NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

Contents:

The following documents are made available to consultees and commentators:

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

1. **Company submission** from **Bayer HealthCare**

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submission** from:
   a. Association of British Clinical Diabetologists and UK Kidney Association Joint Committee (endorsed by the Royal College of Physicians)
   b. Kidney Care UK
   c. Primary Care Diabetes Society

4. **Evidence Review Group report** prepared by Peninsula Technology Assessment Group (PenTAG)

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

6. **Technical engagement response from company**
   - Company response
   - New evidence
   - New evidence appendix

7. **Technical engagement responses & expert statements from experts:**
   a. Professor Stephen Bain – clinical expert, nominated by Association of British Clinical Diabetologists
   b. Dr Kieran McCafferty – clinical expert, nominated by Bayer Healthcare

8. **Technical engagement response from consultees and commentators:**
   a. United Kingdom Kidney Association (UKKA) and Association of British Clinical Diabetologists (ABCD) Joint Committee
   b. AstraZeneca
   c. UK Renal Pharmacy Group

9. **Evidence Review Group critique of company response to technical engagement** prepared by Peninsula Technology Assessment Group (PenTAG)
   - ERG Technical Engagement response

- ERG Addendum

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

Document B

Company evidence submission

[UPDATED CONFIDENTIAL MARKING APRIL 2022]

File name	Version	Contains confidential information	Date
ID3773 FINERENONE company- evidence-submission – Document B_[ACIC]	Final	Yes	27.08.2021

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Abbreviations

Abbreviation	Definition
ACEI(s)	Angiotensin-converting-enzyme inhibitor(s)
ACR	Albumin-to-creatinine ratio
ADPKD	Autosomal dominant polycystic kidney disease
AE	Adverse event
AF	Atrial fibrillation
AKI	Acute kidney injury
ARB(s)	Angiotensin receptor blocker(s)
BMI	Body mass index
BT	Background therapy
CADTH	Canadian Agency for Drugs and Technologies in Health
CB	Calcium-based binder
CBA	Cost-benefit analysis
CE	Cost-effectiveness
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CEC	Clinical Event Committee
CG	Clinical Guideline
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CI-AKI	Contrast-induced acute kidney injury
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CRD	Centre for Reviews and Dissemination
CSR	Clinical study report
CUA	Cost-utility analysis
Cum.	Cumulative
CV	Cardiovascular
CVD	Cardiovascular disease
CYP3A4	Cytochrome P450 3A4
DAG	Diagnostic coronary angiography
DARE	The Database of Abstracts of Reviews of Effects
DBP	Diastolic blood pressure
DKD	Diabetic kidney disease
DPP(4)	Dipeptidyl peptidase-4 inhibitors
DSA	Deterministic sensitivity analysis
DSP	Diastolic blood pressure
EC	European Community
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EOS	End of study
EPAR	European public assessment report
EQ-5D(-5L)	EuroQol 5 dimensions (five levels) questionnaire
ERG	Evidence Review Group
ESRD	End stage renal disease
EU	European Union
FAS	Full analysis set
FDA	U.S. Food and Drug Administration
FIN	Finerenone
GCP	Good clinical practice
GLP(-1)	Glucagon-like peptide 1
GP	General practitioner
HAS	The Haute Autorité de Santé

Hb	Haemoglobin
HD	Haemodialysis
HF	Heart failure
HK	Hyperkalaemia
HR	Hazard ratio
HRG	Healthcare Resource Group
HRQoL	Health-related Quality of Life
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
ICH	Intracerebral haemorrhage
IQR	Interquartile range
IS	Ischaemic stroke
ITT	Intention to treat
KDIGO	The Kidney Disease: Improving Global Outcomes
KDQOL-36	Kidney Disease Quality of Life questionnaire (36 questions)
KM	Kaplan Meier
LC	Lanthanum carbonate
LYG	Life-years gained
MAA	Marketing Authorisation Application
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram(s)
MHRA	Medicines & Healthcare products Regulatory Agency
MI	Myocardial infarction
Ml	Millilitre(s)
mmHg	Millimetres of Mercury
MMRM	Mixed model repeated measures
MR	Mineralocorticoid receptor
MRA	Mineralocorticoid receptor antagonist
MRF	Multiple risk factors
NA	Not applicable
NDD	Non-dialysis-dependant
Ng	Nanogram(s)
NHS	National Health Service
NHS EED	NHS Economic Evaluation Database
NICE	The National Institute for Health and Care Excellence
NR	Not reported
NYHA	New York Heart Association
o.d.	omne in die (once a day)
OE	Outcome event
PAOD	Peripheral arterial occlusive disease
PAS	Patient access scheme
PCI	Percutaneous coronary intervention
PD (clinical section)	Premature discontinuation
PD	Peritoneal dialysis
PI	Probability interval
PPS	Per protocol set
Prob.	Probability
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PT	Preferred term
p-years	Patient-years
QALY	Quality-adjusted life years
QoL	Quality of life
RAS	Renin-angiotensin system
RAAS	Renin-angiotensin aldosterone system
RCT	Randomised controlled trial

REACH	Reduction of Atherothrombosis for Continued Health
RRR	Relative risk reduction
RRT	Renal replacement therapy
SAE	Serious adverse event
SAF	Safety analysis set
SBP	Systolic blood pressure
SD	Standard deviation
SGLT2	Sodium-glucose Cotransporter 2
SHPT	Secondary hyperparathyroidism
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
SoC	Standard of care
SOC	System Organ Class
T2D	Type 2 diabetes mellitus
TA	Technology Appraisal
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TLR	Targeted literature review
TTO	Time-trade off
UACR	Urinary albumin-to-creatinine ratio
UK	United Kingdom
UKRR	UK Renal Registry
USA	United States
VDR	Vitamin D receptor

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

B.1.1 Decision problem

The submission covers the technology's full marketing authorisation for this indication.

Table 1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with type 2 diabetes and chronic kidney disease	Adults with chronic kidney disease (stage 3 and 4 with albuminuria) and type 2 diabetes.	This is the proposed indication submitted to EMA.
Intervention	Finerenone	Finerenone	N/A
Comparator(s)	• Established clinical management without finerenone, alone or in combination with angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers or direct renin inhibitors • SGLT2 inhibitors	The comparator to finerenone is standard of care established in clinical practice which is ACEi/ARB. Finerenone is an add-on therapy to ACEi/ARB.	Bayer do not consider that SGLT2i 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 (1). Section 6.2.2 of the 'Guide to the methods of technology appraisal 2013' (1) 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. When considering SGLT2i inhibitors 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 SGLT2 inhibitors as part of the treatment pathway (2). Their place in CG update 2021 is considered but this CG states that *"NICE are reviewing the evidence on SGLT2 inhibitors 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)(3). Most importantly, sales data estimate the market share (by volume) of SGLT2 inhibitors at less than [redacted]% as compared against oral and parenteral hypoglycaemics (4). The guiding principle for comparator selection of section 6.2.3, has not been met. SGLT2 inhibitors do not represent part of established practice in the NHS. As such, comparison should not be made either against the class or any

			particular SGLT2 inhibitor. Importantly, consultee feedback on the draft scope also confirmed that SGLT2is 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 • disease progression • mortality • adverse effects of treatment • health-related quality of life	The outcomes evaluated include: • CKD progression • 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	N/A

B.1.2 Description of the technology being appraised

See appendix C for the draft summary of product characteristics.

Please note – the summary of product characteristics is draft pending finalisation of the marketing authorisation application process. There is no EPAR at this stage.

Table 2. Technology being appraised

UK approved name and brand name	Finerenone (Kerendia)
Mechanism of action	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, HF 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. In vitro affinity assays show that finerenone combines high selectivity and potency for the MR and has no relevant affinity for androgen, progesterone, oestrogen and glucocorticoid receptors. Pre-clinical models demonstrate that, through the selective MR blockade, finerenone exerts its anti-inflammatory and antifibrotic effects in the kidneys, heart and blood vessels, and also counteracts sodium retention and hypertrophic processes (5-8). Clinical evidence of finerenone's novel mode of action is provided by results from FIDELIO-DKD, where finerenone was studied in patients with CKD and T2D. Significant benefits on both renal and CV outcomes were observed, along with only modest effects on systolic blood pressure and no effect on glycated haemoglobin levels (9).
Marketing authorisation/CE mark status	• The application for the marketing authorisation based on the FIDELIO-DKD trial has been made to the EMA. EC Decision Reliance

	Procedure (ECDRP) is the process that will be followed with MHRA. • The EU MAA was submitted in November 2020 (EMA centralised procedure) • CHMP positive opinion for the marketing authorisation is expected in November 2021 It is anticipated that finerenone will receive the marketing authorisation for use in the UK/GB in January 2022
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The proposed indication to EMA is: To delay the progression of kidney disease and to reduce the risk of cardiovascular mortality and morbidity in adults with chronic kidney disease (stage 3 and 4 with albuminuria) and type 2 diabetes. It is likely that caution will be advised for initiation in those patients with an eGFR below 25ml/min/1.73m^2 due to limited clinical data. Therefore, the data presented in this submission is for patients from the FIDELIO-DKD trial with an eGFR≥ 25ml/min/1.73m^2 (10)
Method of administration and dosage	**Method of administration (10):** • Finerenone is administered in an oral tablet form. • Tablets may be taken with a glass of water and with or without food. • Tablets should not be taken with grapefruit or grapefruit juice. • For patients who are unable to swallow whole tablets, Finerenone tablets may be crushed and mixed with water or softs foods, such as apple sauce, directly before oral use. **Dosage (10):** • The starting dose is 10mg finerenone once daily • The recommended dose is 20mg finerenone once daily • The maximum recommended dose is 20mg finerenone once daily
Additional tests or investigations	**Initiation of treatment (10):** Serum potassium and estimated glomerular filtration rate (eGFR) have to be measured to

<table>
<tr><td></td><td>determine if finerenone treatment can be initiated.
• If serum potassium ≤ 4.8 mmol/L, finerenone treatment can be started at 10 mg once daily.
• If serum potassium > 4.8 to 5.0 mmol/L, initiation of finerenone treatment may be considered at 10 mg once daily with additional serum potassium monitoring within the first 4 weeks based on patient characteristics and serum potassium levels
• If serum potassium > 5.0 mmol/L, initiation of finerenone treatment is not recommended
• If eGFR ≥ 25 mL/min/1.73 m2, finerenone treatment can be started at 10 mg once daily.
• If eGFR < 25 mL/min/1.73 m2, initiation of finerenone treatment is not recommended

Continuation of treatment (10):

Serum potassium and eGFR have to be remeasured in all patients 4 weeks after initiation, re-start or increase in dose of finerenone. Thereafter, serum potassium has to be assessed periodically and as needed based on patient characteristics and serum potassium levels.

Continuation of finerenone treatment and dose adjustment
<table>
<tr><th>Serum potassium (mmol/L)</th><th>Treatment instructions and recommended finerenone dose (once daily)</th></tr>
<tr><td>≤ 4.8</td><td>For patients on 10 mg, increase the dose to 20 mg if eGFR has not decreased > 30% compared to the prior measurement.
For patients already on 20 mg, maintain dose.</td></tr>
<tr><td>> 4.8 to 5.5</td><td>Maintain dose.</td></tr>
<tr><td>> 5.5</td><td>Withhold finerenone treatment. Re-start treatment at 10 mg if serum potassium ≤ 5.0 mmol/L.</td></tr>
</table>
</td></tr>
<tr><td>List price and average cost of a course of treatment</td><td>The indicative list price is £55.20 per 30-day supply.</td></tr>
<tr><td>Patient access scheme (if applicable)</td><td>N/A</td></tr>
</table>

CKD=chronic kidney disease; HF=heart failure; MR=mineralocorticoid receptor; T2D=Type 2 diabetes mellitus;

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

Disease overview

Chronic kidney disease (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 3 months, in accordance with current KDIGO guidelines (11). 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 (12). 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 (11-13).

There are multiple possible causes and risk factors for chronic kidney disease (CKD) and its progression, including hypertension, diabetes mellitus, CV 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).

In England, the cost of CKD was estimated at between £1.44 - £1.45 billion (2009-2010), around 1.3% of all NHS spending in that year (14). Healthcare costs for end stage renal disease (ESRD), which affects around 2% of the CKD population are disproportionately expensive with more than half of all CKD costs spent on Renal Replacement Therapy (RRT) (14). Cardiovascular complications associated with CKD e.g. myocardial ischaemia, strokes also have significant financial implications (14).

This submission relates to finerenone, a treatment for delaying the progression of CKD in patients with Type 2 diabetes mellitus (T2D) and will therefore describe CKD in T2D from hereon.

T2D is the leading cause of CKD worldwide (15, 16), with approximately 40% of T2D patients developing CKD (17, 18). The latest QoF publication (2019-2020) estimates the recorded prevalence of diabetes at 7.1% (in ages 17+) (19). Applying this

prevalence to the English (2019, aged 18+) population, this equates to ~ 3.15 million people (20). 90% of cases of diabetes are T2D (21), so it is estimated that approximately, 2.83 million people are currently diagnosed with T2DM.

CKD in patients with T2D is a progressive disease associated with increased risk of kidney and cardiovascular (CV) complications and mortality (11, 22-24). The presence of both CKD and T2D exacerbates CV risk, with a 3 to 6-fold increase in the risk of CV mortality and CV events, respectively, in T2D patients with CKD compared to those with T2D alone (22).

CKD decreases quality of life (QoL) in patients with T2D (25, 26) and is associated with considerable economic burden, with the cost per patient significantly higher than for CKD or T2D alone (27). Over time, CKD can progress to end stage renal disease (ESRD), which can be fatal. The onset of ESRD is associated with high individual and socioeconomic burden and necessitates RRT with chronic dialysis or kidney transplantation to manage kidney failure. As expected, medical resource utilisation and associated costs increase as patients progress to more advanced CKD stages (28).

Diagnosis

CKD is often asymptomatic during the early stages of disease. At later stages, symptoms include lethargy, breathlessness, itchy skin, haematuria, uraemia, cognitive impairment, poor appetite, vomiting, weight loss, and taste disturbance (often present with end-stage disease).

CKD is detectable by screening - confirmatory signs being a persistent reduction in renal function shown by an estimated glomerular filtration rate (eGFR) of < 60 mL/min/1.73 m^2 and/or presence of markers of kidney damage such as proteinuria (urinary albumin : creatinine ratio [UACR] greater than 3 mg/mmol). eGFR is estimated using creatinine-derived equations, such as the Chronic Kidney Disease Epidemiology Collaboration Equation (CKD-EPI) (29).

Due to the asymptomatic character of the early stages of CKD, it is important to ensure patients with diabetes are routinely screened for CKD, in order to detect it early, when

the disease can be slowed or stopped. Screening for CKD typically takes place within the primary care setting and is usually recommended annually for patients with diabetes (see Table 5). In line with NICE CG182 (Chronic kidney disease in adults: assessment and management) (2) , and the recently published NG203 (3), more frequent testing could take place depending on patient choice, eGFR / UACR category on the previous test (see Table 3), underlying cause of CKD, past patterns of eGFR and ACR, comorbidities (including heart failure diabetes and hypertension) or any changes to treatment.

Classification of CKD

The most widely used CKD classification system is based on cause, eGFR (6 categories), and proteinuria (3 categories) and was developed by KDIGO (Kidney Disease: Improving Global Outcomes) (see Table 4). This classification is used within the UK and referred to within the NICE Clinical Guideline for CKD assessment and management that was “live” during the development of this submission (NICE CG182)(2) and in the recently published NG205 (3).

Increasing albuminuria (UACR) and decreasing eGFR are robust independent and additive predictors of increasing risk of CV events, mortality and accelerated progression of kidney disease (30). Indeed, both are considered to fulfil the criteria for surrogacy as end points in phase 3 clinical trials for chronic kidney disease progression by The National Kidney Foundation (NKF) in collaboration with the EMA and FDA (31).

Both primary and secondary renal composite endpoints in the FIDELIO-DKD study described within this submission, incorporated eGFR measures.

The primary composite endpoint included ‘a sustained decrease of eGFR ≥40% from baseline over at least 4 weeks’ which is an established surrogate that predicts progression to kidney failure. Patients with an eGFR below 60 ml/min/1.73 m^2 who have a decline in the eGFR of ≥40% from baseline have a ten-fold higher risk of kidney failure over two years than those with a stable eGFR (32).

The secondary renal composite endpoint in FIDELIO-DKD included ‘a sustained decrease in eGFR of ≥57% from baseline over at least 4 weeks’. This relates to a doubling of serum creatinine from the baseline and is considered a late event in CKD (33). In FIDELIO-DKD, a sustained decrease in eGFR ≥57% from baseline over at least 4 weeks occurred in 167 patients (5.9%) in the finerenone arm and 245 patients (8.6%) in the placebo arm (HR 0.68, 95% CI 0.55- 0.82, log-rank test p<0.0001). Although this analysis was exploratory, due to hierarchical statistical testing, the treatment effect of finerenone in delaying progression of CKD is clearly demonstrable within this outcome.

Change in UACR from baseline to 4 months was also an exploratory endpoint in FIDELIO-DKD. Patients with a UACR >300 mg/g have almost twice the risk of CV death compared to patients with a UACR 30-300 mg/g (34). By analysis of covariance (ANCOVA) test, finerenone was associated with a 31% greater reduction in the UACR from baseline to month 4 than placebo (ratio of least-squares [LS] mean change from baseline [LS means ratio] [finerenone vs. placebo], 0.69; 95% CI, 0.66 to 0.71, p<0.0001), and a lower mean urinary albumin-to-creatinine ratio with finerenone than with placebo was maintained thereafter. Although the statistical testing for this endpoint was exploratory, this result corroborates the treatment effect of finerenone observed for the primary renal composite endpoint.

Table 3. Minimum number of monitoring checks (eGFRcreatinine) per year for adults, children and young people with or at risk of chronic kidney disease (NICE NG203;(3))

Note: ACR monitoring should be individualised based on a person's individual characteristics, risk of progression and whether a change in ACR is likely to lead to a change in management.

	ACR category A1: normal to mildly increased (less than 3 mg/mmol)	ACR category A2: moderately increased (3 to 30 mg/mmol)	ACR category A3: severely increased (over 30 mg/mmol)
GFR category G1: normal and high (90 ml/min/1.73 m^2 or over)	0 to 1	1	1 or more
GFR category G2: mild reduction related to normal range for a young adult (60 to 89 ml/min/1.73 m^2)	0 to 1	1	1 or more
GFR category G3a: mild to moderate reduction (45 to 59 ml/min/1.73 m^2)	1	1	2
GFR category G3b: moderate to severe reduction (30 to 44 ml/min/1.73 m^2)	1 to 2	2	2 or more
GFR category G4: severe reduction (15 to 29 ml/min/1.73 m^2)	2	2	3
GFR category G5: kidney failure (under 15 ml/min/1.73 m^2)	4	4 or more	4 or more

Abbreviations: ACR, albumin creatinine ratio; GFR, glomerular filtration rate.

Table 4. Prognosis of CKD by GFR and albuminuria category developed by KDIGO (11)

Prognosis of CKD by GFR and albuminuria categories: 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 per 1.73 m^2) Description and range	G1	Normal or high	≥90			
	G2	Mildly decreased	60–89			
	G3a	Mildly to moderately decreased	45–59			
	G3b	Moderately to severely decreased	30–44			
	G4	Severely decreased	15–29			
	G5	Kidney failure	<15			

Green = low risk (if no other markers of kidney disease, no CKD)
Yellow = moderately increased risk
Orange = high risk
Red = very high risk.

A=urinary albumin:creatinine ratio category; CKD= chronic kidney disease; G=GFR category; GFR=(estimated) glomerular filtration rate; KDIGO= Kidney Disease: Improving Global Outcomes

Table 5. Summary of NICE, and International key guideline recommendations concerning CKD in T2D

Guideline recommendation:	UACR / eGFR Monitoring frequency	ACEI or ARB	Other
NICE CG 182: Chronic kidney disease in adults: assessment and management (2014) (35)	Variable according to disease status.	In patients with CKD and diabetes with ACR ≥ 3 mg/mmol offer renin-angiotensin system antagonist.	
NICE NG 203: Chronic Kidney Disease: assessment and management. August 2021(3).	Variable according to disease status, see Table 3.	For adults with CKD, hypertension and an ACR of 30mg/mmol or less, follow the recommendations in NICE guideline on hypertension in adults. For patients with CKD who have hypertension and an ACR over 30mg/mmol, offer ACEI or ARB (titrated to the highest licensed dose that the person can tolerate). For adults with CKD and diabetes and related persistent proteinuria if ACR is 3 mg/mmol or more, offer an ACEI or ARB (titrated to the highest licensed dose that the person can tolerate).	NICE are reviewing the evidence on SGLT2 inhibitors in people with CKD and type 2 diabetes and may update recommendations as a result of this. The consultation on this review is scheduled to begin on 1 September 2021, and the review will publish in November 2021.
KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease (2020) (11)	Assess kidney function (e.g., eGFR and ACR) every 3–12 months.	ACEI or ARB initiated in patients with diabetes, hypertension, and albuminuria, - titrated to highest approved dose that is tolerated	An SGLT2i can be added to other anti-hyperglycaemic medications for patients whose glycaemic targets are not currently met or who are meeting glycaemic targets but can safely attain a lower target.

Guideline recommendation:	UACR / eGFR Monitoring frequency	ACEI or ARB	Other
ADA 2020 Microvascular Complications and Foot Care: Standards of Medical Care in Diabetes 2020 (36)	Annually. Twice a year in patients with UACR > 30 mg/g and/or an eGFR<60 mL/min/1.73m^2 to guide therapy.	Optimise blood pressure control to reduce the risk or slow the progression of CKD.	In patients with CKD who are at increased risk for CV events, use of a glucagon-like peptide 1 receptor agonist may reduce risk of progression of albuminuria, CV events, or both. In patients with T2D and CKD consider use of SGLT2i in patients with an eGFR > 30 mL/min/1.73 m^2 and UACR > 30 mg/g creatinine, particularly those >300 mg/g.
2019 ESC / EASD ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD (37)	It is recommended that patients with diabetes are screened annually for kidney disease by assessment of eGFR and urinary albumin: creatinine ratio.	On-treatment SBP to <130 mmHg should be considered for patients at high risk of cerebrovascular events or diabetic kidney disease. ACEIs and ARBs are the preferred antihypertensive drugs in patients with albuminuria.	SGLT2 inhibitors are recommended to reduce progression of diabetic kidney disease
IDF 2017 Clinical Practice Recommendations for managing Type 2 Diabetes in Primary Care	Screen for albumin in urine every year (microalbuminuria)	Patients with T2D and hypertension should be treated to a diastolic BP target of 80 mmHg and an SBP target of 130 to 140 mmHg. Consider the lower target when they are younger or when additional CV risk factors or microvascular disease are present.	

Guideline recommendation:	UACR / eGFR Monitoring frequency	ACEI or ARB	Other
		Persistent albuminuria requires treatment with an ACE inhibitor or an ARB.	

ACEI=Angiotensin-converting enzyme inhibitor; ADA=American Diabetes Association; ARB=angiotensin receptor blocker; CG=clinical guideline; CKD=chronic kidney disease; CV=cardiovascular; EASD= European Association for the Study of Diabetes; eGFR=estimated glomerular filtration rate; ESC=European Society of Cardiology; IDF= International Diabetes Federation; KDIGO= Kidney Disease: Improving Global Outcomes; NICE= National Institute for Health and Care Excellence; QS=quality standard; SBP=systolic blood pressure; SGLT2i= sodium glucose co-transporter-2 inhibitor; T2D=type 2 diabetes mellitus; UACR=urinary albuminuria – to – creatinine ratio; UK=United Kingdom;

Current Management of CKD in T2D

Optimal treatment of CKD in T2D is facilitated by early detection, hence the importance of regular CKD screening in patients with diabetes. Identification of patients with early signs of CKD enables implementation of disease management strategies to reduce the risk of progression to end-stage renal disease (ESRD) and of CV events (38), thereby improving patient outcomes and reducing the impact of CKD on healthcare resources. There is international consensus on this approach in guidelines on CKD (11, 35-37) (see Table 5 for summary of guideline recommendations concerning CKD in T2D).

