in the parameter estimates of the multivariate regression, as well as the confidence intervals. Therefore, the ERG question whether the removal of the variable *new onset of atrial fibrillation/atrial flutter* does indeed impact the parameter estimates of the remaining variables.

Summary

Overall, the ERG is concerned with the company's approach to estimating and applying utility decrements linked to the occurrence and/or history of given events and considers this to be an important area of uncertainty in the company's model.

4.2.7.4. Adjustments for age

An age-adjustment multiplier was applied to utility values within the model, using multipliers from Janssen *et al.* (2014)[46] which are provided for groups of ages (e.g., 65-74=0.779; 75+=0.726). The average age of patients in the FIDELIO-DKD trial lay within the 65-74 bound at the start of the trial, and so a multiplier of 1.0 is used up until an age of 74 years, after which a multiplier of 0.932 is applied (0.726/0.779 = 0.932). The ERG did not view this methodology as sufficiently appropriate, and so at clarification asked for two alternative methods to be considered:

- Firstly, the ERG asked the company to perform an age-adjustment based on a more specific set of population norms for the UK which could be derived from an alternative study by Ara & Brazier, (2010).[47]

- Secondly, the ERG asked the company to comment on the decision to not use the parameter estimate for age as calculated in the multivariate analysis (see CS Table 57).

The company did not provide the first age-adjustment suggested by the ERG, stating that *"the use of [the] equation proposed by Ara & Brazier (2010) is not appropriate for the FIDELIO-DKD population. The gradual loss of utility over time is likely different for a general population than for patients with CKD and T2D"*.

When considering the second age-adjustment suggested by the ERG, the company presented incremental QALYs and ICERs to demonstrate the impact of the change in age-adjustment methodology. In using the age-related decrement from the multivariate regression analysis rather than the multipliers taken from Janssen *et al.* (2014),[46] the discounted, incremental QALYs increased from [redacted] to [redacted], suggesting this change has minimal impact on the results. The ERG therefore did not explore age adjustment of utilities further in anticipation of its limited impact on results.

4.2.8. Resources and costs

4.2.8.1. Background therapy

All patients in the model receive BT as part of their management of CKD and T2D. In its submission, the company provided a list of common BTs in this patient population, with one representative drug included within the model per treatment class, which were considered to be standard therapies for patients with CKD and T2D – adapted from NICE pathways (clarification question B20). It was stated in the CS that the chosen drug for each class was the most "*frequently administered within each class of the FIDELIO-DKD trial*" and the company considered that "*it was appropriate to consider the pooled* [BT] *distribution*" (clarification question B20). The company also assumed that patients were to be treated with maximum dose. The ERG was satisfied with the approach taken to identify the most common BTs; as drug use appeared to be well-balanced across the FILDEIO-DKD study treatment arms, were derived from a large sample within the FIDELIO-DKD study and were broadly considered representative of the UK population.

In the CS, a tabulated summary of the BT costs assumed for each class was provided (CS Table 64). The ERG attempted to verifying the costs for each BT but was unable to replicate the costs identified and used by the company within its model based on the information provided in the CS (where a source of 'the NHS Dictionary of medicines and devices' was cited, which the

ERG does not recognise as a common reference source used for drug costs in the UK). As an alternative, the ERG sought to identify the costs from first principles to then ascertain where there may be any potential differences in costs chosen by the company versus those identified by the ERG. To find the costs, the ERG took the following iterative approach:

- First, the ERG attempted to identify each BT included in CS Table 64 within the NHS drugs and pharmaceutical electronic market information tool (eMIT) database. The eMIT database is a freely available, standard cost source which provides information about prices and usage for generic drugs and pharmaceutical products for English trusts. The ERG used the version of eMIT last updated on 28 September 2021

- If the BT was not reported within the eMIT database, the ERG then searched the British National Formulary (BNF) to identify the published list price of the BT. As with the eMIT database, the ERG considered the BNF to be a standard cost source to identify drug costs for the purpose of cost-effectiveness modelling

If the BT was not included on either the eMIT or the BNF, the ERG flagged this cost as not listed on 'standard' cost sources for drugs. A comparison of the costs identified by the ERG versus the company is provided in Table 26.

Table 26: Comparison of background therapy costs (company and ERG)

Drug Class	Example used	Daily dose	Pack size	Pack price		New Daily Cost
				Company	ERG	
ACE-is	Ramipril	5mg	28x 5mg	£ 1.55	£0.34	£0.01[eMIT]
ARBs	Losartan	50mg	28x 50mg	£ 1.71	£0.41	£0.01[eMIT]
Beta-blockers	Carvedilol	12.5mg	28x 12.5mg	£ 1.72	£0.36	£0.01[eMIT]
Diuretics	Furosemide	40mg	28x 20mg	£ 0.82	£0.14*	£0.01[eMIT]
Calcium antagonists	Amlodipine	5mg	28x 5mg	£ 0.89	£0.20	£0.01[eMIT]
Statins	Atorvastatin	10mg	28x 10mg	£ 0.93	£0.20	£0.01[eMIT]
PAIs	Acetylsalicylic acid	75mg	28x 75mg	£ 1.38	£0.21	£0.01[eMIT]
Glucose-lowering therapies						
Insulin	Insulin glargine	-	-	-	-	£2.72[†]
Metformin	Metformin	1,500mg	28x 500mg	£ 1.61	£0.20	£0.02[eMIT]
Acarbose	Acarbose[‡]	150mg	90x 50mg	£ 14.58	£4.11	£0.14[eMIT]
Sulfonylurea	Gliclazide	40mg	28x 40mg	£ 1.56	£0.66	£0.02[eMIT]

Drug Class	Example used	Daily dose	Pack size	Pack price		New Daily Cost
				Company	ERG	
DPP-4 inhibitors	Linagliptin	5mg	28x 5mg	£33.26	£33.26	-
GLP-1 agonists	Liraglutide	1.2mg	2x 18mg	£78.48	£78.48	-
SGLT2	Canagliflozin	100mg	30x 5mg	£39.20	£39.20	-
Company's original average BT daily cost						**£2.56**
ERG's revised average BT daily cost						**£2.33**

Abbreviations: ACE-i, angiotensin-converting-enzyme inhibitors; ARB, angiotensin receptor blocker; BNF, British National Formulary; BT, background therapy; DPP-4, dipeptidyl peptidase-4; eMIT, electronic market information tool; GLP-1, glucagon-like peptide-1; PAI, platelet aggregation inhibitor; SGLT-2i, sodium-glucose co-transporter-2 inhibitor.

Notes: *28 tablets 40mg; †Cost taken from Eibich *et al.*, (2017)[48]; ‡50 mg tablets.

Based on Table 26, the ERG found that the majority of the BT costs were considerably reduced when taking costs from eMIT, yet several discrepancies remained regarding the cost calculations from referenced sources:

- **Insulin glargine:** It is stated within the original reference that *"insulin is by far the most expensive first-line therapy with treatment costs of about £975 per year"* (Eibich *et al.*, 2017).[48] Based on the ERG's calculations, this implies a daily cost of £2.67 for this treatment in 2017 which the ERG then understand to have been inflated to the 2020 UK prices using the cost inflation index, though explicit calculations were not presented

- **Liraglutide:** The ERG notes that the cost of two pre-filled 18mg pens was £78.48, and so for a daily dose of 1.2mg, the ERG has assumed that there are 15 doses per pen, meaning the subsequent daily cost was £2.62 per patient as given in the CS

- **Canagliflozin:** There appeared to be a typographical error in the calculation of the canagliflozin cost; within the CS, a pack size of 30 tablets of 5mg was referenced (CS Table 64). The ERG assumes this is instead a pack size of 30 tablets of 100mg since this equated to the given cost of £1.31 within the CS

As noted at the end of Table 26, the ERG's calculations caused the daily BT cost to reduce from £2.56 to £2.34. Since this cost reduction considers both cohorts, and that the use of finerenone is expected to increase survival, this change in BT costs causes the incremental cost associated with finerenone attributable to BT to decrease. Consequently, the company's base-case ICER reduces slightly from £17,552 to £17,452 per QALY gained. The ERG is otherwise satisfied with the company's application of BT costs within the model.

4.2.8.2. Finerenone

As stated in the CS, the indicative NHS list price of finerenone is [redacted] per tablet, regardless of the strength of the tablet (i.e., 10mg and 20mg tablets are both priced at [redacted] per tablet). At clarification stage, the ERG asked the company to confirm the expected availability of finerenone in terms of pack sizes. In response, the company explained that both the 10mg and 20mg tablets are dispensed in packs of 28, leading to an indicative NHS list price of [redacted] per pack for each dose (clarification question B19).

The company also noted in its response to clarification question B19 that the *"frequency of prescription and dispensing will be according to standard hospital/ GP practice prescribing policies and in line with the need to evaluate the patient"*. The ERG notes that the cost of finerenone is applied in the company's model for the cost of a 4-month supply of treatment, in line with the model cycle length, which is then half-cycle corrected. In reality, it is expected that some product wastage would arise for patients that discontinue treatment part-way through a pack of treatment, though this is not explicitly reflected within the model. For simplicity, the ERG has explored within a sensitivity analysis the possibility that the average patient wastes either no treatment (company's base-case analysis) or one whole pack of treatment, not accounting for the impact of discounting by simply adding the cost of one additional pack of finerenone to the total incremental cost in the model. Please refer to Section 6.2 for further details.

Finerenone is administered in combination with BT(s) and is available as a tablet taken orally. Therefore, the company did not apply any treatment administration costs, which the ERG considered a reasonable assumption.

4.2.8.3. Health states

CKD-based health states

The model considers a cost per cycle related to the occupancy of each CKD-based health state. A tabulated summary of the state-specific costs incurred per model cycle is provided in CS Table 65. The costs for each CKD health state were taken from two sources: NICE TA358[49] (tolvaptan for treating autosomal dominant polycystic kidney disease), and NICE NG203[4] (draft guideline for consultation). TA358 was used for states CKD1/2 through to CKD 5 without RRT, whereas NICE NG203 was used for dialysis and transplant costs.

The CS states: *"For patients in CKD 4 a cost of £3,357.65 per year was considered. This cost included inpatient stays, nephrology outpatient visits, antihypertensive drugs and GP visits."* (CS

Section 3.5.2). At clarification stage, the ERG asked the company to comment of the risk of double counting (with respect to the fact that BT is captured separately within the model), and the company confirmed that as double counting of antihypertensive drugs would likely have a negligible effect on the ICER, any calculations in relation to adjusting for BT use were disregarded (clarification question B16). While imperfect, the ERG acknowledges the likely small impact this would have on the ICER and agrees that the unadjusted cost if suitable for informing the model.

At clarification stage, the company also provided additional information concerning the original costs and approach to inflate these for use within the model (clarification question B22). The ERG is satisfied that the approach taken to inflate the costs is suitable. The ERG is generally satisfied that the costs used for the health states CKD1/2 through to CKD5 without RRT are suitable.

The company stated that they had used the *draft* CKD clinical guideline published in March 2021 (NG203 [draft for consultation]) to inform the costs used in its model. The ERG recognises that the final updated CKD NICE guideline (NG203)[4] was published two days before the company provided its submission to NICE; however, the ERG was not able to identify any of the original costs cited from this draft guideline because it is no longer available (i.e., the CS cites a draft which was later updated) and the original documentation was omitted from the company's reference pack provided alongside its submission. Therefore, the ERG is unable to verify the source of these unit costs.

For the cost of dialysis, the CS states *"Furthermore, 15% was added on top of the reference costs for dialysis and transport costs, to account for access procedures, out-patient appointments, and management of complications as stated in the guidelines"* (CS Section 3.5.2). At clarification stage, the ERG asked the company to justify the source of this 15% value, at which stage the company explained that this is a direct quote from the original source material (though, as highlighted previously, the ERG was unable to verify this due to the report no longer being available).