Several key interventions in early-stage CKD take place within primary care. Early treatment includes advice and lifestyle changes to diet, exercise, alcohol intake and cessation of smoking. Alongside dietary and lifestyle interventions, proven pharmacological strategies for CKD prevention and treatment in T2D patients are to reduce the rate of progression of CKD by optimisation of blood pressure control, lipid levels (using statins), and glycaemic control (using anti-diabetics) (39).

To control blood pressure, renin-angiotensin system (RAS)-inhibition using angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), constitute the current standard of care according to many CKD / T2D guidelines including those from KDIGO (11), the American Diabetes Association (ADA) (36), NICE (2, 3) and joint guidelines from the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD) (37). For many years, ACEIs / ARBs have been the standard of care treatments for patients with CKD in T2D for retarding the progression toward end-stage renal disease (40-43).

In more recent clinical studies, the addition of the sodium-glucose cotransporter-2 (SGLT2) inhibitor canagliflozin to a RAS blocker has also shown a benefit on cardiorenal outcomes in T2D patients with CKD (44); and the administration of dapagliflozin in patients with CKD with or without T2D has also shown a benefit on cardiorenal outcomes (45). This has led to international guidelines now recommending SGLT2 inhibitors in addition to RAS blockers for patients with T2D with albuminuria > 300 mg/g if their eGFR is > 30 mL/min/1.73 m^2 (11, 36, 37). The “live” NICE clinical guidelines in place during the development of this submission (2), make no reference

to SGLT2 inhibitors as part of the treatment pathway. Their place in CG update 2021 is considered but this CG states that *"NICE are reviewing the evidence on SGLT2 inhibitors in people with CKD and type 2 diabetes"* and may update recommendations as a result of this (consultation during September 2021 and publication in November 2021) (3). Due to SGLT2s being only a recent addition to international guidelines, and their place in therapy is being reviewed by NICE, this evidence has not yet translated into widespread changes in established clinical practice in the UK. Consultee feedback on the draft scope also confirmed that SGLT2is should not be considered a comparator as they are not part of standard of care. Further, SGLT2i are not appropriate for all patients with type 2 diabetes (46) and CKD and there have been a number of MHRA safety updates about their use (47-50).

Despite standard of care therapy and recent emerging therapies, overall, there remains a high residual risk of cardiorenal events in patients with CKD and T2D (42, 44, 51). Hence, there is a need for additional treatment options to further reduce cardiorenal morbidity and mortality in patients with CKD and T2D.

Finerenone – a new treatment modality for CKD

Contemporary models of CKD in T2D propose haemodynamic, metabolic, inflammatory and fibrotic factors as interrelated pathophysiological drivers of CKD progression (18). There is substantial evidence from experimental models that pathophysiological mineralocorticoid receptor (MR) overactivation is a key trigger of inflammation and fibrosis, contributing to the high rate of cardiorenal morbidity and mortality in affected individuals (52). Existing therapies for CKD in T2D primarily target metabolic and haemodynamic factors but not MR overactivation or resultant inflammation and fibrosis. This leaves scope for introduction of further effective therapies to address this underlying disease mechanism.

Finerenone selectively targets MR overactivation and thus prevents pro-inflammatory and pro-fibrotic processes leading to organ damage and dysfunction. By its selectivity to the MR with its non-steroidal structure and accompanying properties, finerenone offers a viable treatment to address the unmet medical need in patients with CKD and T2D (see section B2.12 Innovation for further information). This therapeutic approach

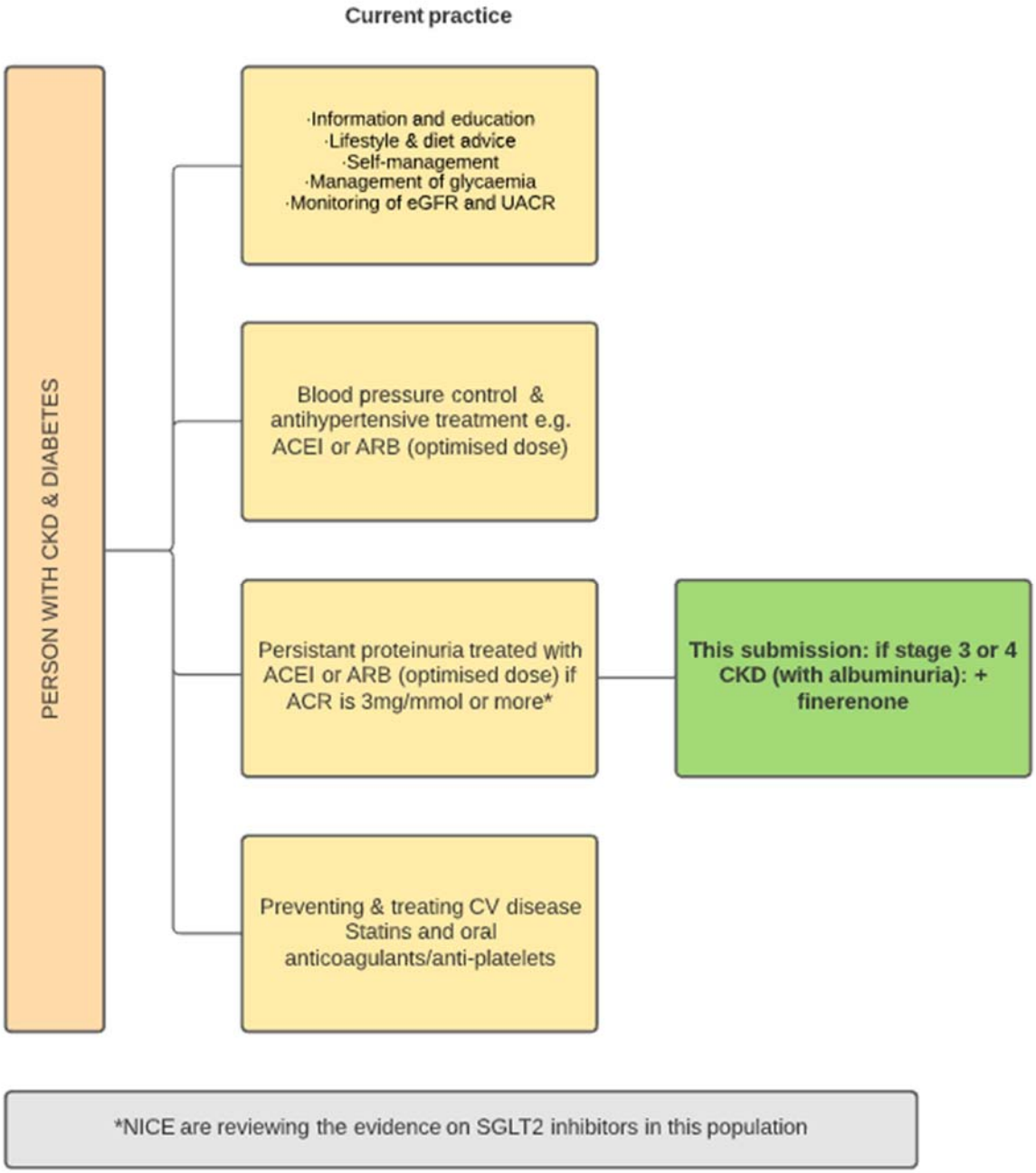
in patients with CKD and T2D was investigated in FIDELIO-DKD, a phase 3 RCT which investigated whether the non-steroidal MRA, finerenone, can slow the progression of kidney disease in patients with the clinical diagnosis of CKD. Results of FIDELIO-DKD, presented within this submission, demonstrate significant benefits of finerenone treatment added to standard of care RAS inhibitors, on both renal and CV outcomes (9).

The introduction of finerenone and its effect on the current management pathway

As described above, UK and global established clinical practice in patients with CKD in T2D, has been the administration of ACEIs and ARBs to slow the progression toward end-stage renal disease.

Finerenone would be introduced into clinical practice as an add-on therapy to ACEI / ARB to reduce the residual risk of CV and renal events and would not displace any treatment. The proposed indication for finerenone to EMA is 'to delay the progression of kidney disease and to reduce the risk of cardiovascular mortality and morbidity in adults with chronic kidney disease (stage 3 and 4 with albuminuria) and type 2 diabetes'. This target population was based on the staging system for CKD as defined by KDIGO guidelines (11) and is considered to best represent the FIDELIO-DKD study population which consists of approximately 90% of patients with CKD stages 3 and 4.

Figure 1. Current management pathway for patients with CKD and T2D (adapted from NICE pathways: management of chronic kidney disease)



ACEI=Angiotensin-converting enzyme inhibitor; ARB=angiotensin receptor blocker; CG=clinical guideline; CKD=chronic kidney disease; CV=cardiovascular; NICE= National Institute for Health and Care Excellence; T2D=type 2 diabetes mellitus; UACR=urinary albuminuria – to – creatinine ratio;

The clinical results from FIDELIO-DKD demonstrates finerenone's ability to delay the progression of CKD and reduce adverse CV outcomes. Any intervention which will reduce pressure on NHS services, considering the inevitable backlog as a result of the COVID-19 pandemic, could be considered a priority (53). By reducing important and costly CV events and delaying progression of CKD in T2D, finerenone would be a

timely addition to the treatment options available to clinicians in order to meet the needs of different patients in the NHS.

B.1.4 Equality considerations

Bayer considers there may be equality issues associated with this appraisal when considering race and socioeconomic status.

Principle 9, of the principles that guide the development of NICE guidance (54) is “aim to reduce health inequalities.” The Equality Act 2010, refers to groups with protected characteristics (55), including race. NICE should also take account of inequalities arising from socioeconomic factors.

Chronic kidney disease may disproportionately affect patients from lower socio-economic groups and those from Black, Asian and minority Ethnic populations. Finerenone is a treatment which has been shown to be efficacious in delaying progression of CKD and can therefore help to address these health inequalities.

A report by Kidney Research UK (56)reported that:

- People from lower socio-economic groups are more likely to:
    - Have risk factors associated with CKD such as diabetes and hypertension
    - Develop CKD
    - Progress faster towards kidney failure
    - Die earlier with CKD
    - Be diagnosed at a later stage of the disease
    - Have poorer survival rates on dialysis
- People from lower socio-economic groups are less likely to:
    - Be offered peritoneal dialysis (potentially related to the home environment)
    - Have a transplant

- People from Black, Asian and Minority Ethnic populations:
    - Have a greater burden of risk factors for kidney disease such as diabetes and hypertension
    - Are more likely to progress faster towards kidney failure
    - Are less likely to receive a kidney transplant
    - Have a different pattern of uptake of home dialysis therapies

The report states that people from South Asian and Black backgrounds are 3-5 times more likely to start dialysis than people from Caucasian backgrounds. Those of South Asian, Black African and Black Caribbean descent are therefore over-represented on dialysis programmes, making up 22.7% of people in the UK receiving renal replacement therapy. In some London boroughs, this rises to over 60% of people.

Further aspects identified by the report:

- There are more people with kidney disease in areas of high social deprivation
- Access to dialysis services can be very challenging in some rural areas
- There are high rates of severe mental illness amongst people with CKD and those receiving dialysis

The report states that “improving prevention and early detection and ensuring that everyone in the UK has access to the right treatment for them, is key to improving kidney health for the whole UK population.” Further “Reducing health inequalities, particularly preventing the development and progression of kidney disease in all UK populations may help alleviate the burden of kidney care to the NHS.”

Finerenone is a treatment which has been shown to be efficacious in delaying progression of CKD, with the FIDELIO-DKD study including ~37% non-white patients and can therefore help to address these health inequalities as a simple once daily oral medication.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

One completed and published phase 3 clinical study (FIDELIO-DKD) was identified relating to the efficacy of finerenone in delaying the progression of kidney disease and reducing the risk of adverse cardiovascular events in adults with chronic kidney disease (CKD) (stage 3 and 4 with albuminuria) and type 2 diabetes (T2D).

As an event-driven study in 5734 patients with a median follow-up duration of 2.6 years, FIDELIO-DKD is one of the largest contemporary studies to evaluate patients with CKD and T2D.

The design paper of a further phase 3 clinical study (FIGARO-DKD) was also identified but excluded during title and abstract review. This study has recently completed but data is not yet available at the time of this submission (see section B.2.11 Ongoing studies).

Three phase 2 studies (The ARTS studies) were also identified in the systematic literature review; however these were primarily dose-finding studies, establishing the optimal dosing for finerenone in its target population and will not be discussed in this submission (ARTS-DN (57); ARTS (58); ARTS-HF (59)).

See appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised.

B.2.2 List of relevant clinical effectiveness evidence

Table 6. Clinical effectiveness evidence

Study	**FIDELIO-DKD**: **FI**nerenone in reducing ki**D**n**E**y fai**L**ure and d**I**sease pr**O**gression in **D**iabetic **K**idney **D**isease;
Study design	Randomised, double-blind, placebo-controlled, parallel-group, multicentre, event-driven Phase 3 study
Population	Patients with type 2 diabetes mellitus (T2D) and the clinical diagnosis of chronic kidney disease (CKD)
Intervention(s)	Finerenone (in addition to standard of care*) 10 or 20mg o.d. (target dose is 20mg o.d.) N=2866 patients randomised
Comparator(s)	Placebo (in addition to standard of care*)

Study	**FIDELIO-DKD**: **FI**nerenone in reducing ki**D**n**E**y fai**L**ure and d**I**sease pr**O**gression in **D**iabetic **K**idney **D**isease;				
	N=2868 patients randomised				
Indicate if trial supports application for marketing authorisation	Yes	✓	**Indicate if trial used in the economic model**	Yes	✓
	No			No	
Rationale for use/non-use in the model	The FIDELIO-DKD trial provides the only available phase 3 randomised controlled trial (RCT) results in the population of interest.				
Reported outcomes specified in the decision problem	The outcomes listed in the decision problem are: • **CKD progression** • **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**				
All other reported outcomes	• Time to the first occurrence of the composite endpoint of onset of kidney failure, a sustained decrease of eGFR ≥40% from baseline over at least 4 weeks, or renal death (primary endpoint) • Time to first occurrence of CV death, non-fatal MI, non-fatal stroke, or hospitalisation for heart failure (key secondary endpoint) • Change in UACR from baseline to Month 4 (secondary endpoint) • Time to the first occurrence of kidney failure, a sustained decrease in eGFR of ≥57% from baseline over at least 4 weeks, or renal death (secondary endpoint) • Time to all-cause hospitalisation (secondary endpoint)				

* standard of care consists of maximally tolerated doses of ACEI/ARB
ACEI=angiotensin-converting enzyme inhibitor; ARB=angiotensin receptor blocker; CKD=chronic kidney disease; n=number of patients; o.d.=once daily; RCT=randomised controlled trial; T2D=Type 2 diabetes mellitus;

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

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 ACEI (angiotensin-converting enzyme inhibitor) or an ARB (angiotensin receptor blocker).

FIDELIO-DKD: A randomised, double-blind, placebo-controlled, parallel-group, multicentre, event-driven Phase 3 study to investigate the efficacy and safety of finerenone, in addition to standard of care, on the progression of kidney disease in subjects with type 2 diabetes mellitus and the clinical diagnosis of diabetic kidney disease (FIDELIO-DKD - FInerenone in reducing kiDnEy faiLure and dIsease prOgression in Diabetic Kidney Disease); (Study no. 16244) (NCT 02540993) (9, 60-67)

The primary objective of FIDELIO-DKD was to determine whether, in addition to standard of care, finerenone is superior to placebo in delaying the progression of kidney disease, as measured by the composite endpoint of time to first occurrence of kidney failure, a sustained decrease of eGFR ≥40% from baseline over at least 4 weeks, or renal death.

The key secondary objective of the study was to determine whether, in addition to standard of care, finerenone compared to placebo, delayed the time to first occurrence of the composite of cardiovascular (CV) death or non-fatal CV events (i.e. non-fatal myocardial infarction, non-fatal stroke, hospitalisation for heart failure (HF)). Other secondary objectives included assessment of the effect of finerenone on all-cause mortality, hospitalisation, the urinary-albumin to creatinine ratio (UACR) (over the first 4 months of treatment), and the composite endpoint of onset of kidney failure, a sustained decrease of eGFR ≥57% from baseline over at least 4 weeks or renal death.

Key aspects of the study design were published in 2019 (Bakris 2019 (60)). Key results from FIDELIO-DKD were published in October 2020 in The New England Journal of Medicine (Bakris et al. 2020 (9)). Unpublished aspects of the study are drawn from the

Clinical Study Protocol (CSP)(63), manufacturer licence application submission to the European Medicines Agency (EMA)(61, 62, 66), Statistical Analysis Plan (67) and the Clinical Study Report (CSR) (64).

Notes:

- *The proposed indication for finerenone is 'to delay the progression of kidney disease and to reduce the risk of cardiovascular mortality and morbidity in adults with chronic kidney disease (stage 3 and 4 with albuminuria) and type 2 diabetes'. This target population was based on the staging system for CKD as defined by KDIGO guidelines (11) and is considered to best represent the FIDELIO-DKD study population which consists of approximately 90% of patients with CKD stages 3 and 4. It is likely that caution will be advised for initiation in patients with an eGFR below 25ml/min/1.73m^2 due to limited clinical data. Therefore, clinical evidence will be presented in the submission for both the overall FIDELIO-DKD study population and also the anticipated EMA label population i.e. FIDELIO-DKD patients with eGFR ≥ 25 to <60ml/min/1.73 m^2 and albuminuria at baseline.*

- *Throughout the submission*
    - *use of 'Finerenone' and 'placebo' refers to the 'finerenone plus standard of care' and 'placebo plus standard of care' respectively.*
    - *use of 'label population' refers to 'the anticipated EMA label population (see above)'.*

Trial design and methodology (9, 60, 61, 63, 64)

FIDELIO-DKD is an international, phase 3, multicentre, randomised, double-blind, placebo-controlled, event-driven trial.

The study took place in 1024 study centres across 48 countries:

• Western Europe (Austria, Belgium, Denmark, Finland, France, Germany, Ireland, Italy, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, United Kingdom (UK)),

- Eastern Europe (Bulgaria, Czech Republic, Greece, Hungary, Lithuania, Poland, Romania, Russia, Slovakia, Turkey, Ukraine)
- Middle East (Israel)
- Africa (South Africa)
- North America (United States [US], Canada),
- Central & South America (Argentina, Brazil, Chile, Colombia, Mexico, Puerto Rico)
- Australia, New Zealand and Asia (China, Hong Kong, Japan, Malaysia, Philippines, Singapore, South Korea, Taiwan, Thailand, Vietnam).

There were [redacted] clinical trial centres in the UK, randomising a total of [redacted] patients. [redacted]

Study enrolment started in September 2015 and was completed June 2018, during which time a total of 13,911 patients underwent screening and 5734 patients with CKD and T2D were randomised in a 1:1 ratio to receive oral finerenone (10 mg or 20 mg once daily) or placebo, in addition to standard of care. The starting dose of finerenone was determined by the estimated glomerular filtration rate [eGFR] at the screening visit. The dose was titrated up or down according to potassium and eGFR changes (see 'Intervention'). The final patient visit in the study was 14th April 2020.

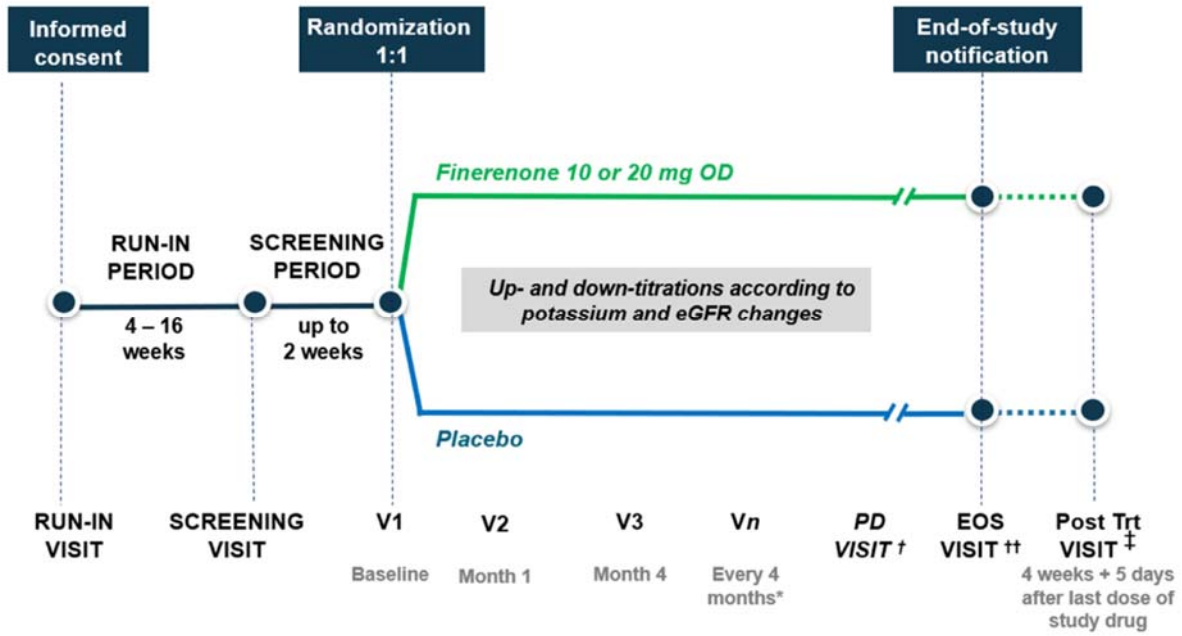
Prior to screening and subsequent randomisation, the design of FIDELIO-DKD (see Figure 2) included a run-in period of 4 to 16 weeks duration to optimise guideline-directed standard of care therapy with renin–angiotensin system (RAS) inhibitors. ACEIs or ARBs were adjusted to the maximum dose on the manufacturer's label that did not cause unacceptable side effects.

After randomisation, trial visits were conducted at month 1, month 4, then every 4 months until trial completion. FIDELIO-DKD continued until the protocol-required number of primary efficacy endpoint events was reached (approx. 712 events) and the end of study was notified. Patients were assessed at follow-up visits for outcome and

adverse events. Study visits also included central laboratory values, including serum potassium and serum creatinine, physical examinations (including measurements of weight and vital signs) and 12-lead electrocardiograms (ECG). Health-related quality-of-life (HRQoL) questionnaires (EQ-5D-5L and Kidney Disease Quality of Life) were completed at baseline and yearly thereafter.

Patients were monitored and followed for efficacy and safety events until the study end, even if study drug treatment had been discontinued. Patients who experienced a health event considered for the pre-specified primary or secondary endpoints, were encouraged to continue study drug until the trial was completed provided there were no safety grounds for discontinuing treatment (63). Permanent discontinuation of study drug was recommended if a recurrent hyperkalaemia event was experienced soon after a previous hyperkalaemia event with interruption of study drug if there was no explanation for the recurring event other than intake of study drug.

Figure 2. FIDELIO-DKD study design



* Scheduled visits continued even if treatment with study drug was discontinued
† PD Visit conducted only after permanent withdrawal from treatment
†† EOS Visit conducted after notification of end-of-study by Bayer
‡ Post-treatment Visit for all subjects on study drug treatment at EOS

eGFR=estimated glomerular filtration rate; EOS=end-of-study; OD=once daily; PD=premature discontinuation; Post Trt=post-treatment; V=visit;

Method of randomisation (63)

Randomisation was performed within ≤2 weeks after the screening visit, via an interactive telephone / web-based system. Using a computer-generated random sequence, a unique 9-digit subject identification (SID) number was assigned to each patient for unambiguous identification throughout the study.

Eligible patients were randomised 1: 1 to receive once-daily treatment with either finerenone or placebo, with stratification 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])

Masking

Patients and investigators were blinded to treatment with the aid of a unique 9 digit identification number, assigned to each patient, used throughout the trial, including on treatment packs and trial administration forms. Packaging and labelling was also designed to maintain blinding, and finerenone and placebo tablets were identical in appearance (size, shape, colour) (63).