CV-event based health states

As the model separates patients according to their CV event history through the specification of CV-event based 'sub-models', the company also included the costs of CV events. The cost of a CV event is considered in two parts: the cost in the acute period (i.e., the cycle in which the CV

event occurs), and the cost in the post-acute period (i.e., all subsequent cycles until death). All costs for CV events were taken from a published study by Alva *et al.*, (2015).[50] Alva *et al.* aimed to *"estimate the immediate and long-term inpatient and non-inpatient costs for T2D-related complications"* (Alva *et al.*, 2015).[50]

To calculate an average cost for the acute and post-acute periods in the model, the company took a weighted average of CV event costs reported by Alva *et al.* and weighted these based on the relative occurrence of events in the FIDELIO-DKD study. This yielded an average cost of £4,763 for the acute period following the first CV event, and £819 for the post-acute period. The ERG considers this to be a reasonable approach to assign unit costs for CV events, though owing to the limited reporting in the CS, the ERG was not able to fully verify the costs applied in the company's model.

The ERG questions the application of a cost of £819 applied per year for all people with CV event history, given that some patients will have entered the FIDELIO-DKD study with CV event history, though this will not be captured within the model structure (as CV event history is defined on the basis of CV events that occurred within the study period). Based on a study publication concerning the FIDELIO-DKD population, 45.9% of patients had a history of CV disease at baseline (n=2,602 of 5,674 [FAS population]).[18] Therefore, it is the ERG's view that this cost should theoretically be applied to nearly half of patients for the entirety of the model time horizon. This point is explored further as part of the ERG's exploratory analyses (see Section 6.2).

4.2.8.4. Events

The company includes a summary of costs used to capture the resource use associated with the resolution of several clinical events (CS Table 72). These include costs for subsequent CV events, hyperkalaemia, sustained decrease in eGFR ≥ 40% from baseline (over at least 4 weeks), and new onset of atrial fibrillation / atrial flutter. The ERG considers the costs used to be broadly appropriate, but notes the following:

- The cost of hyperkalaemia is substantially lower dependent on whether or not it leads to hospitalisation (£82 for non-hospitalised cases versus £1,452 for hospitalised cases). While the ERG acknowledges that a higher cost is expected for hospitalised cases, it notes that no corresponding difference in the impact on patient utility is assumed according to whether or not patients are hospitalised due to hyperkalaemia. Taking these two features of the

model together, the ERG does not consider it appropriate to consider the same utility impact but a large difference in costs

- The CS states that it was *"conservatively assumed that no additional costs were accounted for patients with a sustained decrease in eGFR ≥40% from the baseline (over at least 4 weeks)"* (CS Section B.3.6.3). The ERG notes that were an arbitrary cost of £82 included for this event (i.e., taking the cost of non-hospitalised hyperkalaemia), the base-case ICER reduces markedly from £17,552 to £16,933. Therefore, while the ERG agrees with the company's conclusion that were this cost added it would cause the ICER to decrease, it is unclear based on the CS what a suitable cost would be, and so the ERG has opted to leave this cost unchanged

- The cost of a subsequent CV event was assumed to be equal to the cost of the first CV event, and no continued cost is captured by the model as it is assumed that the ongoing costs related to the post-acute period following the first CV event should cover the long-term costs related to CV event history. The ERG notes however that the acute cost applied for the secondary CV event would likely be higher than the first CV event, owing to the likely increase complexities associated with managing patients for a CV event in the presence of CV event history. However, in light of limited evidence to recommend an increase in the unit cost assigned for subsequent CV events, the ERG has opted to leave this cost unchanged

4.2.8.5. Death

The company's model assigns a cost upon death dependent on the type of death. Three types of death were captured in the model, associated with the following costs:

- CV death – £1,306
- Renal death – £1,553
- Non-CV & non-renal (i.e., 'other') death – £0

The ERG acknowledges that the NICE reference case stipulates the only relevant costs and outcomes should be reflected in the company's model. However, the ERG is concerned that by omitting the costs related to 'other' deaths, the company's model may bias in favour of finerenone through a reduction in specific types of death deemed to be directly relevant (i.e., CV and renal deaths). This is because costs of any non-CV & non-renal death costs are omitted, which implies that there are no costs related to other deaths (i.e., while other types of death will

likely also be associated with costs, these are not reflected within the company's model, and so finerenone is associated with a cost saving within the context of modelled deaths). While the ERG highlights this as a potential area of concern, it is unlikely that editing the cost of other deaths would have a marked impact on the cost-effectiveness results, and so the ERG has not explored further scenarios related to death-related costs.

5. COST-EFFECTIVENESS RESULTS

5.1. Company's cost-effectiveness results

5.1.1. Base case results

The results reported by the company are shown in Table 27. The deterministic and probabilistic results for the label population are associated with incremental cost-effectiveness ratios (ICERs) of £17,552 and £17,843 per QALY gained, respectively.

Table 27: Company base case results

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained
Company deterministic base case					
Finerenone + BT	[redacted]	6.11	-	-	-
BT	[redacted]	6.01	[redacted]	0.10	£17,552
Company probabilistic base case					
Finerenone + BT	[redacted]	NR*	-	-	-
BT	[redacted]	NR*	[redacted]	0.10	£17,843

Abbreviations: QALYs, quality adjusted life years

Note: *The company's PSA does not output total, discounted costs and QALYs individually by treatment arm.

In discussing the base-case results, the company highlights that there are *"aspects of* [HRQoL] *that are not captured within the QALY calculation so these estimates may be considered conservative"* (CS Section B.3.7). The company elaborates on this point further by explaining that dialysis has a substantive impact on the life of patients and those around them (including family, friends, and caregivers), and so any treatment that delays progression to kidney failure and the need for dialysis has benefits that extend beyond those reflected by the model. However, as these aspects were not reflected within the company's model, the ERG was unable to consider these additional benefits within the context of the economic model.

5.1.2. Deterministic sensitivity analysis

The company presented the results of a deterministic sensitivity analysis (DSA) to explore the sensitivity of the base-case results by varying key parameters within plausible ranges. The included parameters and their respective ranges were presented in CS Table 73, with the

corresponding results presented as a tornado plot (CS Figure 28). The company explained that based on the DSA, key parameters of influence on the model included utility values for health states, HRs for CV events and CV death, as well as the "baseline patient distribution". The baseline patient distribution bounds refer to setting the model to assume all patients were CKD3 ("lower bound") or CKD4 ("upper bound") at baseline.

The ERG raises several issues with the company's DSA. First, some parameters are grouped together (such as baseline patient distribution and utilities) whereas others are explored in isolation (such as specific risks and utility decrements), which the company does not explain the rationale behind which parameters were grouped and which were not. The ERG accepts that in some cases, grouping parameters is suitable where there is known covariance or when parameters are interrelated (e.g., proportions that sum to 100%), yet there are some parameters excluded from being varied simultaneously which would seem relevant (e.g., the utility estimates which come from a multivariate regression model fitted to the FIDELIO-DKD data).

Focusing on utilities, the ERG notes that the range of values explored in the sensitivity analysis appear to substantially over-estimate the volume of uncertainty in the values. For example, the utility for CKD3 is varied between bounds of [redacted] and [redacted], centred at [redacted]. The ERG is also unclear how the lower and upper bounds were estimated, and some other parameters also appear to have very large bounds of uncertainty; for example, the cost of an IS stroke (acute, base-case: £7,470) is associated with bounds of £4,199 to £11,319. The ERG suspects that this range of uncertainty represents the bounds of uncertainty at the *individual* level, as opposed to the bounds of uncertainty at the *cohort* level, though this is unclear.

In summary, the ERG does not consider the specific outputs of the DSA to be relevant for decision making, except to highlight the impact some parameters have on the model results. For example, it is the ERG's view that the plausible lower bound for the utilities should not cause the ICER to increase from £17,552 to £42,410 (CS Table 76), because the lower bounds of the utility values lack face validity.

5.1.3. Probabilistic sensitivity analysis

The company conducted a probabilistic sensitivity analysis (PSA) to explore parameter uncertainty, by running the model 1,000 times and simulating parameters for each run from their respective distributions. The company presented the results of its PSA using mean results, a

PSA scatterplot, and a cost-effectiveness acceptability curve (CEAC) – of all which are presented in CS Section B.3.8.1. At willingness-to-pay thresholds of £20,000 and £30,000, the probabilities finerenone is cost-effective in the company's base-case analysis were 60.4% and 78.1%, respectively. Notably, the company's model outputs only incremental costs and QALYs, and due to the extensive VBA code used to run the PSA, the ERG was unable to re-program the PSA to output additional results within the timeframe of this review.

The ERG's criticisms of the PSA are similar to those raised in the context of the DSA, as the spread of uncertainty in the parameters included in the PSA appears to be over-inflated, rendering findings from the PSA highly uncertain. However, the ERG raises several additional concerns with the PSA:

- The CKD progression rates are not varied within the PSA (based on the omission of these parameters on the 'PSA – Simulations' sheet of the company's model). This means that the main transitions in the model are assumed fixed, which the ERG considers a major limitation of the PSA
- Costs were varied using a gamma distribution, though it is the ERG's view that the normal distribution is a more appropriate reflection of the uncertainty in a given cost, owing to the role of the Central Limit Theorem in the context of a cohort-level model
- Some parameters appear to be sampled according to user-specified limits – for example, the duration of sustained decrease in eGFR >=40% from baseline is varied from 0 to the base-case value, and a lognormal distribution is seemingly calibrated around these values

In summary, the ERG has serious concerns with the approach taken by the company to produce its PSA and does not consider findings from the PSA to be a suitable basis on which to inform decision making.

5.1.4. Scenario analyses

The company undertook a range of scenario analyses to consider alternative data sources and assumptions applied in the model, full details of which are provided in CS Section B.3.8.3. The ERG considers the range of scenarios presented by the company to have limited applicability to the decision problem, as only four scenarios provided an exploration of alternative data and assumptions relevant to the decision problem within the NICE reference case. These scenarios form the focus of the ERG's critique and are described in turn below.

5.1.4.1. Scenario 2: Utilities taken from the literature

ERG re-produced this scenario by manually setting utility values based on the description provided in the CS

While not immediately possible to generate this scenario based on functionality built into the model, the ERG was able to run this scenario based on information provided in the CS. This scenario applies utility values taken mostly from the literature (where available, else default values were applied per the company's base-case analysis) which causes the ICER to decrease from £17,552 to £14,966.

The ERG notes that this scenario considers edits to 14 different input cells within the company's model, and so the individual impact of changing *some* utility values may be masked by the fact that all values are changed simultaneously. However, further inspection of this scenario suggests the main driver of the impact on results is that specification of notably lower values for the dialysis and transplant health states. If only these values are edited, the ICER reduces from £17,552 to £14,736.

5.1.4.2. Scenario 3: Treatment discontinuation impacts costs only (efficacy unchanged)

ERG was able to re-produce this scenario using a switch in the company's model

In this scenario, treatment discontinuation with finerenone does not impact the application of transitions or risks within the model, causing the ICER to decrease from £17,552 to £5,924. While the ERG maintains a strong preference towards the company's base-case approach to set the efficacy of finerenone equal to that of BT after discontinuation, this scenario illustrates the large impact the relative effect of finerenone has on modelled QALYs, where the incremental QALY gain increased from [redacted] in the base-case analysis to [redacted] in this scenario.

5.1.4.3. Scenario 6: Progression to dialysis delayed for 3 cycles

ERG was able to re-produce this scenario using a switch in the company's model

In this scenario, progression to dialysis is delayed for 1 year to align with the Kaplan-Meier estimate obtained from the FIDELIO-DKD study. At clarification, the ERG asked the company why (in light of the discrepancy between the Kaplan-Meier estimate and the assumption of a constant risk from baseline) the scenario was not applied in the base-case analysis (clarification question B12). In response, the company explained: *"It was decided not to omit transitions to dialysis within the first year to be consistent with the pre-specified method of delivering model*

inputs based on the FIDELIO-DKD data, so that all transitions are derived the same way. The functionality to disable transitions to dialysis for the first year was added at the time of model validation. Omitting transition to dialysis in the first year is more aligned with the trial results but in our opinion the base case scenario better reflects clinical practice as dialysis would be possible within year 1 in the real world but was not seen in the trial due to patient numbers".