The independent Clinical Event Committee (CEC), adjudicating all renal and CV endpoint events, as well as all deaths and hospitalisations, were also blinded to treatment allocations (61).

Patient selection

Selection criteria were chosen to adequately define a DKD study population at high risk of progressing with their CKD towards end stage renal disease (ESRD) or developing CV events, but excluding patients who may be exposed to particular risks after study drug administration or those with conditions that may have an impact on the aims of the study (63).

Eligibility criteria

Table 7. FIDELIO-DKD inclusion and exclusion criteria (9)

Inclusion criteria	Exclusion criteria
Aged ≥18 years with: • T2D as defined by the American Diabetes Association in the 2010 Standards of Medical Care in Diabetes, and • a diagnosis of CKD based on meeting persistent albuminuria (≥2 out of 3 morning void samples taken on consecutive days assessed by the central laboratory) and eGFR† criteria at the run-in and screening visits – specifically, either: o Persistent moderately elevated ('high') albuminuria (UACR ≥30–<300 mg/g [≥3.4–<33.9 mg/mmol]) and eGFR ≥25–<60 mL/min/1.73 m^2 and presence of diabetic retinopathy in the medical history, or o Persistent severely elevated ('very high') albuminuria (UACR	Any history of or current: • Known significant non-diabetic kidney disease, including clinically relevant renal artery stenosis • Glycated haemoglobin >12% at the run-in visit or the screening visit • Uncontrolled arterial hypertension with mean sitting SBP≥170 mmHg or mean sitting DBP ≥110 mmHg at the run-in visit or mean sitting SBP ≥160 mmHg or mean sitting DBP ≥100 mmHg at the screening visit • A mean SBP <90 mmHg at the run-in visit or screening visit • Clinical diagnosis of chronic heart failure with reduced ejection fraction and persistent symptoms (NYHA class II–IV) at the run-in visit (i.e., a class IA

≥300–≤5000 mg/g [≥33.9–≤565 mg/mmol]) and an eGFR ≥25–<75 mL/min/1.73 m^2) • Prior treatment with an ACEI or ARB as follows: o For ≥4 weeks prior to the run-in visit, treated with either an ACEI or an ARB or both o Starting with the run-in visit, treated with only an ACEI or ARB o 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 ACEI or an ARB (not both) preferably without any adjustments to dose • Serum potassium ≤4.8 mEq/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	recommendation for a mineralocorticoid receptor antagonist) • Stroke, transient ischaemic cerebral attack, acute coronary syndrome, or hospitalisation for worsening heart failure, in the 30 days before the screening visit • Receiving dialysis for acute kidney failure ≤12 weeks prior to the run-in visit • A kidney transplant, or scheduled for a kidney transplant within 12 months of the run-in 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

ACEI=angiotensin-converting enzyme inhibitor; ARB= angiotensin receptor blocker; CKD=chronic kidney disease; DBP=diastolic blood pressure; eGFR=estimated glomerular filtration rate; mmHg= millimetres of mercury; NYHA= New York Heart Association; SBP=systolic blood pressure; T2D=Type 2 diabetes; UACR=urinary-albumin-to-creatinine ratio;

† eGFR, calculated with the use of the Chronic Kidney Disease Epidemiology Collaboration formula, with adjustment for race in Black patients (29)

The number of patients with eGFR ≥60 to <75 mL/min/1.73 m2 and very high albuminuria was capped at approximately 10% of the total population with very high albuminuria at screening. The number of patients with high albuminuria and presence of diabetic retinopathy in the medical history was capped at approximately 10% of the total population at screening.

Interventions

The starting dose of study drug was selected based on eGFR measured 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.

Study drug tablets were taken orally, once daily around the same time every day. A 2-step titration scheme allowed for an individualised dose adaptation depending on patient clinical status and tolerability. Up-titration of study drug to the target dose of 20 mg / day was permitted from Month 1 onwards and down-titration to 10 mg / day at any time after start of treatment (see Table 8). Sham titration occurred for placebo patients. 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.

Table 8. Study drug administration (9, 63)

eGFR value at screening	25 to <60 mL/min/1.73m^2		≥60 mL/min/1.73m^2	
Randomised assigned treatment	**Finerenone** 10mg o.d. + standard of care[a]	**Placebo** o.d. + standard of care[a]	**Finerenone** 20mg o.d. + standard of care[a]	**Placebo** o.d. + standard of care[a]
Missed tablet	• If > 8 hours before the next scheduled dose, tablet should be taken as soon as possible. • If <8 hours before next scheduled dose, patient should wait and take next tablet at the usual time.			
Up-titration of dose	From Visit 2 if: • Potassium ≤ 4.8 mmol/L [b] • eGFR had not decreased > 30% from previous visit [b]			
	to 20mg finerenone o.d. and maintain standard of care[a]	Sham-titrate and maintain standard of care[a]	Not applicable	Not applicable
Down-titration of dose Permitted only for safety reasons at any time during study.	• If at 20mg o.d. dose, down-titrate to 10mg o.d. and maintain standard of care[a]. • If at 10mg o.d. dose, interrupt study drug, while maintaining standard of care[a].			

eGFR=estimated glomerular filtration rate; mg=milligram(s); min=minute; o.d.=once daily;
[a] ACEIs and ARBs are considered as standard of care therapy in patients with CKD and T2D. Maximum tolerated labelled dose for ACEIs or ARBs were administered or according to local labels, as applicable, for which the patient could safely tolerate. The dose was not to be below the minimum labelled dose to maximise therapeutic benefit of background standard of care.
[b] potassium and eGFR according to local laboratory values

Missed tablets - see Table 8

Treatment compliance

Drug dispensing logs were maintained for each study participant. Patients were instructed to return all study drug packaging including unused study drug and empty packaging with accountability checked and recorded at each visit (63).

Mean adherence to the study regimen (the percentage of administered doses relative to the number of planned doses) was 92.1% in the finerenone group and 92.6% in the placebo group, and the mean daily dose was 15.1 mg and 16.5 mg in the respective groups (9).

Mean treatment duration was 26.88 months for the finerenone group and 27.16 months in the placebo group (62).

Permitted and disallowed concomitant medications (9, 62)

Disallowed concomitant medications are outlined in the exclusion criteria (Table 7).

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 the patient started study drug, showed comparable results for the 2 treatment arms (90.6% in finerenone, 90.8% in placebo). Usage of new non-anti-diabetic medications of interest was recorded for 81.5% finerenone patients and 82.4% placebo patients. The most frequent new medications were diuretics (used by 42.8% finerenone patients, 45.4% placebo patients), calcium channel blockers (35.3% finerenone, 41.5% placebo) and loop diuretics (32.5% finerenone, 34.8% placebo). Other new non-antidiabetic medications of interest were statins (29.4% finerenone, 30.3% placebo), alpha-blocking agents (28.5% finerenone, 31.0% placebo), and beta-blockers (27.1% finerenone, 30.1% placebo). In general, a lower proportion of patients were initiated on anti-hypertensive therapy in the finerenone arm compared to placebo. More patients in the finerenone arm (10.8%) compared to placebo (6.5%) started potassium-lowering agents, while less patients started potassium supplements in the finerenone arm (6.7%) than in the placebo arm (8.7%).

New anti-diabetic medication was recorded for 63.3% finerenone patients and 64.8% placebo patients. Most frequently these were insulins and analogues (47.1% finerenone, 48.7% placebo) followed by biguanides (18.2% finerenone, 17.4% placebo) and Dipeptidyl peptidase-4 (DPP-4) inhibitors (16.7% in both arms). GLP-1 (glucagon-like peptide 1) receptor agonists were started by 9.2% of finerenone patients and 9.3% in the placebo arm; SGLT2 (sodium–glucose cotransporter 2) inhibitors were started by 6.6% of finerenone patients and 7.6% in the placebo arm.

Efficacy outcome measures used in the economic model or specified in the scope

The primary efficacy outcome in FIDELIO-DKD was the composite of time to first occurrence of kidney failure, a sustained decrease of eGFR ≥40% from baseline over at least 4 weeks, or renal death. Table 9 summarises all relevant FIDELIO-DKD study endpoints, including details of when / how each were measured.

All endpoints described were pre-specified in the analyses and were appropriate measures for this events-driven trial. All evaluations were in accordance with Good Clinical Practice (GCP) to ensure safety of patients participating in research.

An independent CEC blinded to treatment allocations adjudicated all potential endpoint events, as well as all deaths and hospitalisations, using pre-specified definitions. For eGFR-based endpoints, consecutive central laboratory measurements of eGFR were necessary.

Pre-defined disease-related outcome events categorized as efficacy variables were not documented as (serious) adverse events ([S]AEs).

Table 9. Relevant endpoints and measures in FIDELIO-DKD (9, 62)

Endpoint	Definition & timing of assessment / measure
Primary Efficacy Endpoint	
Composite of: • **kidney failure,** • **a sustained decrease of eGFR† ≥40% from baseline over at least 4 weeks, or** • **renal death**	Time (in days) from randomisation to first occurrence of any of the endpoint components. Kidney failure was defined as • ESRD included 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 † < 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 (29) 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. Sustained decrease ≥40% in eGFR compared to baseline over ≥4 weeks was defined by evidence of ≥2 consecutive central laboratory assessments of eGFR. The confirmatory sample for

Endpoint	Definition & timing of assessment / measure
	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. 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.
Key Secondary Endpoint	
Time to first occurrence of CV mortality and morbidity **A composite of:** • **first occurrence of CV death,** • **non-fatal myocardial infarction (MI),** • **non-fatal stroke, or** • **hospitalisation for heart failure**	Time (in days) from randomisation to first occurrence of any of the endpoint components. Full details of Cardiovascular endpoint definitions are presented in Appendix O. 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 **Acute myocardial infarction (MI)** was defined based on detection of rise and/or fall in cardiac biomarkers (preferably cardiac troponin [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 • Electrocardiogram (ECG) changes indicative of new ischaemia (new ST-T changes or new left bundle branch block [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 Percutaneous coronary intervention (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

Endpoint	Definition & timing of assessment / measure
	with a procedural complication, or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality, were required. Coronary artery bypass grafting (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. **Stroke:** 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. **Hospitalisation due to heart failure** 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
Other Secondary Endpoints (in order of sequential hierarchical testing)	
Time to all-cause mortality	Time (in days) from randomisation to mortality by any cause. Causes of death were classified into three categories: • cardiovascular (CV) death (see key secondary endpoint for definition), • renal death (see primary endpoint 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.
Time to all-cause hospitalisation	Time (in days) from randomisation to the first hospitalisation by any cause.
Change in UACR from baseline to 4 months	

Endpoint	Definition & timing of assessment / measure
A secondary renal composite endpoint of: • **kidney failure or** • **sustained decrease in eGFR† ≥57% from baseline over at least 4 weeks or** • **renal death.**	Time (in days) from randomisation to first occurrence of any of the endpoint components. Kidney failure – see primary endpoint for definition Sustained decrease in eGFR≥57% from baseline over at least 4 weeks. See primary endpoint for definition and rules for assessment. Renal death – see primary endpoint for definition
Other endpoints	
Individual components of the primary and secondary outcomes	As described under primary and secondary outcomes.
New diagnosis of atrial fibrillation or atrial flutter	Any new diagnosis of atrial fibrillation or atrial flutter. This endpoint was independently adjudicated by the CEC.
Health Related Quality of Life (HRQoL): **Kidney Disease Quality of Life (KDQOL-36)** **European Quality of Life (EuroQol) – 5 Dimension (EQ-5D-5L)**	The health-related quality of life questionnaires (KDQOL-36 and EQ-5D-5L) were completed by patients at Visit 1, the yearly visits and at the PD and EOS Visits. KDQOL-36 is a specific measure of health-related quality of life for CKD that includes effects and burden of kidney disease as well as physical and mental health scores. KDQOL-36 consists of 36 questions and contains the SF-12 (general health aspects-physical and mental components summary) and the disease-specific part has 3 subscales with 4 items for burden of kidney disease, 12 items for symptoms and problems, and 8 items for effects of kidney disease on daily life. The domain scores are calculated by summation of the relevant item scores and transformation into a range from 0 to 100, with higher scores indicating better health related quality of life. The EQ-5D-5L was introduced in 2005. The EQ-5D-5L consists of 2 pages: the EQ-5D-5L descriptive system and the EQ Visual Analogue scale (EQ VAS). The descriptive system comprises the same 5 dimensions as the EQ- 5D-3L (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). However, each dimension now has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems.
Safety	Adverse event (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 Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0. Laboratory tests (serum potassium and creatinine) were measured at all trial visits. Vital signs, weight and BMI were also assessed at each visit.

AE=adverse events; AKI=Acute Kidney Injury; BMI=body mass index; BNP= B-type natriuretic peptide; CKD=chronic kidney disease; 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; MI=myocardial infarction; MedDRA=Medical Dictionary for Regulatory Activities; PD=premature discontinuation; RRT=renal replacement therapy; TEAE=Treatment-emergent adverse event; URL=Upper reference limit;
† For eGFR-based endpoints, consecutive central laboratory measurements of eGFR were necessary. Estimations of GFR were calculated based on the CKD-EPI formula (29)

Other exploratory efficacy variables included the composite endpoint of time to CV death, kidney failure, eGFR decrease of ≥57% sustained over at least 4 weeks or renal death; Change in UACR from baseline; Change in eGFR from baseline. These endpoints are not included in the economic model / decision problem; hence their results are not presented within this submission.

See section B2.7 for details of pre-planned subgroups.

Patient Baseline characteristics

Patient baseline characteristics are presented in Table 10.

Overall FIDELIO-DKD population (9)

Baseline demographics and disease characteristics of patients were similar between treatment groups. The overall FIDELIO-DKD trial population is predominately male (70.2%) and white (63.3%), with a mean age of 65.6 years. More than 40% of the patients were recruited in Europe.

At baseline, mean eGFR was 44.3 mL/min/1.73 m^2, mean serum potassium 4.37 mmol/litre, and median UACR 852 mg/g. Most patients (88.4%) had eGFR < 60 mL/min/1.73 m^2 and 54.9% eGFR < 45 mL/min/1.73 m^2; the majority of patients (87.5%) had very high albuminuria (≥300 mg/g) at baseline.

The mean duration of diabetes was 16.6 years and mean glycosylated haemoglobin was 7.7%. Anti-diabetic treatments were taken by almost all patients (97.5%) at baseline, mostly insulins and analogues (64.1%). A medical history of diabetic retinopathy and neuropathy was recorded for 46.9% and 25.6% of patients respectively.

Nearly all patients (97.2%) had hypertension as concomitant disease at baseline, and 45.9% patients had a history of cardiovascular disease.

The most frequently used non-antidiabetic treatments at baseline were RAS inhibitors (ARBs: 65.7%; ACEIs: 34.2%) and statins (74.3%).

Label population (*Patients with 25 <= eGFR <60ml/min/ 1.73m^2 and albuminuria at baseline*) (65)

The label population (n = 4860 / 5674; 85.7% of full analysis set (FAS)) generally resembled characteristics of the overall population.

Mean eGFR was slightly lower at 41.8 mL/min/1.73 m^2 and by definition of the subpopulation, all patients had 25 to <60 ml/min/1.73m^2.

Similarly to the overall population, the majority of patients (87.3%) had very high albuminuria (≥300 mg/g) at baseline.

NB. Derivation of the label population mainly involved removal of one of the study's capped populations i.e. patients with eGFR ≥60 to 75 mL/min/1.73m^2 and very high albuminuria. This was approximately 11% of the total study population.

Table 10. Baseline demographic and disease characteristics for overall FIDELIO-DKD study population and 'label' population (FAS) (9, 65)*

	FIDELIO-DKD population		Label population	
	Finerenone (N=2833)	Placebo (N=2841)	Finerenone (N=2437)	Placebo (N=2423)
Age (yr)	65.4±8.9	65.7±9.2	[redacted]	[redacted]
Male, n (%)	1953 (68.9)	2030 (71.5)	[redacted]	[redacted]
Race, n (%) †				
White	1777 (62.7)	1815 (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	1182 (41.7)	1176 (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]

	FIDELIO-DKD population		Label population	
	Finerenone (N=2833)	Placebo (N=2841)	Finerenone (N=2437)	Placebo (N=2423)
Duration of diabetes (yr)	16.6±8.8	16.6±8.8		
Glycated haemoglobin (%)	7.7±1.3	7.7±1.4		
Systolic blood pressure (mmHg)	138.1±14.3	138.0±14.4		
eGFR				
Mean	44.4±12.5	44.3±12.6		
Distribution, n (%)				
≥60 ml/min/1.73m^2	318 (11.2)	338 (11.9)		
45 to <60 ml/min/1.73m^2	972 (34.3)	928 (32.7)		
25 to <45 ml/min/1.73m^2	1476 (52.1)	1505 (53.0)		
<25 ml/min/1.73m^2	66 (2.3)	69 (2.4)		
Missing data	1 (<0.1)	1 (<0.1)		
UACR ‡				
Median (IQR)	833 (441-1628)	867 (453-1645)		
Distribution, n (%)				
<30	11 (0.4)	12 (0.4)		
30 to <300	350 (12.4)	335 (11.8)		
≥300	2470 (87.2)	2493 (87.8)		
Missing data	2 (<0.1)	1 (<0.1)		
Serum potassium (mmol/litre)	4.37±0.46	4.38±0.46		
Medical history				
Hypertension, n (%)	2737 (96.6)	2768 (97.4)		
Diabetic retinopathy, n (%)	1312 (46.3)	1351 (47.6)		
Diabetic neuropathy, n (%)	738 (26.1)	716 (25.2)		
History of CV disease, n (%)	1303 (46.0)	1302 (45.8)		
Coronary artery disease	842 (29.7)	860 (30.3)		
Myocardial infarction	378 (13.3)	388 (13.7)		
PAOD	470 (16.6)	453 (15.9)		
Ischaemic stroke	329 (11.6)	360 (12.7)		
Heart failure, n (%)	195 (6.9)	241 (8,5)		
Baseline medications, n (%)				
ACE inhibitor §	950 (33.5)	992 (34.9)		

	FIDELIO-DKD population		Label population	
	Finerenone (N=2833)	Placebo (N=2841)	Finerenone (N=2437)	Placebo (N=2423)
ARB §	1879 (66.3)	1846 (65.0)	[redacted]	[redacted]
Diuretic	1577 (55.7)	1637 (57.6)	[redacted]	[redacted]
Statin	2105 (74.3)	2110 (74.3)	[redacted]	[redacted]
Potassium-lowering agent ¶	70 (2.5)	66 (2.3)	[redacted]	[redacted]
Glucose-lowering therapy	2747 (97.0)	2777 (97.7)	[redacted]	[redacted]
Insulin	1843 (65.1)	1794 (63.1)	[redacted]	[redacted]
GLP-1 receptor agonist	189 (6.7)	205 (7.2)	[redacted]	[redacted]
SGLT2 inhibitor	124 (4.4)	135 (4.8)	[redacted]	[redacted]

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;

* 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.

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

Analysis sets

The primary population for efficacy analysis was the full analysis set (FAS), which includes all randomised patients apart from 60 subject IDs that were prospectively excluded from all analyses due to critical GCP violations [1]. The population for safety analysis consisted of all randomly assigned patients without critical GCP violations who received at least one dose of finerenone or placebo.

Table 11. Main analysis sets in FIDELIO-DKD (9, 65)

Analysis set	Definition	FIDELIO-DKD population	Label population

[1] A total of 60 patients were prospectively excluded from all analyses in the study due to critical Good Clinical Practice violations. This affected one site in the US that was subsequently closed during the conduct of the trial leading to the exclusion of 29 patients. In addition, during trial conduct it was detected that several patients were randomised simultaneously at multiple trial sites in the same locality in Florida, USA. This led to the exclusion of a total of 31 patient IDs (Bakris 2020).

		Finerenone o.d.	Placebo o.d.	Finerenone o.d.	Placebo o.d.
Randomised patients		**N=2866**	**N=2868**	[redacted]	[redacted]
Full analysis set (FAS)	All randomised patients except those excluded for GCP violations.	N=2833 (100%)	N=2841 (100%)	[redacted]	[redacted]
	Patients excluded for GCP violations	*n=33*	*N=27*	[redacted]	[redacted]
Safety analysis set (SAF)	All patients in the FAS who received at least one dose of study medication.	N=2827 (99.8%)	N=2831 (99.6%)	[redacted]	[redacted]
	Excluded from SAF as did not receive study medication	*6 (0.2%)*	*10 (0.4%)*	[redacted]	[redacted]
Per protocol set (PPS)	All patients in the FAS without any protocol deviations	*N=2391 (84.4%)*	*N=2451 (86.3%)*	[redacted]	[redacted]
	Excluded from PPS (mainly due to reduced compliance)	*442 (15.6%)*	*417 (13.7%)*	[redacted]	[redacted]

GCP=good Clinical Practice; N=number; o.d.=once daily;

Overview of statistical analyses

Table 12. Summary of statistical analyses in FIDELIO (9, 60, 62, 67)

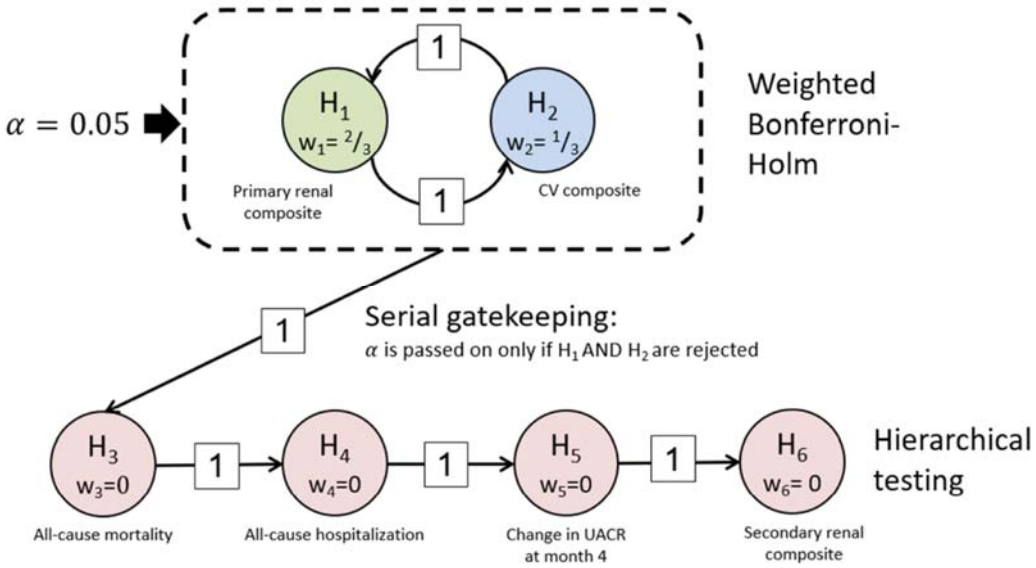
Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
FIDELIO-DKD	The null hypothesis tested to evaluate if finerenone is superior to placebo in prolonging the time to the first event of the primary composite endpoint, was: H0: $\lambda_{finerenone,k}(t) = \lambda_{placebo,k}(t)$ for all time points $t \geq 0$ and each stratum *k* The alternative hypothesis was: H1: $\lambda_{finerenone,k}(t) \neq \lambda_{placebo,k}(t)$ for at least one time point $t \geq 0$ and at least one stratum *k*, where $\lambda_{finerenone,k}$ denotes the hazard rate of the finerenone treatment group in stratum *k* and $\lambda_{placebo,k}$ denotes the	In time-to-event analyses for primary and secondary outcomes, the superiority of finerenone over placebo was tested by stratified log-rank test (stratification factors geographic region, eGFR category and albuminuria category at screening). Treatment effects were expressed as hazard ratios (HR) with corresponding confidence intervals (CI) from stratified Cox proportional-hazards models. The statistical analyses followed the intention-to-treat principle and was performed on the FAS. To account for multiple testing, the weighted Bonferroni-Holm procedure was used for the primary and key secondary endpoints, followed by hierarchical testing of the remaining efficacy endpoints (see Figure 3) The following adjusted alpha levels accounting for one formal interim analysis were used which apply for an information fraction of 2/3: • If the primary renal composite endpoint achieved statistical significance at a two-sided logrank p value ≤0.03282695, the secondary CV endpoint was tested at the two-sided 0.04967388 level. • If the secondary CV endpoint achieved statistical significance at a two-sided p value ≤0.01576184, the primary renal composite endpoint was tested at the two-sided 0.04967388 level.	A total of 1068 primary efficacy endpoint events provided a minimum 90% power to demonstrate superiority of finerenone to placebo using a log-rank test at a two sided significance level of 3.3333%, assuming a 20% relative risk reduction, i.e. a true hazard ratio of 0.80. Further assumptions included an annual placebo event rate of 12% (assumed to be unaffected by treatment discontinuations), a common annual lost-to-follow-up rate of 0.7% in both treatment groups, an annual finerenone discontinuation rate of 5%, and a total treatment duration between 44 and 48 months, consisting of a recruitment period of 33 and 41 months with an	**Handling of missing data:** - Concomitant medications with missing start and stop date was considered to have started prior to study medication start and end after stop of study medication. - A 'worst-case' approach was applied to impute the start and end dates of study medication intake as the minimum and maximal possible dates, i.e.: first month of the year, or first day of the month for a partially missing start date, and last month of the year, or last day of the month for a partially missing end date. - A median imputation rule was used for partial dates for clinical events or deaths e.g. missing date in July, day 16 is chosen. - A worst case approach was applied for determining whether an AE with partially missing dates is treatment-emergent or not, i.e. if it is possible that the AE start date is within a period

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
	hazard rate of the placebo treatment group in stratum *k*.	• Only if both the renal and CV endpoints achieved formal statistical significance, the remaining secondary endpoints were tested at a two-sided level of 0.04967388 hierarchically. If the testing strategy stopped at one point due to a non-significant result, the testing of the remaining secondary efficacy variables was performed in an explorative manner. The secondary efficacy outcome of change in UACR from baseline to month 4 was tested with an analysis of covariance (ANCOVA) model adjusting for treatment group, stratification factors and baseline value. Changes in UACR and eGFR over time were analysed with mixed models, assuming an unstructured covariance matrix and adjusting for treatment group, stratification factors, visit, interaction between treatment group and visit, baseline value and interaction between baseline value and visit. **New diagnosis of atrial fibrillation** was summarised for presence or absence of event using logistic regression with the factors treatment group and stratification levels. Pairwise differences between the finerenone and the placebo treatment group were calculated and corresponding two-sided 95% CIs were computed. For **subgroup analyses**, HRs were derived from stratified Cox proportional hazards models, including treatment subgroup and a subgroup by treatment interaction term as fixed effects.	equal recruitment pattern during the accrual period and a maximum treatment period of the last recruited patient of 11 and 7 months, respectively. Taking the ramp-up time during recruitment into consideration, this leads to an estimated required number of approximately 4,800 patients to be randomised. Assuming a screening failure rate of 50%, 9,600 patients need to be screened. To account for the lower-than-assumed event rates for the primary endpoint as observed during the conduct of the trial, the originally planned number of randomised patients was increased by approximately 1,000 patients.	of study drug intake +3 days, then the AE is considered treatment-emergent. If AE intensity was missing, it was considered severe. If drug relationship was missing, it was considered study drug-related. **Censoring rules:** Events were counted from randomisation to the end-of-trial visit, and data on patients without an event were censored at the date of their last contact with complete information on all components of the respective outcome. In case a non-renal death occurs within 5 months from the last visit and a subsequent clinic visit had been planned, the non-renal death date will be used as the censoring date. The supportive analyses using the per protocol set (PPS) and FAS 'on treatment' were censored to include only events occurring within 30 days after permanent treatment discontinuation. **Handling of dropouts:** Dropouts were not replaced.