The ERG considers the scenario analysis to better reflect the FIDELIO-DKD study, and that even though transitions to dialysis would be possible within the first year of the model, these did not occur within the FIDELIO-DKD trial. The impact of mis-aligning the transitions to dialysis in the model on other transitions has not been addressed, and so the ERG prefers to delay transitions to dialysis by 1 year for consistency across the model transitions. The scenario increases the ICER from £17,552 to £18,158.

5.1.4.4. Scenario 7: Finerenone stopped after initiation of RRT

ERG was able to re-produce this scenario using a switch in the company's model

In the company's model, finerenone is stopped based on either death or a constant discontinuation probability, though this is not explicitly linked to health state occupancy. In this scenario, patients that enter the acute dialysis state immediately (and permanently) stop treatment with finerenone. This scenario causes the ICER to decrease from £17,552 to £15,556.

The ERG is unclear as to whether this scenario is to be considered in clinical practice, though there is a risk that by including this rule discontinuations are double counted. To illustrate this, the ERG has prepared a comparison of the modelled proportion of patients on treatment with finerenone over time projected by the model versus the observed FIDELIO-DKD data, as shown in Figure 6. Here, it can be seen that this scenario further exacerbates the discrepancy noted in Section 4.2.6.4, and so the ERG does not consider this scenario to provide a suitable basis to inform decision making with respect to the use of finerenone after RRT has been initiated.

Figure 6: Modelled discontinuation base-case versus scenario

Abbreviations: RRT, renal replacement therapy.

5.2. Model validation and face validity check

In its submission, the company explains that the submitted model structure underwent *"multiple levels of review from clinical and health economics experts"* (CS Section B.3.10.1), and three UK clinical experts were *"interviewed remotely to seek their advice on the applicability and suitability of various parameters and assumptions applied in the economic modelling"* (CS Section B.3.10.2). However, as highlighted throughout the ERG's report, a number of issues were identified concerning the face validity of the model inputs and the structural decisions underpinning the model calculations, which in turn are associated with concerns with the model results. Furthermore, details of the interviews held were not provided by the company within its submission.

The company also stated that two independent modelling agencies assessed the technical validity of the model to ensure calculations were correct and that results were logical and consistent. Details of the technical validity were not provided by the company, though the ERG did not identify any technical errors as part of its review (with the exception of the discordance between the modelled and estimated rate of treatment discontinuation, described further in Section 4.2.6.4).

In addition to the model validation exercises highlighted above, the company also sought to compare data from the FIDELIO-DKD versus the outputs of the CE model, considering the modelled versus observed frequency of specific clinical events. While the ERG accepts that this exercise provides reassurance that the model does not yield estimated event rates that are entirely discordant with FIDELIO-DKD study, this approach is only capable of reflecting a comparison up to a 4-year time horizon (in line with the follow-up period of the FIDELIO-DKD study). Acknowledging also that the events considered within the model were relatively uncommon when considered individually, the ERG considers this exercise to provide relatively limited information concerning the validity of the modelled event rates when considering the full modelled time horizon.

6. EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

The ERG identified a number of limitations within the company's base case and has explored the impact of parameter values, and assumptions, which the ERG believes are more plausible.

This section is organised as follows: Section 6.1 details the impact of corrections identified in the ERG's validation of the executable model. Section 6.2 details a series of scenario analyses exploring the robustness of the cost-effectiveness results to specific assumptions and additional uncertainties identified by the ERG. These analyses were conducted within the company corrected base-case analysis.

The scenario analyses presented in Section 6.2 focus on exploring the following issues and uncertainties:

- Transitions and risks
- Mortality
- Treatment effects expressed as HRs
- CV event history
- Utility values (both related to CKD stage and CV events)
- Finerenone wastage, BT, and death costs

In Section 6.3, the ERG base-case is presented based on a combination of the exploratory analyses presented in Section 6.2.

6.1. ERG corrections and adjustments to the company's base case model

As noted in Section 4.2.6.4, the ERG edited the rate of treatment discontinuation applied in the company's base-case analysis to ensure the modelled proportion of patients on treatment at 4 years aligned with the proportion observed in the FIDELIO-DKD study. To illustrate how the recalibration impacts treatment discontinuation, the ERG has re-produced the plot of discontinuation presented previously (Figure 5) to compare the unadjusted and adjusted proportions of patients on treatment over time outputted by the model (Figure 7).

Figure 7: ERG's re-calibrated treatment discontinuation

The impact of this edit on the company's base-case deterministic analysis is presented in Table 28. Owing to the issues found in the company's PSA, only deterministic analysis is presented.

Table 28: ERG-corrected company base case results

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained
ERG corrected company deterministic base case					
Finerenone + BT	[redacted]		-	-	-
BT	[redacted]		[redacted]	0.11	£17,882

Abbreviations: QALYs, quality adjusted life years

6.2. Exploratory and sensitivity analyses undertaken by the ERG

6.2.1. Risk of CV events

In the company's model, the risks of CV events vary according to treatment arm based on the two factors: (i) treatment arm (captured via an HR), and (ii) by CKD stage (where transitions were estimated separately for each arm). The ERG considers the independence of these two aspects of the model to lead to the risk of double counting the potential cardio-protective effects of finerenone.

Based on the above, the ERG considered an analysis in which the risk of CV events was assumed fixed by CKD stage, but that the overall reduction in the risk of a CV event is expressed solely by the HR obtained from the FIDELIO-DKD study. For the purpose of this analysis, the ERG set the risk of a CV event to be equal to the base-case value attributed to the CKD3 state in the company's model (given that this state represents the majority of patients at baseline) and recorded the impact on the ICER. The company's base-case ICER increased from £17,552 increased to £17,976. While this reflects a relatively small change in the ICER, the ERG considers this to represent a more reasonable approach to model the potential cardioprotective effects of finerenone without introducing a risk of double counting.