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
		The **number needed to treat** to prevent one event during 3 years was calculated as the reciprocal of the Kaplan–Meier estimates for the between-group difference in the cumulative incidence probability at 3 years. **Supportive analyses** included: 1). PPS (primary, secondary and exploratory variables). 2). FAS 'on treatment' (primary and key secondary variable) **Health-related quality of life** The KDQOL-36 domain scores were presented by visit and treatment group including changes from baseline (repeated for patients with or without ESRD and/or dialysis at any point during the study). Summary scores for EQ-5D were calculated out of the 5 dimensions, along with the values and changes from baseline of the summary scores and the EQ-VAS.		Data from patients who prematurely terminated the study were used to the maximum extent possible.

AE=adverse event; ANCOVA= analysis of covariance; CI=confidence interval; CV=cardiovascular, DKD=Diabetic kidney disease; eGFR=estimated glomerular filtration rate; EQ-5D=European quality of life – 5 dimension questionnaire; ESRD=End stage renal disease; FAS=full analysis set; FIDELIO-DKD; FInerenone in reducing kiDnEy faiLure and dIsease prOgression in Diabetic Kidney Disease; HR=hazard ratio; ITT=intention-to treat; KDQOL=kidney disease quality of life; PPS=per-protocol set; UACR=urinary albumin-to-creatinine ration; VAS=visual analogue scale;

Figure 3. Simplified scheme of weighted Bonferroni-Holm testing strategy (60)



CV= Cardiovascular, UACR = Urinary albumin-to-creatinine ratio

Interim analyses

One planned interim analysis was conducted when 2/3 (approx. 712 events) of the required total number of primary efficacy endpoints were observed. On the basis of interim analysis, the decision of the independent Data Monitoring Committee (on 25th September 2019) was to continue FIDELIO-DKD without change to protocol until the total number of primary endpoint events had accrued.

To guide the decision, the Haybittle-Peto rule was used, which required a two-sided p value below 0.00270 for both the null hypotheses corresponding to the primary renal efficacy endpoint and the key secondary CV endpoint to be rejected and leading to a minimal alpha adjustment for the respective tests at the final analysis stage (67).

See Appendix D for 'Participant flow in the FIDELIO-DKD study'.

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

Table 13 presents a quality assessment of the FIDELIO-DKD study, one of the largest contemporary studies to evaluate patients with CKD and T2D.

FIDELIO-DKD was completed to the highest standard with adequate randomisation and blinding procedures. Please see Appendix D1.3 for a more detailed quality assessment.

Table 13. Quality assessment results for FIDELIO-DKD

Trial number (acronym)	FIDELIO-DKD study
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes
Were there any unexpected imbalances in drop-outs between groups?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes / Yes / Yes
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination'	

It is considered that the clinical evidence provided by FIDELIO-DKD is both relevant and applicable to routine clinical practice in England. This is discussed in more detail in section 2.13.

B.2.6 Clinical effectiveness results of the relevant trials

Information in the Results section is presented for the FIDELIO-DKD population (i.e. all FAS patients) followed by the 'label population' (i.e. FAS patients with 25 <= eGFR <60 ml/min/1.73m^2 and albuminuria at baseline).

Summary of efficacy results

FIDELIO-DKD, one of the largest contemporary studies to evaluate patients with CKD and T2D, met its primary and key secondary objectives, demonstrating that finerenone was significantly superior to placebo in reducing the risk of CKD progression and cardiovascular events, as measured by the primary renal composite and key secondary CV composite endpoints (see Table 14).

A primary outcome event (kidney failure, sustained decrease of ≥40% in the eGFR from baseline, or death from renal causes) occurred in 504 patients (17.8%) in the finerenone group and 600 patients (21.1%) in the placebo group (hazard ratio [HR]=0.82; 95% confidence interval [CI], 0.73-0.93; P = 0.001).

A key secondary outcome event (CV death, non-fatal MI, non-fatal stroke, or hospitalisation for heart failure) occurred in 367 patients (13.0%) in the finerenone group and 420 patients (14.8%) in the placebo group (HR=0.86; 95% CI, 0.75-0.99; P = 0.03).

The treatment benefit of finerenone over placebo for the primary and key secondary endpoints persisted throughout the duration of the study and was consistent across all components of the composite endpoints except for non-fatal stroke.

In other secondary endpoints, the results for all-cause mortality and all-cause hospitalisation favoured finerenone, although the treatment differences were not statistically significant. A reduction in risk of the secondary renal composite endpoint (HR=0.76; 95% CI, 0.65-0.90, p=0.0012) which included the component 'a sustained eGFR decline of 57%', and a 31.2% reduction in UACR at Month 4 further support the assessment of the primary endpoint that finerenone is superior to placebo in delaying the progression of kidney disease. Also, fewer events of new onset of atrial fibrillation or atrial flutter were observed in the finerenone arm compared to placebo.

Treatment differences in favour of finerenone were robust across all prespecified sensitivity analyses (FAS on-treatment and PPS) and were indicative of a larger treatment effect with finerenone. Subgroup analyses of the primary and secondary efficacy endpoints confirmed that the treatment benefit with finerenone was generally consistent across the subpopulations evaluated; there was no subgroup that had a significant interaction across all endpoints.

Overall, HRQoL results (KDQOL 36 and EQ-5D-5L/VAS) showed small changes that were in favour of finerenone.

Label population – see Table 15 **for summary of efficacy results**

In the label population, the primary objective of delaying the progression of CKD with finerenone was met. A primary outcome event occurred in 433 patients (17.8%) in the finerenone group and 600 patients (20.9%) in the placebo group (HR=0.82; 95% CI, 0.74-0.94; P = 0.006).

While not statistically significant, finerenone also had a positive treatment effect on reducing the risk of a key secondary outcome event (CV death, non-fatal MI, non-fatal stroke, or hospitalisation for heart failure), which occurred in 318 patients (13.0%) in the finerenone group and 338 patients (14.4%) in the placebo group (HR=0.89; 95% CI, 0.76-1.03; P = 0.13).

Similarly, to the overall study population, the treatment benefits of finerenone over placebo persisted throughout the duration of the study, and was consistent across all components of the composite endpoints except for non-fatal stroke. Results of other endpoints (e.g. all-cause mortality and all-cause hospitalisation, secondary renal composite endpoint) also favoured a treatment benefit for finerenone in the label population.

Based on results from the FIDELIO-DKD study, finerenone treatment is demonstrated to be efficacious in delaying the progression of kidney disease and reducing the risk of major CV events in patients with CKD and T2D.

Summary of Efficacy Outcome results

FIDELIO-DKD trial population

Table 14. Efficacy result summary (FAS population) (9, 62)

Outcome		Finerenone o.d. N=2833 (100%)	Placebo o.d. N=2841 (100%)	Finerenone vs placebo	
				HR (95% CI)	P value
Primary composite outcome	**Crude incidence n (%)**	**504 (17.8)**	**600 (21.1)**	**0.82 (0.73-0.93)**	**0.001***
	Incidence rate per 100 patient-years (95% CI)	**7.59 (6.94-8.27)**	**9.08 (8.37-9.82)**		
Kidney failure	Crude incidence n (%)	208 (7.3)	235 (8.3)	0.87 (0.72-1.05)	1.409
	Incidence rate per 100 patient-years (95% CI)	2.99 (2.60-3.41)	3.39 (2.97-3.83)		
-End stage Renal disease	*Crude incidence n (%)*	*119 (4.2)*	*139 (4.9)*	*0.86 (0.67-1.1)*	*0.219*
	Incidence rate per 100 patient-years (95% CI)	*1.60 (1.33-1.90)*	*1.87 (1.57-2.20)*		
-Sustained decrease in eGFR <15ml /min/ 1.73m^2	*Crude incidence n (%)*	*167 (5.9)*	*199 (7.0)*	*0.82 (0.67-1.01)*	*0.646*
	Incidence rate per 100 patient-years (95% CI)	*2.40 (2.05-2.78)*	*2.87 (2.48-3.28)*		
Sustained decrease ≥ 40% in eGFR from baseline	Crude incidence n (%)	479 (16.9)	577 (20.3)	0.81 (0.72-0.92)	0.0009
	Incidence rate per 100 patient-years (95% CI)	7.21 (6.58-7.87)	8.73 (8.03-9.46)		
Renal death	Crude incidence n (%)	2 (<0.1)	2 (<0.1)	-	-
	Incidence rate per 100 patient-years (95% CI)	-	-		
Key secondary composite outcome	**Crude incidence n (%)**	**367 (13.0)**	**420 (14.8)**	**0.86 (0.75-0.99)**	**0.03**
	Incidence rate per 100 patient-years (95% CI)	**5.11 (4.60-5.64)**	**5.92 (5.37-6.50)**		
CV death	Crude incidence n (%)	128 (4.5)	150 (5.3)	0.86 (0.68-1.08)	0.193
	Incidence rate per 100 patient-years (95% CI)	1.69 (1.41-2.00)	1.99 (1.68-2.32)		
Non—fatal MI	Crude incidence n (%)	70 (2.5)	87 (3.1)	0.80 (0.58-1.09)	0.154
	Incidence rate per 100 patient-years (95% CI)	0.94 (0.73-1.17)	1.17 (0.94-1.43)		
Non-fatal stroke	Crude incidence n (%)	90 (3.2)	87 (3.1)	1.03 (0.76-1.38)	0.858
	Incidence rate per 100 patient-years (95% CI)	1.21 (0.97-1.47)	1.18 (0.94-1.44)		
Hospitalisation for HF	Crude incidence n (%)	139 (4.9)	162 (5.7)	0.86 (0.68-1.08)	0.182
	Incidence rate per 100 patient-years (95% CI)	1.89 (1.59-2.21)	2.21 (1.89-2.57)		
Death from any cause	**Crude incidence n (%)**	**219 (7.7)**	**244 (8.6)**	**0.90 (0.75-1.07)**	**0.235**
	Incidence rate per 100 patient-years (95% CI)	**2.90 (2.53-3.29)**	**3.23 (2.84-3.65)**		
Hospitalisation from any cause	**Crude incidence n (%)**	**1263 (44.6)**	**1321 (46.5)**	**0.95 (0.88-1.02)**	**0.162**
	Incidence rate per 100 patient-years (95% CI)	**22.56 ([redacted])**	**23.87 ([redacted])**		
Secondary composite kidney outcome	**Crude incidence n (%)**	**252 (8.9)**	**326 (11.5)**	**0.76 (0.65-0.90)**	**0.001**
	Incidence rate per 100 patient-years (95% CI)	**3.64 [redacted]**	**4.74 [redacted]**		

Outcome		Finerenone o.d. N=2833 (100%)	Placebo o.d. N=2841 (100%)	Finerenone vs placebo	
				HR (95% CI)	P value
Sustained decrease ≥ 57% in eGFR from baseline	Crude incidence n (%)	167 (5.9)	245 (8.6)	0.68 (0.55-0.82)	[redacted]
	Incidence rate per 100 patient-years (95% CI)	2.41 ([redacted])	3.54 ([redacted])		

CI=confidence interval; CV=cardiovascular; eGFR=estimated glomerular filtration rate; HF=heart failure; HR=hazard ratio; MI=myocardial infarction; o.d.=once daily;
* Indicates statistical significance

Label population

Table 15. Efficacy result summary (Label population†;FAS) (65)

Outcome		Finerenone o.d. N=2437 (100%)	Placebo o.d. N=2423 (100%)	Finerenone vs placebo	
				HR (95% CI)	P value
Primary composite outcome	**Crude incidence n (%)**	[redacted]	[redacted]	[redacted]	[redacted]
	Incidence rate per 100 patient-years (95% CI)	[redacted]	[redacted]		
Kidney failure	Crude incidence n (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Incidence rate per 100 patient-years (95% CI)	[redacted]	[redacted]		
-End stage Renal disease	*Crude incidence n (%)*	[redacted]	[redacted]	[redacted]	[redacted]
	Incidence rate per 100 patient-years (95% CI)	[redacted]	[redacted]		
-Sustained decrease in eGFR <15ml /min/ 1.73m²	*Crude incidence n (%)*	[redacted]	[redacted]	[redacted]	[redacted]
	Incidence rate per 100 patient-years (95% CI)	[redacted]	[redacted]		
Sustained decrease ≥ 40% in eGFR from baseline	Crude incidence n (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Incidence rate per 100 patient-years (95% CI)	[redacted]	[redacted]		
Renal death	Crude incidence n (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Incidence rate per 100 patient-years (95% CI)	[redacted]	[redacted]		
Key secondary composite outcome	**Crude incidence n (%)**	[redacted]	[redacted]	[redacted]	[redacted]
	Incidence rate per 100 patient-years (95% CI)	[redacted]	[redacted]		
CV death	Crude incidence n (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Incidence rate per 100 patient-years (95% CI)	[redacted]	[redacted]		
Non—fatal MI	Crude incidence n (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Incidence rate per 100 patient-years (95% CI)	[redacted]	[redacted]		
Non-fatal stroke	Crude incidence n (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Incidence rate per 100 patient-years (95% CI)	[redacted]	[redacted]		
Hospitalisation for HF	Crude incidence n (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Incidence rate per 100 patient-years (95% CI)	[redacted]	[redacted]		
Death from any cause	**Crude incidence n (%)**	[redacted]	[redacted]	[redacted]	[redacted]
	Incidence rate per 100 patient-years (95% CI)	[redacted]	[redacted]		
Hospitalisation from any cause	**Crude incidence n (%)**	[redacted]	[redacted]	[redacted]	[redacted]
	Incidence rate per 100 patient-years (95% CI)	[redacted]	[redacted]		
Secondary composite kidney outcome	**Crude incidence n (%)**	[redacted]	[redacted]	[redacted]	[redacted]
	Incidence rate per 100 patient-years (95% CI)	[redacted]	[redacted]		
Sustained decrease ≥ 57% in eGFR from baseline	Crude incidence n (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Incidence rate per 100 patient-years (95% CI)	[redacted]	[redacted]		

CI=confidence interval; CV=cardiovascular; eGFR=estimated glomerular filtration rate; HF=heart failure; HR=hazard ratio; MI=myocardial infarction; o.d.=once daily;
† Patients with 25 <= eGFR <60 and albuminuria at baseline
* Indicates statistical significance

Primary efficacy outcome

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

FIDELIO-DKD trial population

During a median follow-up of 2.6 years, a primary outcome event occurred in 504 of 2833 patients (17.8%) in the finerenone group and 600 of 2841 patients (21.1%) in the placebo group (hazard ratio [HR]=0.82; 95% confidence interval [CI], 0.73 to 0.93; P = 0.001). Therefore, the primary renal composite endpoint achieved statistical significance. The incidences of the primary outcome components were consistently lower with finerenone than with placebo.

Table 16. Summary of results for the adjudicated primary renal composite endpoint and its components (FAS) (9, 62)

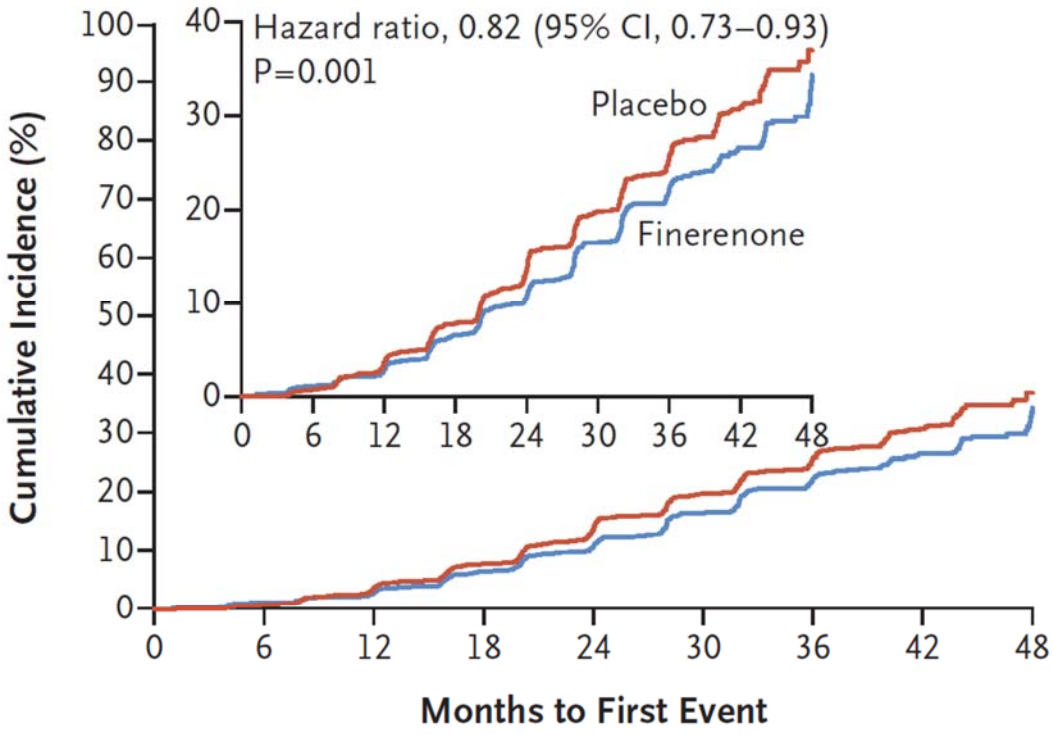
Outcome		Finerenone o.d. N=2833 (100%)	Placebo o.d. N=2841 (100%)	Finerenone vs placebo	
				HR (95% CI)	P value
Primary composite outcome	**Crude incidence n (%)**	**504 (17.8)**	**600 (21.1)**	**0.82 (0.73-0.93)**	**0.001***
	Incidence rate per 100 patient-years (95% CI)	**7.59 (6.94-8.27)**	**9.08 (8.37-9.82)**		
Kidney failure	Crude incidence n (%)	208 (7.3)	235 (8.3)	0.87 (0.72-1.05)	1.409
	Incidence rate per 100 patient-years (95% CI)	2.99 (2.60-3.41)	3.39 (2.97-3.83)		
-End stage Renal disease	*Crude incidence n (%)*	*119 (4.2)*	*139 (4.9)*	*0.86 (0.67-1.1)*	*0.219*
	Incidence rate per 100 patient-years (95% CI)	*1.60 (1.33-1.90)*	*1.87* (1.57-2.20)		
-Sustained decrease in eGFR <15ml /min/ 1.73m^2	*Crude incidence n (%)*	*167 (5.9)*	*199 (7.0)*	*0.82 (0.67-1.01)*	*0.646*
	Incidence rate per 100 patient-years (95% CI)	*2.40 (2.05-2.78)*	*2.87 (2.48-3.28)*		
Sustained decrease ≥ 40% in eGFR from baseline	Crude incidence n (%)	479 (16.9)	577 (20.3)	0.81 (0.72-0.92)	0.0009
	Incidence rate per 100 patient-years (95% CI)	7.21 (6.58-7.87)	8.73 (8.03-9.46)		
Renal death	Crude incidence n (%)	2 (<0.1)	2 (<0.1)	-	-
	Incidence rate per 100 patient-years (95% CI)	-	-		

CI=confidence interval; CV=cardiovascular; eGFR=estimated glomerular filtration rate; HF=heart failure; HR=hazard ratio; MI=myocardial infarction; o.d.=once daily;

Kaplan-Meier curves for finerenone and placebo are similar up until Month 12. Thereafter, the Kaplan-Meier curves separate with a consistent treatment effect observed over the duration of the study. The stepwise course of the finerenone and placebo curves indicate the substantial contribution of the eGFR laboratory component that was primarily determined at the 4-monthly visits.

In both treatment arms a comparably low number of events occurred during the first year after randomisation, which is reflected by the respective cumulative incidence probabilities at Month 12 of 2.8% in the finerenone arm and 3.7% in the placebo arm. Thereafter, the Kaplan-Meier curves separate with a consistent treatment effect observed over the duration of the study.

Figure 4. Kaplan-Meier of time to primary composite outcome of kidney failure, a sustained decrease of at least 40% in the estimated glomerular filtration rate (eGFR) from baseline, or death from renal causes (FAS) (9)



No. at Risk									
Placebo	2841	2724	2586	2379	1758	1248	792	453	82
Finerenone	2833	2705	2607	2397	1808	1274	787	441	83

CI=confidence interval

The treatment effect in favour of finerenone was generally consistent across prespecified subgroups (see Appendix E). Additional analyses of the primary efficacy endpoint confirmed the primary efficacy analysis results (see Appendix P).

Primary efficacy outcome - Label population (65)

[redacted] in patients with CKD and T2D, with an eGFR ≥ 25 - <60 ml /min /1.73m2 and albuminuria (see Table 17). A primary outcome event occurred in [redacted] patients ([redacted]%) in the finerenone group and [redacted] patients ([redacted]) in the placebo group (HR=[redacted] 95% CI, [redacted] P=[redacted]).

Table 17. Summary of results for the adjudicated primary renal composite endpoint and its components (Label population†;FAS) (65)

Outcome		Finerenone o.d. N=2437 (100%)	Placebo o.d. N=2423 (100%)	Finerenone vs placebo	
				HR (95% CI)	P value
Primary composite outcome	**Crude incidence n (%)**	[redacted]	[redacted]	[redacted]	[redacted]
	Incidence rate per 100 patient-years (95% CI)	[redacted]	[redacted]		
Kidney failure	Crude incidence n (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Incidence rate per 100 patient-years (95% CI)	[redacted]	[redacted]		
-End stage Renal disease	*Crude incidence n (%)*	[redacted]	[redacted]	[redacted]	[redacted]
	Incidence rate per 100 patient-years (95% CI)	[redacted]	[redacted]		
-Sustained decrease in eGFR <15ml /min/ 1.73m²	*Crude incidence n (%)*	[redacted]	[redacted]	[redacted]	[redacted]
	Incidence rate per 100 patient-years (95% CI)	[redacted]	[redacted]		
Sustained decrease ≥ 40% in eGFR from baseline	Crude incidence n (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Incidence rate per 100 patient-years (95% CI)	[redacted]	[redacted]		
Renal death	Crude incidence n (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Incidence rate per 100 patient-years (95% CI)	[redacted]	[redacted]		

CI=confidence interval; eGFR=estimated glomerular filtration rate; HR=hazard ratio; o.d.=once daily;
† Patients with 25 <= eGFR <60 and albuminuria at baseline
* Indicates statistical significance

[redacted]

A sustained ≥40% decrease in eGFR from baseline is an established surrogate that predicts progression to kidney failure – patients with an eGFR below 60 ml/min/1.73 m² who have a decline in eGFR of ≥40% from baseline have a 10-fold higher risk of kidney failure over 2 years than those with a stable eGFR (32).

Figure 5. Kaplan-Meier of time to primary composite outcome of kidney failure, a sustained decrease of at least 40% in the eGFR from baseline, or death from renal causes (Label population†)(FAS) (65)

BAY-94-8862=finerenone; eGFR=estimated glomerular filtration rate; FAS=full analysis set;
† Patients with 25 <= eGFR <60 and albuminuria at baseline

[redacted] (see Appendix E).

See Appendix E for further subgroup analysis of the primary efficacy analysis.

See Appendix P for additional analyses of the primary efficacy endpoint in overall trial population.

Further details of the individual components of all composite endpoints are presented at the end of this section.

Secondary efficacy outcomes

Key secondary outcome

Composite of CV death, non-fatal MI, non-fatal stroke, or hospitalisation for heart failure

FIDELIO-DKD trial population

Designed to explore the cardioprotective effects of finerenone, a key secondary composite outcome event occurred in 367 finerenone-treated patients (13.0%) and 420 placebo group patients (14.8%) (HR=0.86; 95% CI, 0.75 to 0.99; P= 0.03). The endpoint reached statistical significance.

The incidences of the components were lower with finerenone than with placebo except for nonfatal stroke, which had a similar incidence in the two groups.

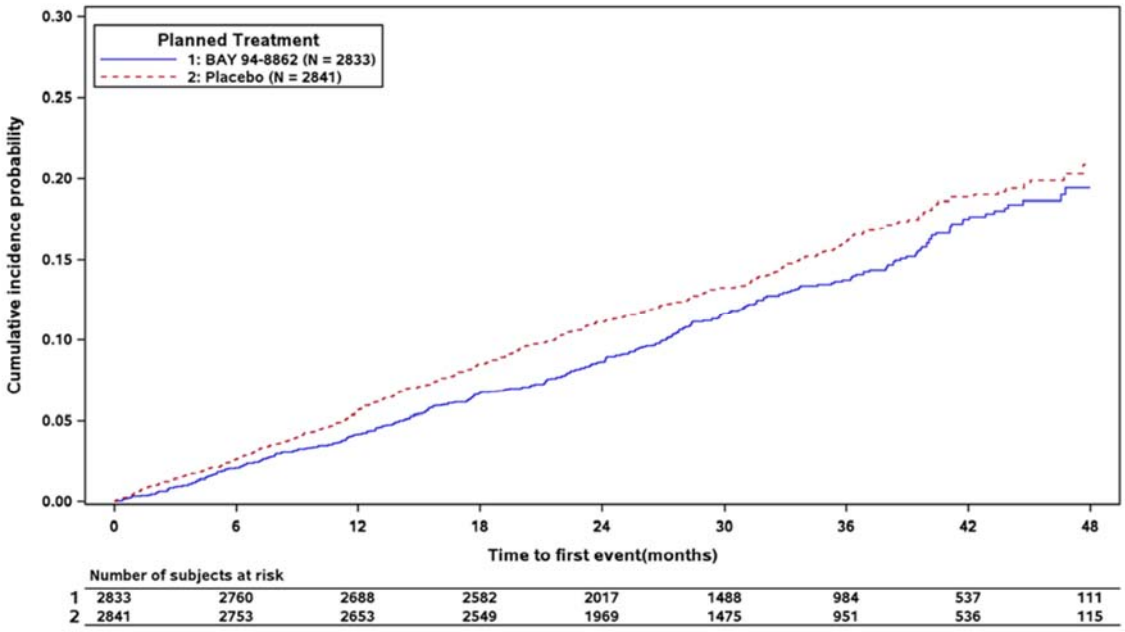
Table 18. Summary of results for the adjudicated Key secondary composite endpoint and its components (FAS) (9, 62)

Outcome		Finerenone o.d. N=2833 (100%)	Placebo o.d. N=2841 (100%)	Finerenone vs placebo	
				HR (95% CI)	P value
Key secondary composite outcome	**Crude incidence n (%)**	**367 (13.0)**	**420 (14.8)**	**0.86 (0.75-0.99)**	**0.03**
	Incidence rate per 100 patient-years (95% CI)	**5.11 (4.60-5.64)**	**5.92 (5.37-6.50)**		
CV death	Crude incidence n (%)	128 (4.5)	150 (5.3)	0.86 (0.68-1.08)	0.193
	Incidence rate per 100 patient-years (95% CI)	1.69 (1.41-2.00)	1.99 (1.68-2.32)		
Non—fatal MI	Crude incidence n (%)	70 (2.5)	87 (3.1)	0.80 (0.58-1.09)	0.154
	Incidence rate per 100 patient-years (95% CI)	0.94 (0.73-1.17)	1.17 (0.94-1.43)		
Non-fatal stroke	Crude incidence n (%)	90 (3.2)	87 (3.1)	1.03 (0.76-1.38)	0.858
	Incidence rate per 100 patient-years (95% CI)	1.21 (0.97-1.47)	1.18 (0.94-1.44)		
Hospitalisation for HF	Crude incidence n (%)	139 (4.9)	162 (5.7)	0.86 (0.68-1.08)	0.182
	Incidence rate per 100 patient-years (95% CI)	1.89 (1.59-2.21)	2.21 (1.89-2.57)		

CI=confidence interval; CV=cardiovascular; HF=heart failure; HR=hazard ratio; MI=myocardial infarction; o.d.=once daily;

Kaplan-Meier curves for finerenone and placebo diverge from Month 1 with a consistent course up until Month 24; thereafter the risk associated with finerenone is consistently less than the risk associated with placebo.

Figure 6. Kaplan-Meier of time to key secondary composite outcome of CV death, non-fatal MI, non-fatal stroke, or hospitalisation for heart failure (FAS) (9)



BAY 94-8862=finerenone; CI=confidence interval; CV=cardiovascular; FAS=full analysis set; MI=myocardial infarction

RRRs of 14%, 20%, and 14% for the components CV death, non-fatal MI, and hospitalisation for heart failure, respectively, indicated a similar magnitude of risk reduction compared to the overall RRR of 14.0% for the key secondary CV composite. Non-fatal stroke occurred in a similar number of patients in both treatment arms (finerenone: n=90 (3.2%); placebo: n=87 (3.1%) - the occurrence by stroke type (ischaemic vs haemorrhagic) was balanced between the arms (see at the end of results section for further details of individual components of primary and secondary composite endpoints).

[redacted]

Figure 7. Kaplan-Meier curves for time to first occurrence of the composite of CV death, non-fatal MI and hospitalisation for heart failure (FAS)(post hoc analysis) (62)

BAY-94-8862=finerenone; CV=cardiovascular; FAS=full analysis set; MI=myocardial infarction

Label population (65)

A key secondary outcome event occurred in [redacted] patients ([redacted]%) in the finerenone group and [redacted] patients ([redacted]%) in the placebo group ([HR=[redacted] 95% CI, [redacted] P = [redacted]) (see Table 19). [redacted]

Table 19. Summary of results for the adjudicated Key secondary composite endpoint and its components (Label population†;FAS) (65)

Key secondary composite outcome	**Crude incidence n (%)**	[redacted]	[redacted]	[redacted]	[redacted]
	Incidence rate per 100 patient-years (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
CV death	Crude incidence n (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Incidence rate per 100 patient-years (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Non—fatal MI	Crude incidence n (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Incidence rate per 100 patient-years (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Non-fatal stroke	Crude incidence n (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Incidence rate per 100 patient-years (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]

Hospitalisation for HF	Crude incidence n (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Incidence rate per 100 patient-years (95% CI)	[redacted]	[redacted]		

CI=confidence interval; CV=cardiovascular; HF=heart failure; HR=hazard ratio; MI=myocardial infarction; o.d.=once daily;
† Patients with 25 <= eGFR <60 and albuminuria at baseline

Figure 8. Kaplan-Meier of time to key secondary composite outcome of CV death, non-fatal MI, non-fatal stroke, or hospitalisation for heart failure (Label population†)(FAS) (65)

BAY-94-8862=finerenone; CV=cardiovascular; FAS=full analysis set; MI=myocardial infarction
† Patients with 25 <= eGFR <60 and albuminuria at baseline

Other secondary endpoints

All-cause mortality

FIDELIO-DKD trial population

Finerenone treatment resulted in a 10.5% RRR in all-cause mortality compared to placebo. The result, though not statistically significant, showed a trend towards a treatment effect in favour of finerenone (HR of 0.90, [95% CI 0.75; 1.07], p=0.235). This was mainly due to the lower number of CV deaths in the finerenone arm compared to placebo.

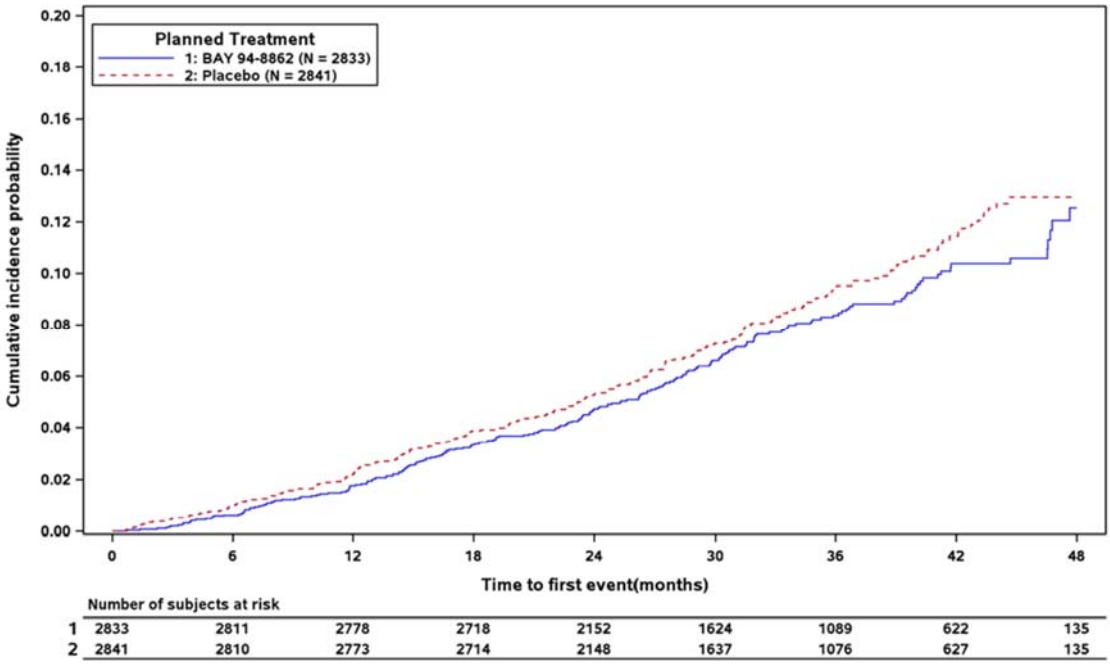
In accordance with the hierarchical statistical testing sequence, as there was no significant between-group difference in the risk of death from any cause, analyses of subsequent prespecified outcomes were exploratory.

Table 20. Summary of results for the All-cause mortality endpoint (FAS) (9, 62)

Outcome		Finerenone o.d. N=2833 (100%)	Placebo o.d. N=2841 (100%)	Finerenone vs placebo	
				HR (95% CI)	P value
Death from any cause	**Crude incidence n (%)**	**219 (7.7)**	**244 (8.6)**	**0.90 (0.75-1.07)**	**0.235**
	Incidence rate per 100 patient-years (95% CI)	**2.90 (2.53-3.29)**	**3.23 (2.84-3.65)**		
CV death	Crude incidence n (%)	128 (4.5)	150 (5.3)	0.86 (0.68-1.08)	0.193
	Incidence rate per 100 patient-years (95% CI)	1.69 (1.41-2.00)	1.99 (1.68-2.32)		
Renal death	Crude incidence n (%)	2 (<0.1)	2 (<0.1)	-	-
	Incidence rate per 100 patient-years (95% CI)	-	-		
Fatal non-CV / non-renal	Crude incidence n (%)	89 (3.1)	92 (3.2)	0.958 (0.716-1.283)	0.775
	Incidence rate per 100 patient-years (95% CI)	1.18 (0.95-1.43)	1.22 (0.98-1.48)		

CI=confidence interval; CV=cardiovascular; FAS=full analysis set; HR=hazard ratio; o.d.=once daily;

Figure 9. Kaplan Meier analysis, death from any cause (FAS) (9)



BAY-94-8862=finerenone; CI=confidence interval; FAS=full analysis set;

Label population

Table 21. Summary of results for the All-cause mortality endpoint (Label population†; FAS) (65)

Outcome		Finerenone o.d. N=2437 (100%)	Placebo o.d. N=2423 (100%)	Finerenone vs placebo	
				HR (95% CI)	P value
Death from any cause	**Crude incidence n (%)**	[redacted]	[redacted]	[redacted]	[redacted]
	Incidence rate per 100 patient-years (95% CI)	[redacted]	[redacted]		
CV death	Crude incidence n (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Incidence rate per 100 patient-years (95% CI)	[redacted]	[redacted]		
Renal death	Crude incidence n (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Incidence rate per 100 patient-years (95% CI)	[redacted]	[redacted]		
Fatal non-CV / non-renal	Crude incidence n (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Incidence rate per 100 patient-years (95% CI)	[redacted]	[redacted]		

CI=confidence interval; CV=cardiovascular; FAS=full analysis set; HR=hazard ratio; o.d.=once daily;
† Patients with 25 <= eGFR <60 and albuminuria at baseline

Figure 10. Kaplan Meier analysis, death from any cause (Label population†; FAS) (65)

BAY-94-8862=finerenone; FAS=full analysis set;
† Patients with 25 <= eGFR <60 and albuminuria at baseline

Time to all-cause hospitalisation

FIDELIO-DKD trial population

All-cause hospitalisation consisted of CV hospitalisation, hospitalisation for heart failure, and 'other hospitalisation'. The first occurrence of an event after randomisation is considered. Statistical testing for this endpoint was performed in an explorative manner. 1263 patients (44.6%) in the finerenone arm and 1321 patients (46.5%) in the placebo arm were hospitalised for any cause. Treatment with finerenone resulted in a [redacted] RRR of adjudicated all-cause hospitalisations compared with placebo (HR=0.95 [95% CI 0.88; 1.02], p=0.1623) (see Table 22).

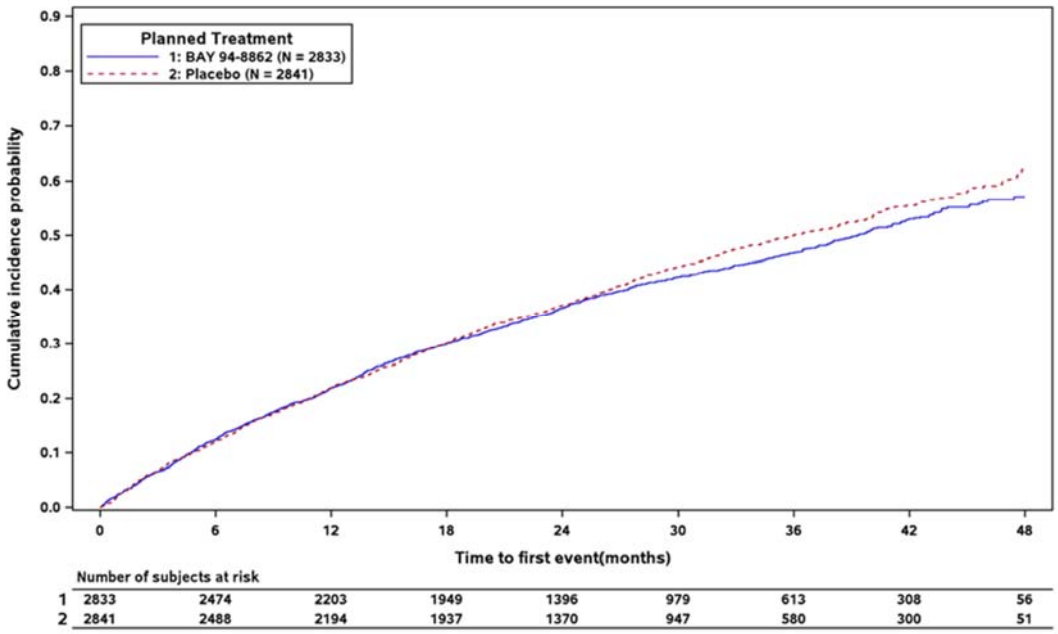
Table 22. Summary of results for All-cause hospitalisation (FAS) (9, 62)

Outcome		Finerenone o.d. N=2833 (100%)	Placebo o.d. N=2841 (100%)	Finerenone vs placebo	
				HR (95% CI)	P value
Hospitalisation from any cause	**Crude incidence n (%)**	**1263 (44.6)**	**1321 (46.5)**	**0.95 (0.88-1.02)**	**0.162**
	Incidence rate per 100 patient-years (95% CI)	**22.56 ([redacted])**	**23.87 ([redacted])**		
CV hospitalisations	Crude incidence n (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Incidence rate per 100 patient-years (95% CI)	[redacted]	[redacted]		
- Hospitalisation for HF	Crude incidence n (%)	139 (4.9)	162 (5.7)	0.86 (0.68-1.08)	0.182
	Incidence rate per 100 patient-years (95% CI)	1.89 (1.59-2.21)	2.21 (1.89-2.57)		
Other hospitalisations	Crude incidence n (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Incidence rate per 100 patient-years (95% CI)	[redacted]	[redacted]		

CI=confidence interval; CV=cardiovascular; FAS=full analysis set; HF=heart failure; HR=hazard ratio; NR=not reported; o.d.=once daily;

The Kaplan-Meier curves indicate a late but sustained separation between the treatment arms at around Month 26.

Figure 11. Kaplan Meier analysis, hospitalisation from any cause (FAS) (9)



BAY-94-8862=finerenone; CI=confidence interval; FAS=full analysis set;

Label population

Results in the label population for hospitalisations from any cause were similar to the overall FIDELIO-DKD study population.

Table 23. Summary of results for Hospitalisations from any cause (Label population†; FAS) (65)

Outcome		Finerenone o.d. N=2437 (100%)	Placebo o.d. N=2423 (100%)	Finerenone vs placebo	
				HR (95% CI)	P value
Hospitalisation from any cause	**Crude incidence n (%)**	[redacted]	[redacted]	[redacted]	[redacted]
	Incidence rate per 100 patient-years (95% CI)	[redacted]	[redacted]		
CV hospitalisations	Crude incidence n (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Incidence rate per 100 patient-years (95% CI)	[redacted]	[redacted]		
- Hospitalisation for HF	Crude incidence n (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Incidence rate per 100 patient-years (95% CI)	[redacted]	[redacted]		
Other hospitalisations	Crude incidence n (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Incidence rate per 100 patient-years (95% CI)	[redacted]	[redacted]		

CI=confidence interval; FAS=full analysis set; HF=heart failure; HR=hazard ratio; NR=not reported; o.d.=once daily;
† Patients with 25 <= eGFR <60 and albuminuria at baseline

Figure 12. Kaplan Meier analysis, hospitalisation from any cause (Label population†; FAS) (65)

BAY-94-8862=finerenone; FAS=full analysis set;
† Patients with 25 <= eGFR <60 and albuminuria at baseline

Change in urinary albumin-to-creatinine ratio (UACR) from baseline to Month 4

FIDELIO-DKD trial population

By analysis of covariance (ANCOVA) test, finerenone was associated with a 31% greater reduction in the UACR from baseline to month 4 than placebo (ratio of least-squares [LS] mean change from baseline [LS means ratio] [finerenone vs. placebo], 0.69; 95% CI, 0.66 to 0.71, p<0.0001) (see Table 24), and a lower mean urinary albumin-to-creatinine ratio with finerenone than with placebo was maintained thereafter (see Figure 13). Although the statistical testing for this endpoint was exploratory, this result corroborates the treatment effect of finerenone observed for the primary renal composite endpoint.

Table 24. UACR – Analysis of covariance for ratio to baseline at month 4 (FAS) (9, 62)

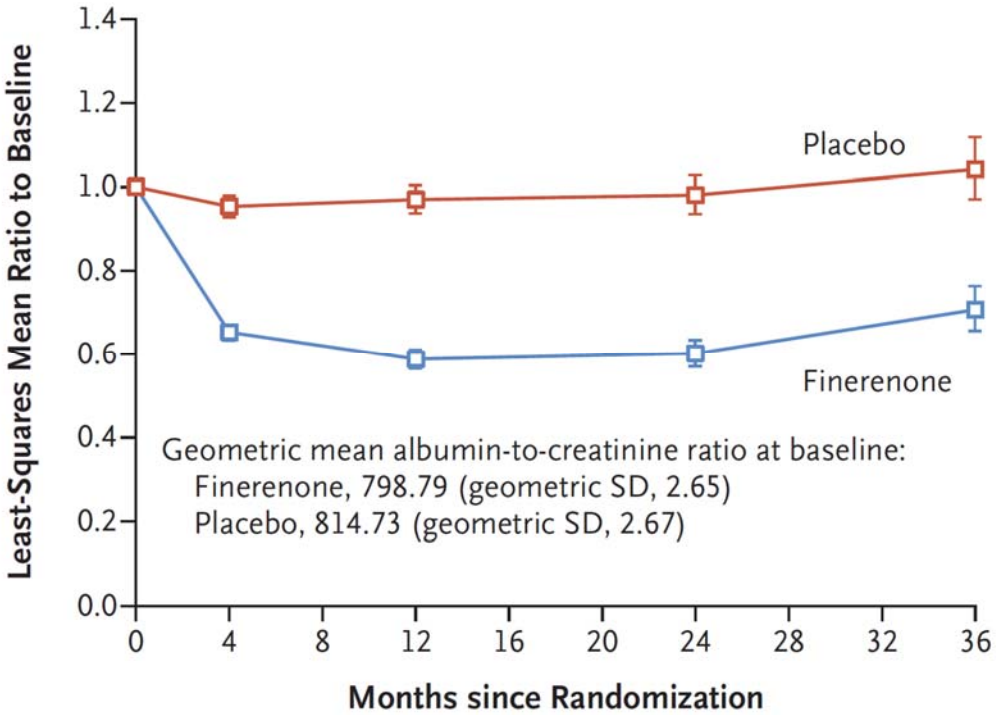
Period	Treatment	N	LS mean	95% CI for LS mean	p-value of F-test [a]	Ratio of LS means	95% CI for ratio of LS means
Month 4 (closest)	Finerenone	[redacted]	[redacted]	[redacted]	<0.0001	0.69	[0.66, 0.71]
	Placebo	[redacted]	[redacted]	[redacted]			

CI = confidence interval, FAS = full analysis set, LS mean(s) = least squares mean(s), N = number of patients, UACR = Urinary albumin-to-creatinine ratio

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.