As an alternative to the analysis described above, the opposite approach was also explored for completeness – in other words, the risk of CV events was set per the company's base-case analysis, but the HR for CV events was set at unity. In this alternative scenario, the company's base-case analysis ICER of £17,552 increased to £26,131. This implies a much larger impact on the model results versus the previous scenario, though estimation of the possible link between CV events and CKD stage is palpably more uncertain versus the estimation of an overall HR regardless of CKD stage. The ERG therefore favours the first scenario in favour of this latter scenario in its preferred base-case analysis.

6.2.2. Renal and CV deaths

As noted in Section 4.2.6.3, the ERG raises several concerns with the company's approach to capturing renal deaths in its model. The ERG therefore explored an alternative approach in which renal deaths were effectively omitted from the model and were instead captured as part of background mortality. The intention of this analysis was to both (i) explore the impact on the ICER, and (ii) ascertain whether or not the impact on the ICER exhibits face validity with respect to the ability for the model to appropriately capture mortality effects.

When renal deaths were effectively omitted from the model, the company's base-case ICER increased from £17,552 to £17,598. This negligible increase in the ICER illustrates that renal deaths have a small impact on the model results, which is concerning given that these deaths were factored into the model structure and that it is the ERG's understanding that renal deaths would be considered a leading cause of death in patients with CKD and/or T2D – for example, a study by van Dieren *et al.*, (2010)[51] suggests that approximately 10% of patients with T2D die of renal failure.

As an additional scenario, the ERG set the HR for renal deaths to be at unity to further explore its impact on the model results. This scenario causes the company's base-case ICER to increase by less than £1, further highlighting the ERG's concern that renal deaths should likely have a larger overall impact on the cost effectiveness of finerenone versus the effect implied by the company's model.

For the same reasons as described with respect to the risk of CV events (see Section 6.2.1), the ERG also considered a scenario wherein the risk of CV deaths was set to be identical by CKD stage but the HR for finerenone was maintained. This caused the company's base-case ICER to decrease from £17,552 to £16,616, driven by an overall smaller QALY gain (+0.10 [base-case analysis] versus +0.09 [scenario]) paired with an overall reduction in incremental costs (+[redacted] [base-case analysis] versus +[redacted] [scenario]). However, the total costs, QALYs, and LYs *increased* for both arms.

The ERG is unclear exactly why reducing the overall risk of CV deaths appears to lead to a marked improvement in the estimated cost effectiveness of finerenone. However, the ERG suspects such an impact on the ICER is likely driven by small changes in the incremental QALY gain having relatively large impacts on the ICER (owing to the properties of the ICER as a ratio). Therefore, overall, the ERG considered the removal of possible double counting to be more appropriate versus the company's base-case analysis (for the same reasons as highlighted in Section 6.2.1 with respect to CV events).

In addition, the ERG considered two further scenarios concerned with CV deaths – first, setting the HR for CV death to unity while keeping the risks by CKD stage aligned with the company's base-case analysis; and second, setting the risk of CV death for CKD1/2 to be the same as CKD3:

- The first scenario (undertaken for the same reasons per Section 6.2.1) caused the company's base-case ICER to increase from £17,552 to £20,367, again implying a much larger impact on results versus the alternative approach of adjusting the risks but maintaining the HR

- The second scenario was undertaken as an alternative approach to the scenario provided by the company at clarification stage (where the company set the risk for CKD3 to be the same as CKD1/2). This caused the company's base-case ICER to increase from £17,552 to £17,745, which while a relatively small increase illustrates that depending on the approach

taken to align the risks with clinical plausibility, the ICER could increase (per the ERG's approach) or decrease (per the company's approach)

Finally, the ERG also considered an additional scenario wherein the HR for CV events (as noted in Section 6.2.1), CV deaths, and renal deaths were all set at unity. This scenario was undertaken to understand how much these three individual HRs influenced the ICER. The company's base-case ICER increased in this scenario from £17,552 to £33,674, highlighting the critical impact of these three HRs and how the potential risk of double counting has a highly important impact on the cost-effectiveness results of the model.

6.2.3. CV event history

The ERG previously noted that the company's model reflects CV history with respect to the FIDELIO-DKD study period only. Given that some elements of the model related to the occurrence of CV events were based on published literature which considered a broader view of CV event history, the ERG considered it more appropriate to assume that the proportion of the FIDELIO-DKD cohort with a recorded CV event history should enter the 'post CV event' sub-model at baseline, as opposed to all patients entering the 'no prior CV event' sub-model at baseline. By assuming 45.9% of patients enter the 'post CV event' sub-model at time zero, the company's base-case ICER increased from £17,552 to £22,152.

6.2.4. Death costs

Due to the separation of costs assigned for different causes of death, the ERG was concerned that the company's base-case analysis may bias in favour of finerenone through illustrating avoided death costs only for the types of deaths finerenone has a direct impact on. However, as death costs are applied upon death, it is the ERG's view that ultimately all patients will likely incur some cost of death, though this is not captured in the model. Therefore, the ERG removed the cost of death in a scenario analysis which caused the company's base-case ICER to increase from £17,552 to £17,601. While this reflects a small change in the ICER, the ERG considers this approach to be a less biased approach to capturing death costs in absence of a clear cost source to use for non-CV and non-renal deaths which is greater than £0.

6.2.5. BT costs

The ERG previously noted that BT costs were higher than those obtained from standard sources available to inform company submissions to NICE (see Section 4.2.8.1 for details).

Therefore, in a scenario, the ERG edited the company's daily BT cost to reflect the cost calculated by the ERG from first principles. As the ERG's daily cost was lower, and the finerenone arm overall incurs more BT costs (due to the modelled extension in survival), this edit caused the company's base-case ICER to reduce from £17,552 to £17,447.

6.2.6. Finerenone wastage

Finerenone is expected to be dispensed in packs providing a 28-day supply. However, in the company's model, patients are modelled to incur the cost of treatment based on half-cycle correct LYs within a model cycle. In other words, patients are costed to receive the precise number of tablets within a model cycle that are needed, with no rounding up included to account for patients that might have discontinued treatment (due to any cause) part-way through a model cycle.