[a] F-test of equal means between the additional factor levels: region, eGFR category at screening and type of albuminuria at screening.

Figure 13. Urinary albumin-to-creatinine ratio (FAS) (9)



No. of Patients					
Finerenone	2831	2725	2582	1841	856
Placebo	2840	2726	2598	1825	834
Mean Change from Baseline (percent)					
Finerenone	Ref.	−34.7	−41.3	−39.9	−29.3
Placebo	Ref.	−4.7	−3.0	−2.0	4.1

FAS=full analysis set; SD=standard deviation;

Label population

[redacted]

Table 25. UACR – Analysis of covariance for ratio to baseline at month 4 (Label population†; FAS) (65)

Period	Treatment	N	LS mean	95% CI for LS mean	p-value of F-test [a]	Ratio of LS means	95% CI for ratio of LS means
Month 4 (closest)	Finerenone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]			

CI = confidence interval; FAS = full analysis set; LS mean(s) = least squares mean(s), N = number of patients, UACR = Urinary albumin-to-creatinine ratio

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.
[a] F-test of equal means between the additional factor levels: region, eGFR category at screening and type of albuminuria at screening.
† Patients with 25 <= eGFR <60 and albuminuria at baseline

Figure 14. Urinary albumin-to-creatinine ratio (Label population†; FAS) (65)

BAY-94-8862=finerenone; FAS=full analysis set; UACR=urinary albumin-to-creatinine ratio
† Patients with 25 <= eGFR <60 and albuminuria at baseline

Composite of kidney failure, a sustained decrease in eGFR of ≥57% from baseline over at least 4 weeks, or renal death (secondary composite renal endpoint)

FIDELIO-DKD trial population (9, 62)

Compared to the primary efficacy endpoint, this secondary composite kidney endpoint considered a greater sustained decrease in eGFR of 57%, which is equivalent to a doubling of serum creatinine. A total of 252 patients (8.9%) who received finerenone and 326 patients (11.5%) who received placebo had a secondary composite kidney outcome event (HR=0.76; 95% CI, 0.65 to 0.90, p=0.001). Statistical testing was exploratory, however the treatment effect of finerenone appeared stronger than that

observed for the primary renal composite, thus substantiating the findings of primary efficacy endpoint.

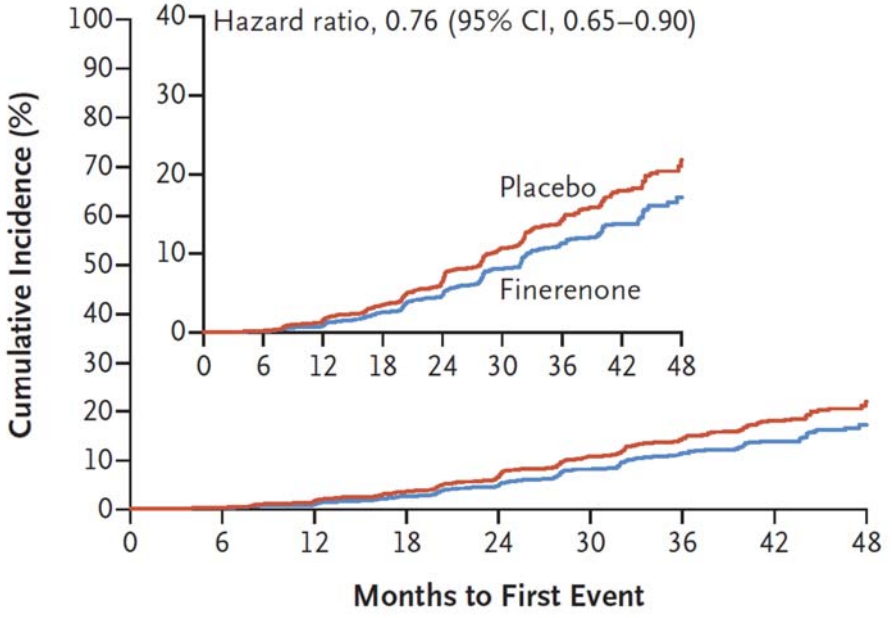
Table 26. Summary of results for the secondary composite kidney endpoint (FAS)

Outcome		Finerenone o.d. N=2833 (100%)	Placebo o.d. N=2841 (100%)	Finerenone vs placebo	
				HR (95% CI)	P value
Secondary composite renal outcome	**Crude incidence n (%)**	**252 (8.9)**	**326 (11.5)**	**0.76 (0.65-0.90)**	**0.001**
	Incidence rate per 100 patient-years (95% CI)	**3.64** [redacted]	**4.74** [redacted]		
Kidney failure	Crude incidence n (%)	208 (7.3)	235 (8.3)	0.87 (0.72-1.05)	1.409
	Incidence rate per 100 patient-years (95% CI)	2.99 (2.60-3.41)	3.39 (2.97-3.83)		
-End stage Renal disease	*Crude incidence n (%)*	*119 (4.2)*	*139 (4.9)*	*0.86 (0.67-1.1)*	*0.219*
	Incidence rate per 100 patient-years (95% CI)	*1.60 (1.33-1.90)*	*1.87 (1.57-2.20)*		
-Sustained decrease in eGFR <15ml /min/ 1.73m^2	*Crude incidence n (%)*	*167 (5.9)*	*199 (7.0)*	*0.82 (0.67-1.01)*	*0.646*
	Incidence rate per 100 patient-years (95% CI)	*2.40 (2.05-2.78)*	*2.87 (2.48-3.28)*		
Sustained decrease ≥ 57% in eGFR from baseline	Crude incidence n (%)	167 (5.9)	245 (8.6)	0.68 (0.55-0.82)	[redacted]
	Incidence rate per 100 patient-years (95% CI)	2.41 ([redacted])	3.54 ([redacted])		
Renal death	Crude incidence n (%)	2 (<0.1)	2 (<0.1)	-	-
	Incidence rate per 100 patient-years (95% CI)	-	-		

CI=confidence interval; eGFR=estimated glomerular filtration rate; FAS=full analysis set; HR=hazard ratio; o.d.=once daily;

The stronger treatment effect of finerenone compared with the primary efficacy renal composite endpoint was also seen in the Kaplan-Meier curves (see Figure 15), with the curves starting to diverge from around Month 12 onwards.

Figure 15. Kaplan-Meier analysis for the secondary composite kidney endpoint (FAS) (9)



No. at Risk									
Placebo	2841	2740	2636	2490	1887	1364	873	499	98
Finerenone	2833	2732	2655	2492	1915	1377	883	501	101

CI=confidence interval; FAS=full analysis set;

Label population

[redacted]

Table 27. Summary of results for the secondary composite kidney endpoint (Label population†; FAS) (65)

Outcome		Finerenone o.d. N=2833 (100%)	Placebo o.d. N=2841 (100%)	Finerenone vs placebo	
				HR (95% CI)	P value
Secondary composite kidney outcome	**Crude incidence n (%)**	[redacted]	[redacted]	[redacted]	[redacted]
	Incidence rate per 100 patient-years (95% CI)	[redacted]	[redacted]		
Kidney failure	Crude incidence n (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Incidence rate per 100 patient-years (95% CI)	[redacted]	[redacted]		
-End stage Renal disease	*Crude incidence n (%)*	[redacted]	[redacted]	[redacted]	[redacted]
	Incidence rate per 100 patient-years (95% CI)	[redacted]	[redacted]		
-Sustained decrease in eGFR <15ml /min/ 1.73m²	*Crude incidence n (%)*	[redacted]	[redacted]	[redacted]	[redacted]
	Incidence rate per 100 patient-years (95% CI)	[redacted]	[redacted]		
Sustained decrease ≥ 57% in eGFR from baseline	Crude incidence n (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Incidence rate per 100 patient-years (95% CI)	[redacted]	[redacted]		
Renal death	Crude incidence n (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Incidence rate per 100 patient-years (95% CI)	-	-		

CI=confidence interval; eGFR=estimated glomerular filtration rate; FAS=full analysis set; HR=hazard ratio; o.d.=once daily;
† Patients with 25 <= eGFR <60 and albuminuria at baseline

Figure 16. Kaplan-Meier analysis for the secondary composite kidney endpoint (Label population†; FAS) (65)

New diagnosis of atrial fibrillation or atrial flutter (FIDELIO-DKD trial population)

A new diagnosis of atrial fibrillation or atrial flutter occurred less frequently in the finerenone arm (for 82 of 2593 patients with no known history of atrial fibrillation or flutter, 3.2%) than in the placebo arm (for 117 of 2620 patients, 4.5%) (Odds ratio 0.698, p=0.0146).

Health-related quality of life (HRQoL) (64)

Health-related quality of life was assessed with KDQOL-36 and EQ-5D-5L questionnaires.

Kidney disease quality of life-36 questionnaire

FIDELIO-DKD trial population

In this diabetic population, with several comorbidities, quality of life [redacted] over time, [redacted] from baseline compared with placebo for some of the domain scores. Estimates of the treatment differences between finerenone and placebo were calculated for each of the KDQOL-36 domain scores using a mixed model. [redacted] were observed with the KDQOL-36 questionnaire [redacted] For patients with ESRD at any time point during the study, [redacted] their quality of life assessments. [redacted] Generally, subjects without ESRD [redacted]

European Quality of Life (EuroQol) – 5 Dimension (EQ-5D)

FIDELIO-DKD trial population

[redacted]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 28. Mixed model repeated measures for changes from baseline to Months 12, 24 and 36 in KDQOL-36 domain scores (FAS) – estimates of treatment differences (64)

Visit	Treatment	N	LS mean change from baseline	95% CI for change from baseline	LS-mean difference finerenone minus placebo	95% CI for difference	p-value of treatment group comparison
Physical component summary							
V5 / Mth 12	Finerenone						
	Placebo						
V8 / Mth 24	Finerenone						
	Placebo						
V11 / Mth 36	Finerenone						
	Placebo						
p-value for main factors [a]							
p-value for interaction [b]							
Mental component summary							
V5 / Mth 12	Finerenone						
	Placebo						
V8 / Mth 24	Finerenone						
	Placebo						
V11 / Mth 36	Finerenone						
	Placebo						
p-value for main factors [a]							
p-value for interaction [b]							
Burden of kidney disease							
V5 / Mth 12	Finerenone						
	Placebo						
V8 / Mth 24	Finerenone						
	Placebo						
V11 / Mth 36	Finerenone						
	Placebo						
p-value for main factors [a]							
p-value for interaction [b]							
Symptoms / problems							
V5 / Mth 12	Finerenone						
	Placebo						
V8 / Mth 24	Finerenone						
	Placebo						
V11 / Mth 36	Finerenone						
	Placebo						
p-value for main factors [a]							
p-value for interaction [b]							
Effects of kidney disease							
V5 / Mth 12	Finerenone						
	Placebo						
V8 / Mth 24	Finerenone						
	Placebo						
V11 / Mth 36	Finerenone						
	Placebo						
p-value for main factors [a]							
p-value for interaction [b]							

CI=Confidence intervals; eGFR=estimated glomerular filtration rate; FAS=full analysis set; KDQOL=Kidney Disease Quality of Life; LS=Least squares; MMRM=mixed model repeated measures; Mth=month; N=number of patients; V=visit;

[a] F-test of equal means between the factor levels: treatment group, region, eGFR category at screening and type of albuminuria at screening, time and baseline value.

[b] F-test of significant interaction between treatment and time and of significant interaction between baseline value and time.

For the statistical evaluation, a MMRM model was applied with factors treatment group, region, eGFR category at screening, type of albuminuria at screening, time, treatment*time, baseline value and baseline value*time as covariate. Separate unstructured covariance patterns are estimated for each treatment group.

Table 29. Mixed model repeated measures for changes from baseline to Months 12, 24 and 36 in EQ-5D summary scores (FAS) – estimates of treatment differences (64)

Visit	Treatment	N	LS mean change from baseline	95% CI for change from baseline	LS-mean difference finerenone minus placebo	95% CI for difference	p-value of treatment group comparison
EQ-5D VAS							
V5 / Mth 12	Finerenone						
	Placebo						
V8 / Mth 24	Finerenone						
	Placebo						
V11 / Mth 36	Finerenone						
	Placebo						
p-value for main factors [a]							
p-value for interaction [b]							
EQ-5D summary score Europe value set							
V5 / Mth 12	Finerenone						
	Placebo						
V8 / Mth 24	Finerenone						
	Placebo						
V11 / Mth 36	Finerenone						
	Placebo						
p-value for main factors [a]							
p-value for interaction [b]							
EQ-5D summary score US value set							
V5 / Mth 12	Finerenone						
	Placebo						
V8 / Mth 24	Finerenone						
	Placebo						
V11 / Mth 36	Finerenone						
	Placebo						
p-value for main factors [a]							
p-value for interaction [b]							

CI=Confidence intervals; eGFR=estimated glomerular filtration rate; EQ-5D=EuroQol group 5 dimensions; FAS=full analysis set; LS=Least squares; MMRM=mixed model repeated measures; Mth=month; N=number of patients; US=United States; V=visit; VAS=visual analogue scale;
For the statistical evaluation, a MMRM model was applied with factors treatment group, region, eGFR category at screening, type of albuminuria at screening, time, treatment*time, baseline value and baseline value*time as covariate. Separate unstructured covariance patterns are estimated for each treatment group. United Kingdom serves as a representative country within Europe.
a F-test of equal means between the factor levels: treatment group, region, eGFR category at screening, type of albuminuria at screening, time and baseline value.
b F-test of significant interaction between treatment and time and of significant interaction between baseline value and time.

Label population

Table 30. Mixed model repeated measures for changes from baseline to Months 12, 24 and 36 in KDQOL-36 domain scores – estimates of treatment differences (Label population†; FAS) (65)

Visit	Treatment	N	LS mean change from baseline	95% CI for change from baseline	LS-mean difference finerenone minus placebo	95% CI for difference	p-value of treatment group comparison
Physical component summary							
V5 / Mth 12	Finerenone						
	Placebo						
V8 / Mth 24	Finerenone						
	Placebo						
V11 / Mth 36	Finerenone						
	Placebo						
p-value for main factors [a]							
p-value for interaction [b]							
Mental component summary							
V5 / Mth 12	Finerenone						
	Placebo						
V8 / Mth 24	Finerenone						
	Placebo						
V11 / Mth 36	Finerenone						
	Placebo						
p-value for main factors [a]							
p-value for interaction [b]							
Burden of kidney disease							
V5 / Mth 12	Finerenone						
	Placebo						
V8 / Mth 24	Finerenone						
	Placebo						
V11 / Mth 36	Finerenone						
	Placebo						
p-value for main factors [a]							
p-value for interaction [b]							
Symptoms / problems							
V5 / Mth 12	Finerenone						
	Placebo						
V8 / Mth 24	Finerenone						
	Placebo						
V11 / Mth 36	Finerenone						
	Placebo						
p-value for main factors [a]							
p-value for interaction [b]							
Effects of kidney disease							
V5 / Mth 12	Finerenone						
	Placebo						
V8 / Mth 24	Finerenone						
	Placebo						
V11 / Mth 36	Finerenone						
	Placebo						
p-value for main factors [a]							
p-value for interaction [b]							

CI=Confidence intervals; eGFR=estimated glomerular filtration rate; FAS=full analysis set; KDQOL=Kidney Disease Quality of Life; LS=Least squares; Mth=month; N=number of patients; V=visit;
MIXED Model with factors treatment group, region, eGFR category at screening, type of albuminuria at screening, time, treatment*time, baseline value and baseline value*time as covariate.
a F-test of equal means between the factor levels: treatment group, region, eGFR category at screening, type of albuminuria at screening, time and baseline value.

b F-test of significant interaction between treatment and time and of significant interaction between baseline value and time.
† Patients with 25 <= eGFR <60 and albuminuria at baseline

Table 31. Mixed model repeated measures for changes from baseline to Months 12, 24 and 36 in EQ-5D summary scores – estimates of treatment differences (Label population†; FAS) (65)

Visit	Treatment	N	LS mean change from baseline	95% CI for change from baseline	LS-mean difference finerenone minus placebo	95% CI for difference	p-value of treatment group comparison
EQ-5D VAS							
V5 / Mth 12	Finerenone	[redacted]					
	Placebo						
V8 / Mth 24	Finerenone						
	Placebo						
V11 / Mth 36	Finerenone						
	Placebo						
p-value for main factors [a]							
p-value for interaction [b]							
EQ-5D summary score Europe value set							
V5 / Mth 12	Finerenone						
	Placebo						
V8 / Mth 24	Finerenone						
	Placebo						
V11 / Mth 36	Finerenone						
	Placebo						
p-value for main factors [a]							
p-value for interaction [b]							
EQ-5D summary score US value set							
V5 / Mth 12	Finerenone						
	Placebo						
V8 / Mth 24	Finerenone						
	Placebo						
V11 / Mth 36	Finerenone						
	Placebo						
p-value for main factors [a]							
p-value for interaction [b]							

CI=Confidence intervals; eGFR=estimated glomerular filtration rate; EQ-5D=EuroQol group 5 dimensions; FAS=full analysis set; LS=Least squares; MMRM=mixed model repeated measures; Mth=month; N=number of patients; US=United States; V=visit; VAS=visual analogue scale;
For the statistical evaluation, a MMRM model was applied with factors treatment group, region, eGFR category at screening, type of albuminuria at screening, time, treatment*time, baseline value and baseline value*time as covariate. Separate unstructured covariance patterns are estimated for each treatment group. United Kingdom serves as a representative country within Europe.
a F-test of equal means between the factor levels: treatment group, region, eGFR category at screening, type of albuminuria at screening, time and baseline value.
b F-test of significant interaction between treatment and time and of significant interaction between baseline value and time.
† Patients with 25 <= eGFR <60 and albuminuria at baseline

Individual components of the primary and secondary efficacy endpoints

FIDELIO-DKD trial population

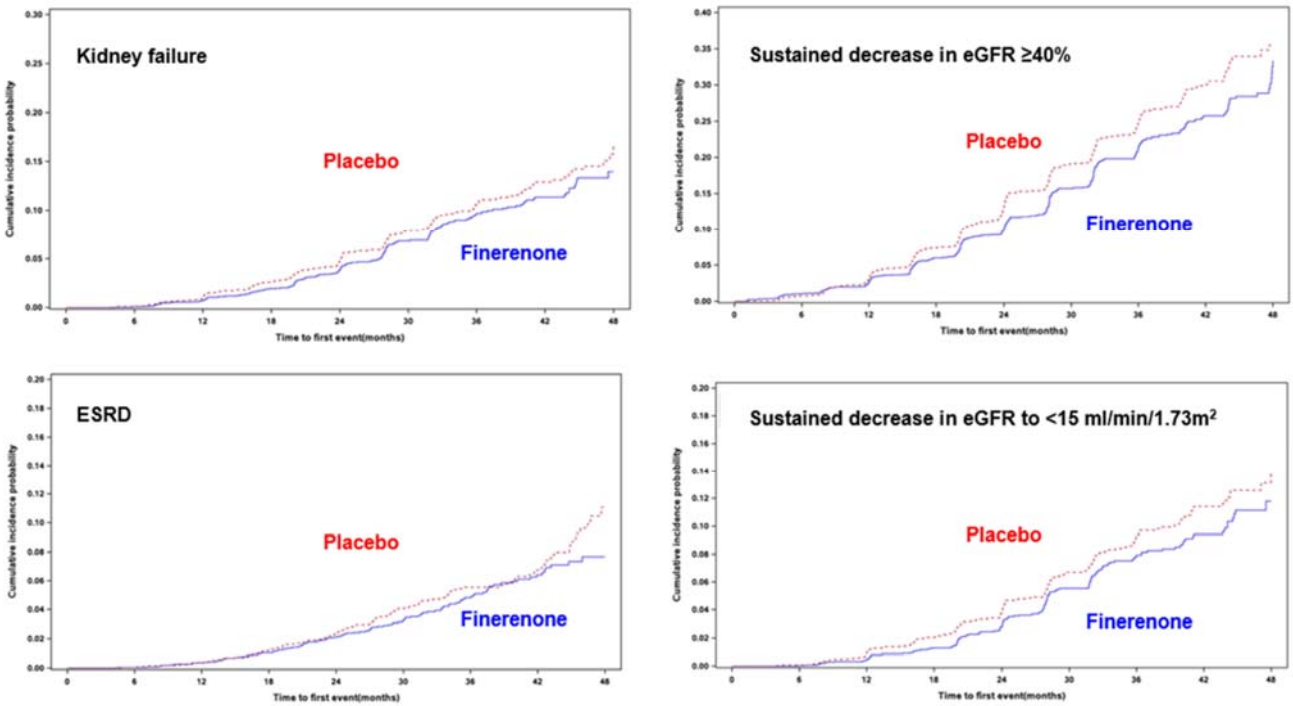
Components of the renal composite endpoints

Renal death - With 2 patients (<0.1%) in each treatment arm, the number of events was too small for a meaningful statistical analysis (see Table 16).

Kidney failure and its subcomponents **ESRD** and **sustained decrease in eGFR to <15 mL/min/1.73m²** were directionally consistent with the overall primary renal composite (RRRs 13%, 14% and 18% respectively) (see Table 16).

Sustained decrease in eGFR ≥40% from baseline over at least 4 weeks. This endpoint was the main driver of the primary renal composite endpoint (RRR 19%)

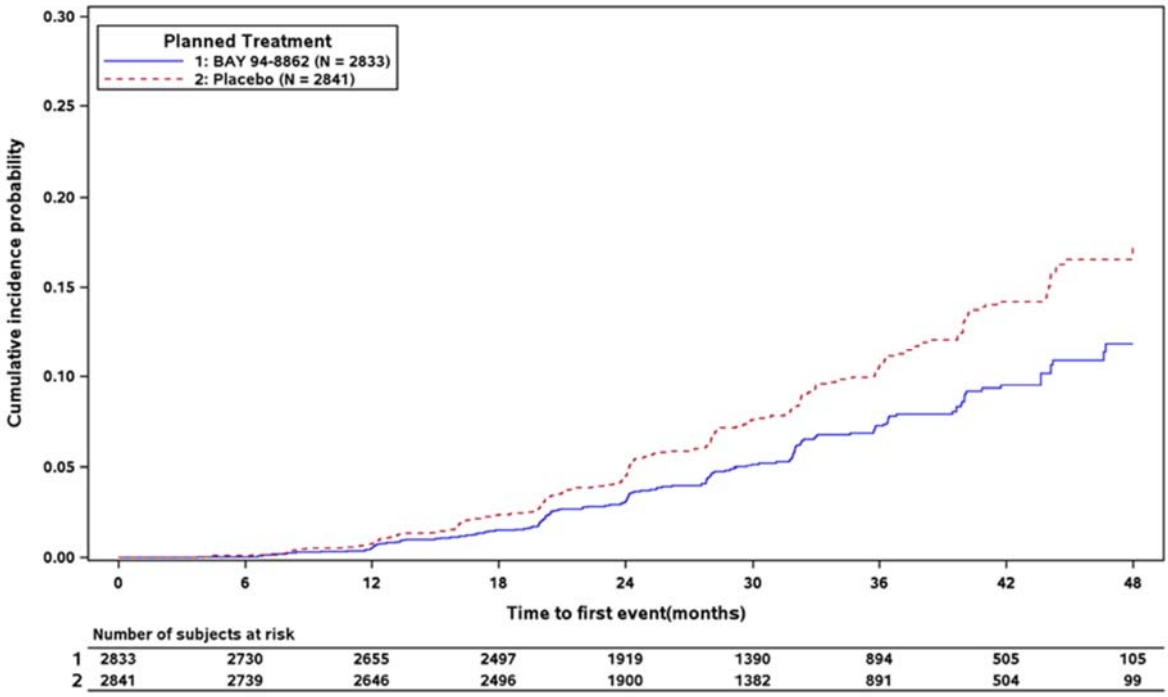
Figure 17. Primary renal composite: display of Kaplan-Meier plots for components (FAS) (61)



eGFR=estimated glomerular filtration rate; ESRD=end-stage renal disease; FAS=full analysis set;
NOTE: The parameters may have differing y-axes.

Sustained decrease in eGFR ≥57% from baseline over at least 4 weeks - occurred in 167 patients (5.9%) in the finerenone arm and 245 patients (8.6%) in the placebo arm (Table 26) (HR 0.68, 95% CI 0.55- 0.82, logrank test p<0.0001).

Figure 18. Kaplan-Meier analysis of Sustained decrease in eGFR ≥57% from baseline (9)



BAY-94-8862=finerenone; eGFR=estimated glomerular filtration rate; FAS=full analysis set; N=number of patients;

Components of the CV composite

The components - '**CV death'** and '**hospitalisation for heart failure'** indicated a similar magnitude of risk reduction compared to the overall RRR of 14.0% for the key secondary CV composite, with RRRs of 14% for both the components, respectively (see Table 18, Figure 19).The component '**non-fatal MI'**, however, indicated a higher magnitude of risk reduction when compared to the overall RRR of 14.0% for the key secondary CV composite, with an RRR of 20%.

Non-fatal stroke had a similar incidence in each treatment arm (finerenone: n=90 [3.2%]; placebo: n=87 [3.1%]) (see Table 18). By stroke type, [redacted]non-fatal ischaemic stroke[redacted]finerenone[redacted]placebo) or nonfatal haemorrhagic stroke[redacted]finerenone,[redacted]placebo) in the two treatment arms (62).

Additional post-hoc analyses for the combined endpoint of non-fatal and fatal stroke events[redacted]vs[redacted]100 patient-years, respectively for finerenone vs placebo)

[redacted]

Stroke is an outcome known to be sensitive to blood pressure, [redacted]. A higher proportion of patients initiating anti-hypertensive medications postbaseline was observed in the placebo arm compared to the finerenone arm.

Figure 19. Key secondary composite endpoint: display of Kaplan-Meier plots for components (FAS) (61)

CV=cardiovascular; FAS=full analysis set;

All-cause mortality components - Table 20

See above for '**Renal death**' and '**CV death**'.

Fatal non-CV / non-renal events – incidence rates were similar between the two treatment groups (1.18/100 patient-years (finerenone) and 1.22/100 patient-years (placebo); HR=0.958 [95% CI 0.716; 1.283; p=0.7751]).

Hospitalisation components – see Table 22

CV hospitalisation - [redacted] was observed in the finerenone arm compared with placebo, [redacted] **hospitalisations for heart failure** (139 patients in the finerenone arm [4.9%] vs 162 in the placebo arm [5.7%]), **non-fatal MI** [redacted] and **new onset of atrial fibrillation/atrial flutter** [redacted]

Other hospitalisation - [redacted]

Label population (65)

Components of the renal composite endpoints

Renal death -

[redacted] (see Table 15).

The **Sustained decrease in eGFR ≥40% from baseline over at least 4 weeks** and **Kidney failure** components, along with kidney failure subcomponents **ESRD** and **sustained decrease in eGFR to <15 mL/min/1.73m^2**

[redacted] (see Table 15, Figure 20).

Sustained decrease in eGFR ≥57% from baseline over at least 4 weeks - occurred in [redacted] patients [redacted] in the finerenone arm and [redacted] patients [redacted] in the placebo arm (Table 26) (HR [redacted] 95% CI [redacted] logrank test p [redacted]

Figure 20. Primary renal composite: display of Kaplan-Meier plots for components (Label population†; FAS) (65)

eGFR=estimated glomerular filtration rate; ESRD=end-stage renal disease; FAS=full analysis set;
† Patients with 25 <= eGFR <60 and albuminuria at baseline

Figure 21. Kaplan-Meier analysis of Sustained decrease in eGFR ≥57% from baseline (Label population†; FAS) (65)

CI=confidence interval; eGFR=estimated glomerular filtration rate;
† Patients with 25 <= eGFR <60 and albuminuria at baseline

Components of the CV composite

The components - '**CV death'** and '**hospitalisation for heart failure**' indicated [redacted] the key secondary CV composite in the label population, with RRRs of [redacted] for the components, respectively (see Table 15 , xxFigure 22). The component '**non-fatal MI'**, however, indicated a higher magnitude of risk reduction when compared to the overall RRR of [redacted]% for the key secondary CV composite, with an RRR of [redacted]%.

This composite endpoint [redacted]

Non-fatal stroke [redacted] (finerenone: n=[redacted]%]; placebo: n=[redacted]%]) (see Table 15). By stroke type, [redacted] non-fatal ischaemic stroke [redacted]%

finerenone [redacted]% placebo) or nonfatal haemorrhagic stroke ([redacted]% finerenone [redacted]% placebo) in the two treatment arms (65).

Similarly to the analysis in the overall trial population, [redacted] (xxFigure 22).

All-cause mortality components – see Table 21

See above for '**Renal death**' and '**CV death**'.

Fatal non-CV / non-renal events – incidence rates [redacted] patient-years (finerenone) and [redacted] patient-years (placebo); HR=[redacted] 95% CI [redacted] p=[redacted]

Hospitalisation components – see Table 23

CV hospitalisation - [redacted] CV hospitalisation [redacted] finerenone arm compared with placebo, mainly due to [redacted] **hospitalisations for heart failure** ([redacted] patients in the finerenone arm [[redacted]%] vs [redacted] in the placebo arm [[redacted]%]) and **non-fatal MI** ([redacted]%] vs [redacted]%]).

Other hospitalisation - [redacted]Figure 22. Key secondary composite endpoint: display of Kaplan-Meier plots for components (Label population†; FAS) (65)

CV=cardiovascular; FAS=full analysis set; HF=heart failure; MI=myocardial infarction;

B.2.7 Subgroup analysis

There were 44 pre-specified subgroups that consisted of demographic and baseline characteristics and concomitant therapy use at baseline. Exploratory subgroup analyses were performed for primary and secondary efficacy variables and some safety variables.

Analyses included descriptive statistics, graphical display of estimated treatment effects with 95% CIs in a Forest plot and a statistical test for interaction. No analysis was performed if the result for a subgroup could not be calculated due to a small sample size or number of events.

Subgroup analyses included the randomisation stratification factors:

- 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).

Other key subgroups:

- 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).

Other subgroups:

- Baseline serum potassium value (≤4.5, >4.5 mmol/L)
- Baseline serum potassium (by quartiles in the FAS: ≤Q1, >Q1 and ≤Q2, >Q2 and ≤Q3, >Q3)
- Baseline serum potassium value (<4.8, ≥4.8 to 5.0, >5.0 mmol/L)
- Baseline haemoglobin A1C (by quartiles in the FAS: ≤Q1, >Q1 and ≤Q2, >Q2 and ≤Q3, >Q3)
- Baseline C-reactive protein (by quartiles in the FAS: ≤Q1, >Q1 and ≤Q2, >Q2 and ≤Q3, >Q3)
- Systolic blood pressure at baseline (<130, 130 to <160, ≥160 mmHg)
- Age at run-in visit (18 to 44 years, 45 to 64 years, 65 to 74 years, 75 years and over)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino, not reported)
- Baseline BMI (<20, 20 to <25, 25 to <30, 30 to <35, ≥35 kg/m^2)
- Baseline weight (<60, 60 to <90, ≥90 kg)
- eGFR at baseline 25 to <45 mL/min/1.73 m² and baseline serum potassium value >4.5 mmol/L (yes, no)
- ACEI at baseline (yes, no)
- ARB at baseline (yes, no)
- Beta-blocker at baseline (yes, no)
- Diuretic at baseline (yes, no)
- Statins at baseline (yes, no)
- Other anti-diabetic treatment at baseline (in addition to SGLT-2 inhibitors and GLP-1 agonists mentioned under key subgroups) (yes, no for each group): insulin and analogues; DPP-4 inhibitors; biguanides; sulfonylureas; alpha-glucosidase inhibitors; meglitinides; thiazolidinediones
- Potassium supplementation at baseline (yes, no)
- Potassium-lowering agents (including binders) at baseline (yes, no)
- Potency of concomitant CYP3A4 inhibitor medication at baseline (strong, unclassified, moderate, weak, none)

- Potency of concomitant CYP3A4 inducer medication at baseline (strong, unclassified, moderate, weak, none)
- Baseline waist circumference (normal [men <94 cm, women<80 cm], increased [men 94 to 102 cm, women 80 to 88 cm], substantially increased [men >102 cm, women >88 cm]).

Exploratory subgroup analyses were performed for the following safety variables:

- Number of subjects with hospitalisation for hyperkalaemia
- Number of subjects discontinuing study drug permanently due to hyperkalaemia
- Number of subjects with hospitalisation for worsening of renal function
- Number of subjects discontinuing study drug permanently due to worsening of renal function

[redacted](62
):[redacted]See
Appendix E for results of subgroup analyses for efficacy considering the randomisation stratification factors as well as key subgroups.

In summary, subgroup analyses of the primary and secondary efficacy endpoints confirmed that the treatment benefit with finerenone was generally consistent across the subpopulations evaluated.

B.2.8 Meta-analysis

Not applicable. Evidence from only one RCT was available for analysis and relevant to the decision problem (FIDELIO-DKD (9, 60)).

B.2.9 Indirect and mixed treatment comparisons

An indirect comparison and/or mixed treatment comparison is not included in the submission. The appropriate comparator for the submission is background therapy

(BT) which is in line with, and is provided by, the finerenone comparator arm in the FIDELIO-DKD trial.

B.2.10 Adverse reactions

Summary

Results of the safety analyses of the FIDELIO-DKD study, demonstrate treatment with finerenone to be well tolerated in patients with CKD and T2D, concomitantly treated with current standard of care of maximum tolerated labeled doses of RAS-inhibitors. The main safety risk of hyperkalaemia was manageable in the context of dose-titration and interruption guidelines based on serum potassium values and changes in eGFR.

Introduction to adverse event data

Data on the safety of finerenone treatment to delay the progression of kidney disease and reduce the risk of CV mortality and morbidity in adults with CKD and T2D is drawn from the FIDELIO-DKD study, an international multicentre phase III double-blind, placebo-controlled, event-driven, randomised clinical trial (RCT) (9).

The population for safety analysis in FIDELIO-DKD comprised all randomly assigned patients without critical GCP violations who received at least one dose of finerenone or placebo (n=2827 finerenone; n=2831 placebo). Safety results in this submission are presented for the overall FIDELIO-DKD population i.e. the study's safety analysis set (SAF) rather than the slightly smaller label sub population. This provides the broadest insight into safety of finerenone in patients with CKD in T2D.

Of the patients valid for safety analysis in FIDELIO-DKD, the mean (SD) duration of exposure was 26.94 [redacted] vs 27.26 [redacted] months, respectively for finerenone vs placebo, and the mean daily dose was 15.14 vs 16.48 mg, respectively. A total of 86.5% of patients in the finerenone arm and 87.3% of patients in the placebo arm took the study drug for at least 12 months. Over half took the study drug for at least 24 months (57.7% finerenone, 58.7% placebo) and approximately a quarter of patients took the study drug for at least 36 months (25.6% finerenone, 25.4% placebo) (66). The total exposure of patients to study drug was [redacted] patient-years, with 6346 patient-years for the finerenone arm and [redacted] patient-years for the placebo arm (66).

[redacted] patients [redacted] %) in the finerenone arm and [redacted] patients [redacted] %) in the placebo arm started treatment with 10 mg

o.d. [redacted] respectively for finerenone vs placebo) were [redacted] Of those who started treatment [redacted] n= [redacted] %] finerenone and n= [redacted] %] placebo), [redacted] patients in the finerenone arm compared to placebo [redacted] The most common reasons [redacted].

Treatment interruption in at least one visit [redacted] finerenone arm compared to placebo [redacted] The treatment arms [redacted] (66). Frequencies compare to those observed for TEAEs of the combined preferred terms (PTs) hyperkalemia and blood potassium increased (18.3 vs 9.0%) (9).

Summary of adverse events

Note: *This study used a targeted approach for the collection of safety data, to differentiate AEs (evaluated as part of safety) from outcome events (potential renal and CV endpoints evaluated as part of efficacy). Potential prespecified efficacy outcome events were submitted for adjudication to an independent CEC and were not documented as (serious) adverse events ([S]AEs). CEC-confirmed efficacy outcome events are presented in section B2.6 'Clinical effectiveness results of the relevant trials' and are generally not included in the AE tables. Such events include kidney failure, renal death, chronic sustained decrease in eGFR, CV death, non-fatal stroke or MI, heart failure hospitalisation, other hospitalisation, new onset of atrial fibrillation or atrial flutter.*

Adverse events in FIDELIO-DKD were classified using MedDRA (Medical Dictionary for Regulatory Activities) Version 23.0.

The safety data from FIDELIO-DKD indicate that finerenone was generally well tolerated (see Table 32). The incidence of TEAEs was similar in the finerenone and

placebo groups (87.3 vs 87.5% of patients in the finerenone vs placebo arms, respectively) and in most cases were mild or moderate. Serious adverse events (SAEs) occurred in 31.9% (n=902) of the patients in the finerenone group and 34.3% (n=971) of those in the placebo group. Drug-related TEAEs was higher in the finerenone arm (22.9%) compared with the placebo arm (15.9%). 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%); however, the incidence of serious TEAEs that led to treatment discontinuation was balanced between the arms (2.7 vs 2.8%). TEAEs resulting in death (excluding outcome events) were reported in fewer patients in the finerenone arm (1.1 vs 1.8%).

Table 32. Overall summary of the number of patients with AEs (SAF) (9, 66)

	Finerenone o.d. N=2827 (100%)	**Placebo o.d. N=2831 (100%)**
Any AE	**2540 (89.8%)**	**2535 (89.5%)**
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)	31 (1.1%)	51 (1.8%)

AE=adverse event; o.d.=once daily; SAF=safety analysis set; TEAE=treatment-emergent adverse event;
*adverse events 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.

The overall incidence of TEAEs was balanced between the finerenone and placebo treatment arms. The most frequently observed TEAE with finerenone was hyperkalaemia, which is related to the mode of action of MR antagonism and was also a commonly observed event in the placebo arm. A higher incidence of hyperkalaemia was observed in the finerenone arm (MedDRA PT hyperkalaemia: 15.8% finerenone vs. 7.8% placebo); however, events of relevant clinical consequence constituted only a small proportion of these events (see below: 'AEs of particular interest' for further discussion of hyperkalaemia). A summary of the most common TEAEs (occurring in ≥ 5% patients in either group) is presented in Table 33.

Of the commonly reported TEAEs (≥5% of patients), hyperkalaemia (15.8% finerenone vs. 7.8% placebo) and decreased GFR (6.3% vs. 4.7%) were more frequently reported in the finerenone arm than in the placebo arm.

The following commonly reported TEAEs were more frequently reported in the placebo arm than in the finerenone arm: peripheral oedema (10.7% placebo vs. 6.6% finerenone), hypertension (9.6% placebo vs. 7.5% finerenone), hypoglycaemia (6.9% placebo vs. 5.3% finerenone), pneumonia (6.4% placebo vs. 4.5% finerenone), and constipation (5.8% placebo vs. 4.6% finerenone).

Table 33. Summary of frequent (≥5% patients) TEAEs (SAF) (9)

Primary system organ class Preferred term	Finerenone o.d. N=2827 (100%)	Placebo o.d. N=2831 (100%)
Number of patients with at least one TEAE	**2468 (87.3%)**	**2478 (87.5%)**
Blood and lymphatic system disorders		
Anaemia	209 (7.4%)	191 (6.7%)
Gastrointestinal disorder		
Diarrhoea	184 (6.5%)	189 (6.7%)
Constipation	131 (4.6%)	163 (5.8%)
General disorders and administration site conditions		
Peripheral oedema	186 (6.6%)	304 (10.7%)
Infections and infestations		
Bronchitis	134 (4.7%)	151 (5.3%)
Nasopharyngitis	241 (8.5%)	250 (8.8%)
Pneumonia	128 (4.5%)	181 (6.4%)
Upper respiratory tract infection	18 (6.4%)	189 (6.7%)
Urinary tract infection	179 (6.3%)	192 (6.8%)
Investigations		
Glomerular filtration rate decreased	179 (6.3%)	133 (4.7%)
Metabolism and Nutrition disorders		
Hypoglycaemia	151 (5.3%)	194 (6.9%)
Hyperkalaemia	446 (15.8%)	221 (7.8%)
Musculoskeletal and connective tissue disorders		
Arthralgia	142 (5.0%)	149 (5.3%)
Nervous system disorders		
Dizziness	146 (5.2%)	153 (5.4%)
Vascular disorders		
Hypertension	212 (7.5%)	273 (9.6%)

od=once daily; SAF=safety analysis set; TEAE=treatment-emergent adverse event;

Drug-related TEAEs

Drug-related TEAEs was higher in the finerenone arm (22.9%) compared with the placebo arm (15.9%), and 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 vs placebo, respectively). No fatal drug-related TEAEs were reported (66).

AEs of particular interest

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).

Hyperkalaemia

The studied population has an inherent risk of hyperkalaemia due to their underlying disease (as serum potassium tends to increase with decreasing eGFR) and due to their background standard of care therapy (ACEI/ARB) (68).

Finerenone led to a mean increase in serum potassium of ~0.2 mmol/l versus placebo in FIDELIO-DKD, with maximum increase in mean serum potassium of 0.23 mmol/l versus placebo at month 4 (9).

Incidences of all treatment-emergent investigator-reported hyperkalaemia events were 18.3% and 9.0% with finerenone and placebo, respectively. However, the clinical impact of these events, as assessed by death, hospitalisation or permanent treatment discontinuation due to hyperkalaemia, was minimal (9):

– No patients died of hyperkalaemia during the study

– Incidences of hyperkalaemia-related hospitalisation were 1.4% with finerenone and 0.3% with placebo

– Overall, 2.3% of patients discontinued finerenone versus 0.9% receiving placebo due to hyperkalaemia

Most treatment-emergent hyperkalaemia events were [redacted].

[redacted]

The identified risk factors for hyperkalaemia in FIDELIO-DKD are in line with those already known in the literature and clinical practice (69). Overall, these findings indicate that hyperkaleamia was manageable when using a serum potassium-guided dose titration regimen in an advanced and multimorbid CKD patient population (see Table 8).

Hypokalaemia was less common among patients who received finerenone than among those who received placebo (1.0% and 2.2%, respectively).

Acute kidney injury-related AEs

Worsening renal function and acute kidney injury–related adverse events and serious adverse events were balanced between the two groups (see Table 34) (9).

Table 34. Investigator-reported renal-related AEs of interest (SAF) (9)

	Finerenone o.d. N=2827 (100%)	Placebo o.d. N=2831 (100%)
Acute kidney injury	129 (4.6%)	136 (4.8%)
Hospitalisation due to acute kidney injury	53 (1.9%)	47 (1.7%)
Discontinuation of study drug due to acute kidney injury	5 (0.2%)	7 (0.2%)
Hospitalisation due to acute renal failure	70 (2.5%)	71 (2.5%)
Discontinuation of study drug due to acute renal failure	31 (1.1%)	36 (1.3%)

AE=adverse event; o.d.=once daily; SAF=safety analysis set;

Blood pressure

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 mm Hg, respectively, with finerenone and −0.1 and 0.9 mm Hg, respectively, with placebo.

Other AEs of interest

A slightly higher frequency of hypotension and hyponatraemia TEAEs was observed in finerenone-treated patients compared to placebo, [redacted] (66).

Glycated haemoglobin levels and body weight were similar in the two groups (9).

[redacted] (66).

Treatment-emergent serious adverse events (TESAEs)

A lower incidence of treatment-emergent serious adverse events (TESAEs) was observed in the finerenone arm compared with the placebo arm of the study (31.9 vs 34.3%). The most frequent TESAEs in both treatment arms were pneumonia (2.5% finerenone vs 3.6% placebo) and acute kidney injury (2.0 vs 1.8%) (66). Drug-related TESAEs were low in both groups (overall 1.7 vs 1.2%), the most common of these being [redacted] and [redacted]

Adverse events leading to premature permanent discontinuation of study drug

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).

Deaths

Fatal events were reported as either outcome events (OEs) or AEs based on the cause of death as defined in the Investigators Outcome Event manual. For the analysis of the efficacy endpoint, all-cause mortality (see section B2.6 ‘Clinical effectiveness results of the relevant trials’), all deaths were adjudicated by the CEC and included all events that occurred after randomisation until the End-of-Study visit.

Cardiac disorders as well as general disorders and administration site conditions were the System Organ Classes (SOCs) with the highest number of patients with fatal events in both arms. All other events occurred in 1 to 3 patients per treatment arm.

The results accounting for both AEs and OEs show that the overall incidence of deaths was lower in the finerenone arm than in placebo.

Table 35. Overview of deaths (SAF) (66)

	Finerenone o.d. N=2827 (100%)	Placebo o.d. N=2831 (100%)
Fatal AEs and OEs	[redacted]	[redacted]
Fatal treatment-emergent AEs and OEs	[redacted]	[redacted]
Fatal treatment-emergent AEs	31 (1.1%)	51 (1.8%)
Post-treatment fatal AEs and OEs	[redacted]	[redacted]
Post-treatment fatal AEs	58 (2.1%)	54 (1.9%)

AE=adverse event; o.d.=once daily; OE=outcome event; SAF=safety analysis set;
Patients can be counted in more than one category (some patients have both fatal AE and OE with one event being treatment-emergent and the other post-treatment. Post-treatment AEs are AEs that occurred more than 3 days after temporary or permanent stop of study drug.

Laboratory values and vital signs

There were no clinically relevant changes in laboratory investigations. In the first 12 months of treatment, the mean reduction in SBP was approximately 3 to 4 mmHg greater in the finerenone arm compared to placebo; the mean reduction in DBP was approximately 1 to 2 mmHg greater in the finerenone arm compared to placebo. No clinically relevant effect on heart rate, weight or BMI was observed during treatment with finerenone or placebo.

Profiles for haematology and clinical chemistry show an overall range of values that are to be expected of a population with advanced CKD. For the majority of parameters, including hepatic enzymes and HbA1c, mean and median changes from baseline over time showed no clinically meaningful differences between the finerenone and placebo groups. Serum potassium is discussed earlier in the safety section.

Subgroup analyses

In analyses of subgroups, no notable differences were observed for TEAEs by age, sex, race and ethnicity (66). Higher incidences of TEAEs were observed for patients with hepatic impairment than for those without impairment; this was seen in both treatment arms and between-treatment arm proportions were balanced.

[redacted]

Higher TEAE rates (in finerenone and placebo groups) were also reported in patients with a lower eGFR at baseline (<45 mL/min/1.73 m^2) reaffirming that ongoing monitoring of renal function should be performed as needed according to standard practice.

[redacted]

Overview of the safety of the technology in relation to the decision problem

FIDELIO-DKD - one of the largest contemporary studies to evaluate patients with CKD and T2D – provided a robust setting in order to assess the safety of finerenone when added to maximally tolerated labelled dose of current standard of care (i.e. ACEI or ARB) in this multimorbid population with advanced CKD and T2D.

Overall, the safety profile of finerenone observed in FIDELIO-DKD was consistent with that of the placebo arm, which represents current standard of care in the UK - angiotensin receptor blockers / angiotensin-converting enzyme inhibitors - for CKD in T2D. The overall incidence of TEAEs was balanced between the finerenone and

placebo treatment arms, and a lower frequency of serious TEAEs was observed in finerenone-treated patients.