As a pragmatic means of incorporating wastage costs within the company's model, the ERG simply added the cost of one additional pack within the overall incremental costs projected by the model to ascertain the potential impact including wastage costs may have on the model results. This causes the company's base-case ICER to increase from £17,552 to [redacted]. While it is unlikely that each patient will waste one full pack of treatment, the ERG highlights that this scenario reflects a plausible 'upper limit' of the likely wastage associated with finerenone, and that the 'true' impact of wastage would likely result in an ICER between the 'no wastage' versus 'one full pack of wastage' scenarios.

6.2.7. Utility by CKD stage

The ERG previously highlighted that the utility for CKD1/2 did not exhibit clear face validity when compared with the utility obtained for CKD3. It is the view of the ERG that the majority of the utility data collected in the FIDELIO-DKD study likely comprises the CKD3 group, and so in an exploratory analysis the ERG set the utility for CKD1/2 to a value of 0.80, reflecting a utility higher than CKD3 which is broadly in keeping with the disutility applied within TA358 cited by the company within its submission (CS, Document B, Table 58). However, the ERG acknowledges that such a utility value is both (i) arbitrary, and (ii) arguably similar to (or even perhaps in excess of) the age- and sex-adjusted general population.

When setting the utility for CKD1/2 to 0.80, the company's base-case ICER increased from £17,552 to £17,833. Though the ERG acknowledges the limitations of using essentially an arbitrary utility value for this health state, in the absence of an alternative approach which

exhibits face validity the ERG deems the use of this value to be preferred over the company's base-case analysis.

6.2.8. Utility for CV events

Upon the occurrence of a given CV event, patients are modelled to experience an initial 'acute' disutility, followed by a 'post-acute' disutility. However, in the company's base-case analysis, the 'acute' and 'post-acute' values are identical, which the ERG does not consider to exhibit face validity. In two scenario analysis, the ERG considered either halving the 'post-acute' disutility or doubling the 'acute' disutility to factor in the expectation that an initial disutility is expected to higher than a longer-term disutility due to a CV event. The former of these analyses caused the company's base-case ICER to increase from £17,552 to £17,908, whereas the latter caused it to decrease to £17,414.

Acknowledging the arbitrary nature of both scenarios, the ERG considered the former scenario to exhibit more face validity versus the company's base-case analysis and considered it more likely that the acute disutility would be reflected by the company's estimated values obtained from the FIDELIO-DKD study.

6.2.9. CKD transitions

The ERG undertook one further, exploratory scenario concerned with the CKD transitions included in the company's model. In this scenario, the transitions estimated for the BT arm were applied also for the finerenone arm, but all other benefits of finerenone were aligned with the company's base-case analysis. This scenario could be viewed, in some respects, as an alternative to the final scenario presented in Section 6.2.2 wherein the three HRs for CV events, CV deaths, and renal deaths were set to unity.

This scenario had a substantial impact on the company's modelled ICER, increasing the base-case ICER from £17,552 to £70,251. While the ERG does not advocate for the use of this scenario to inform any type of base-case analysis, several important findings are relevant to consider that were identified as part of undertaking this analysis:

- Setting the CKD transitions to be equal effectively halved the incremental QALY gain *and* doubled the incremental costs, leading to the ICER effectively quadrupling
    - Such an impact on both costs and QALYs highlights the important relationship between CKD stage. For example, in the company's base-case analysis finerenone

saves approximately £1,500 due to avoided or delayed onset of dialysis, whereas if the transitions are set to be equal, finerenone leads to increased dialysis costs of around £232. This is because finerenone extends survival even if the transitions are set equal owing to the specification of the HR for CV death

- The overall incremental cost due to the use of finerenone is nearly identical across both scenarios: +£3,418 in the company's base-case analysis, versus +£3,323 in this scenario
  - This shows that regardless of CKD stage (including impacts on mortality due to CV death), the overall projected cost of finerenone is largely unaffected, highlighting the independence of treatment discontinuation and modelled benefits with respect to CKD stage inherent within the company's chosen model structure

Therefore, while the ERG re-iterates the exploratory nature of this scenario, its findings illustrate some of the critical limitations associated with the company's model transitions, and further highlight the possible implications of removing some elements of double counting within the company's model.

6.2.10. Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

The ERG made the changes described in Sections 6.2.1 to 6.2.9. Each change has been made individually, and its impact on both the company's original base-case ICER and the ERG's corrected version of the company's base-case ICER was recorded. The results of the ERG's exploratory analyses are provided in Table 29. Please refer to the respective sections of the report in the table for further details of each scenario.

Table 29: ERG's exploratory analyses

Scenario	Section in ERG report	Company's base case		ERG-corrected base case	
		ICER	+/- base case	ICER	+/- base case
Base case	6.1	£17,552	-	£17,882	
Set risk of CV event to be independent of CKD stage by taking only the value of CKD3 and applying it to all states	6.2.1	£17,976	+£424	£18,309	+£427
Set HR for CV events to be 1	6.2.1	£26,131	+£8,579	£26,537	+£8,655
Set risk of CV death in CKD1/2 to be same as CKD3	6.2.2	£17,745	+£194	£18,078	+£196
Omit renal deaths from the model and re-include as part of background mortality	6.2.2	£17,598	+£47	£17,929	+£47
Set HR for renal death to 1	6.2.2	£17,552	+£0	£17,882	+£0
Set HR for CV death to 1	6.2.2	£20,367	+£2,816	£20,732	+£2,850
Set risk of CV death to be independent of CKD stage by taking only the value of CKD3 and applying it to all states	6.2.2	£16,616	-£936	£17,001	-£881
Set HR for CV events, CV death, and renal death to 1	6.2.2	£33,674	+£16,123	£34,062	+£16,180
Assume 45.9% of patients enter the post-CV event sub-model	6.2.3	£22,152	+£4,601	£22,490	+£4,608
Remove all death costs	6.2.4	£17,601	+£49	£17,931	+£49
Switch background therapy cost to ERG's calculations	6.2.5	£17,447	-£104	£17,777	-£105
Include one additional pack of finerenone to reflect wastage	6.2.6	[redacted]	[redacted]	[redacted]	[redacted]
Assume utility for CKD1/2 is 0.80	6.2.7	£17,833	+£282	£18,167	+£285
Assume post-acute disutility is half of acute disutility	6.2.8	£17,908	+£356	£18,236	+£354
Assume acute disutility is double post-acute disutility	6.2.8	£17,414	-£138	£17,739	-£143
Set CKD transitions for finerenone to be same as BT	6.2.9	£70,251	+£52,700	£71,327	+£53,445

Abbreviations: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

Note: ICERs expressed as cost per QALY gained

6.3. ERG's preferred assumptions

The ERG did not consider it possible to provide a preferred ICER which was able to address all of the limitations inherent within the company's submitted model (as described in Section 4 of the ERG's report). However, the ERG has identified a number of alternative settings and assumptions which are considered to represent a more suitable basis from which to inform the cost-effectiveness results.

The ERG's tentative preferred base case ICER is £23,706, as shown in Table 30. The increase in the ICER is mostly driven by the inclusion of some patients in the 'post-CV event' sub-model at baseline, in combination with several other smaller model changes that cause the ICER to increase slightly.

However, the ERG wishes to re-iterate that this ICER is estimated on the basis of a model which suffers from a number of critical limitations and therefore the ERG does not consider this ICER alone to represent a suitable basis from which to inform decision making, particularly in light of the fact it represents a comparison to BT alone. The ERG therefore highlights the relevance of alternative scenarios undertaken and reported within Section 6.2 of this report.

Table 30: ERG's preferred model assumptions

Preferred assumption	Section in ERG report	Cumulative ICER
Company's original base-case	5.1.1	17,552
ERG-corrected company's base-case	6.1	17,882
Set risk of CV events to be independent of CKD stage	6.2.1	18,309
Amend application of renal deaths	6.2.2	18,357
Set risk of CV death to be independent of CKD stage	6.2.2	17,413
Assume 45.9% of patients enter post-CV event sub-model	6.2.3	22,510
Remove all death costs	6.2.4	22,528
Edit BT cost to ERG's calculations	6.2.5	22,423
Include one additional pack of finerenone to reflect wastage	6.2.6	[redacted]
Assume utility for CKD1/2 is 0.80	6.2.7	23,587
Assume post-acute disutility is half of acute disutility	6.2.8	23,706

Abbreviations: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

Note: ICERs expressed as cost per QALY gained

6.4. Conclusions of the cost-effectiveness section

The company's model does not present a comparison to SGLT-2 inhibitors per the final scope issued by NICE

The company's model presents a comparison to BT only, and so the cost effectiveness of finerenone versus SGLT-2 inhibitors is not possible to infer from the company's model. Clinical advice provided to the ERG suggests that SGLT-2 inhibitors are indeed relevant comparators, and this view is aligned with recent clinical guidelines[9] and the final scope[1] issued by NICE. Owing to the structure of the model, and the lack of evidence presented by the company concerned with SGLT-2 inhibitors and how they compare to finerenone, the ERG was unable to provide an estimate of the cost effectiveness of finerenone versus SGLT-2 inhibitors. The ERG considers this omission to be especially important owing to the expectation that SGLT-2 inhibitors will become an increasingly used treatment option in this patient population.

The company's model has a number of important structural limitations

While the company's model broadly reflects the progressive nature of CKD in a population with T2D, it suffers a number of important limitations in capturing the full patient experience (including how different aspects of the model interact and possibly change over time). These include issues with possible double counting of benefits and time-invariant risks for CV events, both of which have marked effects on the cost-effectiveness results depending how these impacts are included or excluded within the model. However, the ERG was only able to partially address some of these limitations within the context of the company's model and information available to the ERG (particularly relating to the FIDELIO-DKD study, as large model components rely upon analysis of individual level data from this study).

Several of the company's model inputs appeared to lack face validity

The ERG raised a number of concerns with respect to the face validity of analyses undertaken of the FIDELIO-DKD study data used to populate aspects of the model. These includes risks which appeared to increase as CKD stage improved, utility values that increased as CKD progressed, and seemingly important aspects of the model which had a near-negligible impact on results if removed (i.e., renal deaths). Owing to the fact that some of these issues featured as part of a broader analysis (e.g., utility regression), the ERG has concerns with the overall approach to inform relatively large aspects of the company's model.

The company's sensitivity analyses were subject to a number of limitations, and were largely inappropriate to inform decision making

The ERG identified several issues with the company's reported sensitivity analyses which render them largely inappropriate to inform decision making. These issues included the approach to parameterise uncertainty in model parameters (some parameters were missing or varied to extremes), meaning that both probabilistic and deterministic analyses were uninformative. Only a small selection of the scenario analyses presented by the company were relevant to the decision problem and aligned with the NICE reference case, and so the ERG undertook a broader range of scenarios presented within this report to examine the uncertainty in model results more thoroughly. Nevertheless, it was beyond the scope of the ERG to re-build and re-parameterise all of the company's model inputs to capture parameter uncertainty more appropriately, and so overall uncertainty in the company's model results remains unquantified.

The ERG's tentative preferred base-case analysis yields an ICER in excess of £20,000 per QALY gained and is subjective to substantial uncertainty owing to limitations of the model that were not possible for the ERG to address

The ERG's tentative preferred base-case analysis included several changes to the company's base-case analysis to address some (but not all) of the limitations highlighted earlier in the ERG's report. When combined, these changes resulted in larger total costs and fewer incremental QALYs, causing an increase in the ICER from £17,552 to £23,706. However, the ERG urges caution when interpretating any of the results produced by the company's model because it is subject to a number of important limitations that the ERG was unable to address. Overall, the ERG does not consider the company's model to form a robust basis on which decision making may be based, especially with respect to the lack of comparison to SGLT-2 inhibitors per the final scope issued by NICE.

7. END OF LIFE

The CS contains no mention of finerenone in terms of an end of life treatment. As average life expectancy in this population is notably longer than two years, and the survival extension (measured as the mean incremental, undiscounted LY gain) is less than 3 months, NICE's end-of-life considerations are not applicable to this appraisal and are therefore not discussed further.

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