The main risk observed with finerenone in FIDELIO-DKD was hyperkalaemia. The studied population has an inherent risk of hyperkalaemia due to their underlying disease (as serum potassium tends to increase with decreasing eGFR) and background standard of care therapy (ACEI/ARB) (68). Hyperkalaemia is also associated with the mode of action of finerenone and mineralocorticoid receptor antagonism. The majority of hyperkalaemia events seen in the study were mild or moderate in intensity and non-serious and only a small proportion of events led to treatment discontinuation (2.3% vs 0.9%) or hospitalisation (1.4 vs 0.3%). There were no treatment-emergent fatal cases of hyperkalaemia observed in either treatment arm. The study protocol included a serum potassium-guided dose titration regimen (see Table 8). Analysis of trial data collected in the context of dose-titration and interruption indicates hyperkalaemia with finerenone treatment to be manageable using the dose-titration regimen.

In summary, finerenone at doses of 10 mg or 20 mg o.d. is well tolerated in patients with advanced CKD and T2D. The expected increased risk of hyperkalaemia (based on finerenone's mode of action) is manageable when used in conjunction with the flexible dose-titration regimen based on serum potassium values and changes in eGFR.

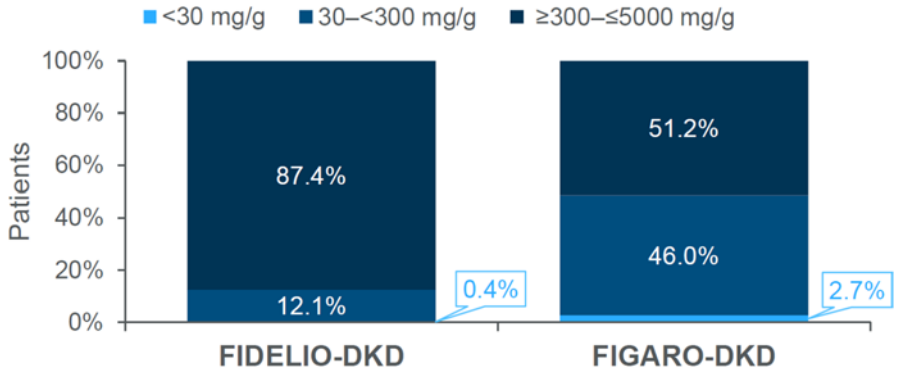
B.2.11 Ongoing studies

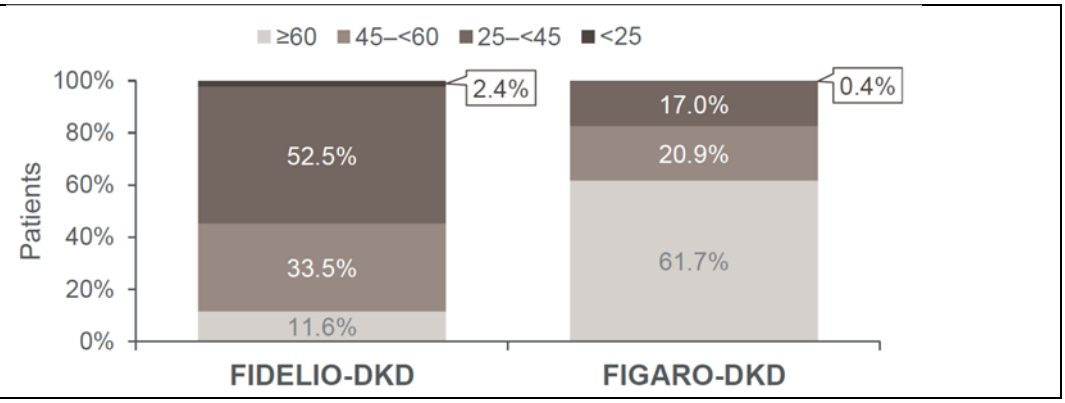
In addition to FIDELIO-DKD, one other phase III trial for finerenone has recently completed in CKD and T2D. FIGARO (NCT02545049) is a randomised, double-blind, placebo-controlled, parallel-group, multicentre, event-driven trial designed to evaluate the efficacy and safety of finerenone in reducing cardiovascular morbidity and mortality in addition to standard of care. Full data are not yet available at the time of this submission.

Key differences between FIGARO and FIDELIO-DKD are in the primary and key secondary composite endpoints and in the study populations (see Figure 23). In effect, the primary and key secondary endpoints are defined in the same way but are

reversed in FIGARO, when compared with FIDELIO-DKD. Thus, in FIGARO, CV morbidity and mortality are the primary focus. The inclusion criteria for FIGARO allows for participants with earlier stage CKD, resulting in very different study populations across the two phase III studies.

Figure 23. Key comparisons between FIDELIO-DKD and FIGARO (60, 70)

<table>
<tr><th>Study</th><th>FIDELIO-DKD</th><th>FIGARO</th></tr>
<tr><td colspan="3">
Clinical efficacy primary endpoint
Composite endpoint: time to onset of kidney failure* or decrease of eGFR ≥40% from baseline or death due to kidney disease
Composite endpoint: time to CV death, non-fatal MI, non-fatal stroke or hospitalisation for HF
Key secondary endpoints
Same as primary endpoint in FIGARO-DKD
Same as primary endpoint in FIDELIO-DKD
</td></tr>
<tr><td rowspan="2">Key inclusion criteria</td><td colspan="2">T2D and CKD, pre-treated with either an ACEI or ARB at maximal tolerated dose and serum potassium ≤4.8 mmol/l</td></tr>
<tr><td>• UACR 30–<300 mg/g and eGFR ≥25–<60 ml/min/1.73 m^2 and a history of diabetic retinopathy
Or
• UACR ≥300–≤5000 mg/g and eGFR ≥25–<75 ml/min/1.73 m^2</td><td>• UACR 30–<300 mg/g and eGFR 25–≤90 ml/min/1.73 m^2
or
• UACR ≥300–≤5000 mg/g and eGFR ≥60 ml/min/1.73 m^2</td></tr>
<tr><td>Randomised patients - Albuminuria categories (mg/g)</td><td colspan="2"> 
</td></tr>
</table>

Randomised patients - eGFR categories (ml/min/1.73 m²)	

ACEI=angiotensin-converting enzyme inhibitor; ARB=angiotensin receptor blocker; CKD=chronic kidney disease; CV=cardiovascular; eGFR=estimated glomerular filtration rate; HF=heart failure; MI=myocardial infarction; T2D=Type 2 diabetes mellitus; UACR=urinary albumin-to-creatinine ratio;

B.2.12 Innovation

Finerenone is considered 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. ACEIs and ARBs (and other background therapy).

There is no known cure for CKD. The focus of treatment of CKD in T2D has until very recently been centred around improving management of hyperglycaemia and hypertension to delay progression of CKD, with the use of antidiabetic agents and ACEIs or ARBs, respectively. In more recent clinical studies, the addition of SGLT2 inhibitors to a RAS blocker has shown a benefit on cardiorenal outcomes (44) (45). However, despite treatments, there remains a significant residual risk for cardiorenal morbidity and mortality among patients with CKD and T2D (41-44).

As well as the haemodynamic and metabolic aspects of kidney disease tackled by existing therapies, contemporary models of the disease suggest that inflammatory / fibrotic factors are also interrelated as pathophysiological drivers of CKD progression (18). Inflammation and fibrosis in the kidney and heart lead to structural changes and injury in the organs, with consequent decline in kidney function and development of CV disease (18, 52, 71). There is substantial evidence that inflammation and fibrosis is caused by mineralocorticoid receptor (MR) overactivation, contributing to the high

rate of cardiorenal morbidity and mortality (7, 52, 72-74). Adding finerenone - a nonsteroidal, selective MR antagonist (MRA) – to current standard of care to slow progression of CKD, is thus based on sound rationale.

Whereas the adverse safety profile and limited and uncertain clinical evidence of steroidal MRAs has prevented their recommendation or application in CKD in T2D (11, 36), the benefits of the non-steroidal structure of finerenone confers the ability to more selectively target the inflammatory / fibrotic elements of CKD progression.

Finerenone has a high potency and selectivity for the MR due to its nonsteroidal molecular structure and bulky binding mode, preventing MR from activating the expression of pro-inflammatory and pro-fibrotic proteins (5, 7, 8, 75-78). In animal models finerenone demonstrates a balanced distribution between the heart and the kidney (5, 79) – meaning its inhibiting effect on inflammation and fibrosis leads to improved endothelial function in the kidney, heart and blood vessels. In addition, it prevents tubular injury in the kidney and reduces cardiac hypertrophy, thereby enabling a slowing of kidney disease progression and preventing further structural and functional damage to the heart and blood vessels (5, 8, 77, 80-83).

Finerenone also has no relevant affinity for androgen, progesterone, oestrogen and glucocorticoid receptors and therefore does not cause sex hormone-related adverse events (e.g. gynaecomastia). [redacted] (66).

In addition, finerenone provides its organ protective effects without impact on blood pressure and blood glucose levels, which confirms lack of engagement of haemodynamic or metabolic mechanisms (5, 9, 84).

The pivotal phase 3 study (FIDELIO-DKD) provides clinical evidence of the success of this novel treatment approach, demonstrating clinically significant renal and CV benefits with finerenone in patients with CKD and T2D already on background

guideline-directed therapy, plus well-controlled glycated haemoglobin and blood pressure levels (9, 85).

Aspects not captured by the QALY calculation

Importantly, there are aspects of innovation that are not captured within the QALY calculation. One of the consequences of progressing to ESRD is chronic dialysis. Dialysis is an intervention that has a substantial impact on the life of patients and their family and/or caregivers. A treatment such as finerenone that can delay the progression to kidney failure and the need for dialysis will offer considerable benefits to both patients and their caregivers.

Indeed, some people with kidney failure will decide not to have dialysis treatment such is the burden it imposes. Some may feel that the treatment will be hard to manage and impact too much on the remainder of their life. They may feel that the journey to the hospital three times a week for a 3-5 hour stay is too much for them if having haemodialysis. Similarly, having regular peritoneal dialysis at home may also be considered too much to manage. For those who are easily confused, for example, people who have dementia, dialysis may seem frightening or upsetting (86).

The impact of dialysis on caregivers may be substantial and life-changing e.g. organising regular lengthy hospital visits or aiding with management of dialysis at home with all the associated home adaptations, equipment, and infection control measures. The considerable burden on care-givers lives, for example, their role within the family, employment, fatigue, anxiety and social isolation and disruption, can in turn influence their quality of life. Several publications have reported a negative impact of dialysis on carers quality of life, with a particular impact on mental health (87-89).

With reference to the NICE methods guide (1), the committee should consider the impact of finerenone, as an innovative treatment to delay the progression of kidney disease, on not only the patient, but the caregivers of those undergoing dialysis for ESRD. Section 3.1.4 of the guide refers to consideration being given to:

- The impact of having the condition
- The experience of undergoing specific treatments for that condition

- The experience of the healthcare system for that condition
- Organisational issues that affect patients and carers

As described above, dialysis has a significant impact on daily life for patients and their caregivers with the need to organise their lives around lengthy dialysis sessions and regular interactions with the multidisciplinary team, including GP, nephrologist, dialysis nurse, dialysis technician, dietitian and social worker.

Section 2.2.8 refers to the consideration of health benefits and adverse effects that are of importance to patients and/or their carers. As described, the impact on the health-related quality of life of carers can be substantial, particularly when considering aspects of mental health and wellbeing.

Lastly, the reference case, in section 5.1 refers to the perspective on outcomes being all direct health effects whether for patients, or when relevant, carers.

It is evident that these aspects are not considered within the current QALY calculation.

B.2.13 Interpretation of clinical effectiveness and safety evidence

2.13.1 Principal findings from the clinical evidence: clinical benefits and harms

Affecting approximately 40% of patients with type 2 diabetes (T2D), chronic kidney disease (CKD) has a high global disease burden (17, 18). Comorbid CKD increases cardiovascular (CV) risk and mortality, which increases with CKD progression (30). Current treatments are associated with a high residual risk of cardiorenal events in patients with CKD and T2D, hence there is an unmet need for new treatments to further improve outcomes in this patient population (42, 44, 51).

The benefit of adding finerenone, a novel nonsteroidal mineralocorticoid receptor antagonist (MRA), to current standard of care in CKD in T2D was investigated in a large, phase III international, randomised double-blind, event-driven trial involving 5734 patients (nearly 13,000 patient-years treatment exposure). FIDELIO-DKD, one of the largest contemporary studies to evaluate patients with CKD and T2D, provides clinical evidence to support the use of finerenone (10 or 20mg o.d.) to delay the progression of kidney disease and reduce the risk of cardiovascular mortality and morbidity in adults with CKD and T2D.

FIDELIO-DKD met its primary and key secondary objectives, demonstrating superior results in delaying CKD progression and reducing CV mortality when finerenone is added to current standard of care treatment compared with current standard of care alone.

An 18% risk reduction of the primary renal composite endpoint assessing CKD progression (kidney failure, sustained decrease of ≥40% in the eGFR from baseline, or death from renal causes) was achieved in the finerenone treatment arm compared with the placebo group (HR=0.82; 95% CI, 0.73-0.93; P = 0.001). A key secondary outcome event (CV death, non-fatal MI, non-fatal stroke, or hospitalisation for heart failure) occurred in 367 patients (13.0%) in the finerenone group and 420 patients (14.8%) in the placebo group (HR=0.86; 95% CI, 0.75-0.99; P = 0.03). Finerenone, therefore, reduced the risk of cardiovascular mortality and morbidity by 14%, when compared with current standard of care treatment of ACEI / ARBs.

The treatment benefit of finerenone over placebo for the primary and key secondary endpoints persisted throughout the duration of the study and was consistent across all components of the composite endpoints except for non-fatal stroke.

FIDELIO-DKD did not have enough statistical power to detect differences in the risk of death from any cause, a secondary endpoint in the study. However, a non-significant trend in reduction of death from any cause favouring finerenone versus placebo was observed (2.90 vs 3.23 patients with event per 100 patient-years, respectively; HR=0.90; [95% CI 0.75–1.07]). Another secondary endpoint, all-cause hospitalisation, also favoured finerenone treatment (HR=0.95 [95% CI 0.88; 1.02].

The positive benefit of finerenone over placebo in delaying CKD progression, as measured by the primary endpoint, was further supported by 24% reduction in risk of the secondary renal composite endpoint (HR=0.76; 95% CI, 0.65-0.90, p=0.0012), which included ‘a sustained eGFR decline of 57%’ as a component, and a 31.2% reduction in UACR at Month 4. Fewer events of new onset of atrial fibrillation or atrial flutter were also observed in the finerenone arm compared to placebo.

Treatment differences in favour of finerenone were robust across all prespecified sensitivity analyses (FAS on-treatment and PPS) and were indicative of a larger treatment effect with finerenone. Subgroup analyses of the primary and secondary efficacy endpoints confirmed that the treatment benefit with finerenone was generally consistent across the subpopulations evaluated; there was no subgroup that had a significant interaction across all endpoints.

In addition, results of the safety analyses in FIDELIO-DKD, demonstrate finerenone to be well tolerated in patients with CKD and T2D, concomitantly treated with current standard of care. The main safety risk was hyperkalaemia, which could be anticipated based on finerenone’s mode of action. During the study this proved manageable using a flexible dose-titration regimen based on serum potassium values and changes in eGFR.

Overall, HRQoL results (KDQOL 36 and EQ-5D-5L/VAS) showed small changes that were in favour of finerenone.

The proposed label population is patients with CKD stages 3 and 4 and albuminuria, representing approximately 90% of the FIDELIO-DKD study population. Detailed results for the proposed label population are presented alongside the full trial population in section B.2.6.

In summary, finerenone 10 or 20mg o.d. was shown to be efficacious and well tolerated with an overall positive risk benefit profile when used as a treatment to delay the progression of kidney disease and reduce the risk of cardiovascular mortality and morbidity in adults with CKD and T2D.

2.13.2 Strengths and limitations of the clinical evidence base

Clinical evidence in this submission is derived from FIDELIO-DKD, one of the largest contemporary studies to evaluate patients with CKD and T2D. This was a well-conducted pivotal study of robust design, with a total of approximately 13,000 patient-years of efficacy and safety follow-up, and for which vital status was known for 99.7% of patients.

The renal composite and individual endpoints, along with their components, in FIDELIO-DKD align with current recommendations for appropriate assessment of kidney failure / progression of CKD in clinical trials (32). Likewise, the assessment of cardiovascular risk involved standardised internationally recognised trial outcomes (90, 91). The mix of renal and CV endpoints in the study reflects the major morbidities experienced by patients with CKD in T2D.

Superior results were observed for both the primary renal and key secondary CV endpoints with finerenone added to current standard of care with maximum tolerated labelled doses of RAS-inhibitors. Results were consistent across all components of the composite endpoints except for non-fatal stroke and were corroborated by subgroup and sensitivity analyses. Treatment benefit persisted throughout the duration of the study. Hierarchical statistical testing rules meant that other secondary endpoints were investigated in an exploratory manner, however, all analyses favoured finerenone treatment and the secondary renal composite and change in UACR added to the robustness of the data and supported the internal validity of the primary renal outcome findings. The positive results with finerenone confirm the ability to further

improve CKD in T2D using a new therapeutic approach other than targeting haemodynamic / metabolic parameters.

In FIDELIO-DKD, finerenone was studied as an add-on therapy to standard of care which consisted of maximally tolerated doses of ACEI/ARB. The finerenone treatment arm was compared against a placebo-controlled arm, in which patients were receiving standard of care of maximally tolerated doses of ACEI/ARB. Although the study was initiated in 2015, ACEI/ARBs are still considered to be standard of care in this indication, which means the results are directly applicable to current clinical practice.

A perceived limitation to the clinical evidence however, is that since FIDELIO-DKD was designed, results demonstrating the additive benefits of SGLT2 inhibitors to ACEI / ARBs in patients with T2D with albuminuria and eGFR ≥ 30 mL/min/1.73 m2 (44, 45), has led to very recent incorporation of the combination of SGLT2 inhibitors with ACEI / ARBs into international guideline recommendations (11). Their place in NICE guidelines is still under review (3).

While FIDELIO-DKD permitted concomitant medications alongside the background of ACEI / ARBs, for control of blood pressure, potassium levels, and diabetes management *including* unrestricted use of SGLT2 inhibitors, at baseline only 4.5% of all randomised patients were treated with SGLT2 inhibitors. During the trial, the use of SGLT2 increased slightly but was still low (< 10% of patients), hence there is limited evidence with finerenone for this scenario in clinical practice. The pattern of SGLT2 inhibitor use in FIDELIO-DKD is reflective of UK clinical practice, as measured by current sales data for SGLT2i which suggests a market share of [redacted]% of drugs for T2D. As such, these drugs cannot be considered established standard of care and this was borne out in the consultation on the draft scope for this appraisal. Indeed, SGLT2i are not appropriate for all patients with type 2 diabetes (46) and CKD and there have been a number of MHRA safety updates about their use (47-50).

Hyperkalaemia was the main risk associated with finerenone in FIDELIO-DKD, which could be anticipated due to the mode of action of MR antagonization, the presence of CKD and background ACEI / ARB therapy. While this may have limited some patients occasionally from taking the maximum dose of finerenone, the clinical impact of hyperkalaemia was minimal with no deaths from hyperkalaemia during the study and

the incidences of hyperkalaemia-related hospitalisation 1.4% with finerenone and 0.3% with placebo. Overall, hyperkalaemia was manageable when using the recommended serum potassium-guided dose titration regimen (see Table 8).

Relevance of the evidence base to the decision problem

The decision problem population addressed in the submission is 'adults with T2D and CKD'. The proposed label population, as submitted to EMA is 'adults with chronic kidney disease (stage 3 and 4 with albuminuria) and type 2 diabetes.' This target population was based on the staging system for CKD as defined by KDIGO guidelines (11) and is considered to best represent the FIDELIO-DKD study population which consists of approximately 90% of patients with CKD stages 3 and 4. Data on the full trial population and the proposed label population are presented in this submission.

Relevance to the population in the decision problem

The population included within the FIDELIO-DKD study is generally reflective of the population defined within the decision problem and likely to be encountered within clinical practice in England. The study was an international study across 48 countries, reflecting the global widespread nature of the disease and enabling broad applicability, with a population that was racially and geographically diverse.

Selection criteria were chosen to adequately define a DKD study population at high risk of progressing with their CKD towards end stage renal disease (ESRD) or developing CV events, but excluding patients who may be exposed to particular risks after study drug administration or those with conditions that may have an impact on the aims of the study (63). Inclusion criteria for FIDELIO-DKD selected a CKD population with albuminuria with UACR ranging from ≥30–≤5000 mg/g and eGFR ≥25–<75 mL/min/1.73 m^2. An advanced CKD population was included with mean eGFR of 44.3 mL/min/1.73 m^2 and median UACR of 852 mg/g at baseline. Subgroup analyses by eGFR category at screening (eGFR 25 to <45, 45 to <60, ≥60 mL/min/1.73 m2) or type of albuminuria at screening (high albuminuria, very high albuminuria) revealed a consistent trend in favour of finerenone treatment in all categories. Some patients (2.4%) in FIDELIO-DKD had eGFR <25 mL/min/1.73 m^2 at initiation of treatment and due to this limited clinical experience, initiation of finerenone is not recommended for

patients with eGFR <25 mL/min/1.73 m^2. There was no clinical experience in FIDELIO-DKD in patients with eGFR <20 mL/min/1.73 m^2 at initiation of treatment and very few patients with an eGFR below 15 mL/min/1.73 m^2 continued finerenone during the course of the study. Based on this limited experience, treatment with finerenone should be continued with caution in patients with eGFR <15 mL/min/1.73 m^2 (ESRD).

The prevalence of comorbidities was similar to that observed in other studied cohorts of CKD (44) and based on the optimised use at baseline of evidence-based therapy with RAS-inhibitors, and the frequent use of statins (74%) and beta-blockers (54%), a well-treated population was included. Relevant baseline characteristics were well-balanced between the finerenone and placebo treatment groups. The pre-specified subgroup analysis evaluated efficacy and safety according to the wide variation of baseline characteristics such as age, gender, race, region, history of CVD, baseline albuminuria, potassium, eGFR, systolic blood pressure, concomitant medication. These analyses were consistent with the overall study results, including consistency across regions and subgroups regarding renal and cardiovascular risk factors and medical history. This suggests that the FIDELIO-DKD study population, and hence the efficacy and safety results would be generalisable to the population found in clinical practice in England.

Relevance of the comparator

As discussed above, for decades the standard of care for slowing progression toward ESRD in CKD has been ACEIs and ARBs. In more recent clinical studies, the addition of an SGLT2 inhibitor to a RAS blocker has shown a benefit on cardiorenal outcomes (44, 45). This has led to international guidelines now recommending SGLT2 inhibitors in addition to RAS blockers for patients with T2D with albuminuria > 300 mg/g if their eGFR is > 30 mL/min/1.73 m^2 (11, 36, 37).

The “live” NICE clinical guidelines in place during the development of this submission (2), make no reference to SGLT2 inhibitors as part of the treatment pathway. Their place in CG update 2021 is considered but this CG states that *“NICE are reviewing the evidence on SGLT2 inhibitors in people with CKD and type 2 diabetes”* and may update recommendations as a result of this (consultation during September 2021 and publication in November 2021) (3).

Due to SGLT2s being only a recent addition to international guidelines, and their place in therapy is being reviewed by NICE, this evidence has not yet translated into widespread changes in established clinical practice in the UK. Consultee feedback on the draft scope also confirmed that SGLT2is should not be considered a comparator as they are not part of standard of care.

The mode of action of the two classes of drugs are also different; finerenone is a drug designed to work at the molecular level on the kidney to address inflammation and fibrosis. Further, SGLT2i are not appropriate for all patients with type 2 diabetes (46) and CKD and there have been a number of MHRA safety updates about their use (47-50).As such, the comparator of standard of care with ACE/ARB in FIDELIO-DKD is directly relevant to the decision problem and UK clinical practice.

Relevance of the intervention

As described in section B2.12 Innovation, use of finerenone for CKD in T2D offers an additional therapeutic approach on top of current standard of care medicine. The focus of treatment of CKD in T2D to date has centred around improving management of hyperglycaemia and hypertension to delay progression of CKD, with the use of antidiabetic agents and ACEIs or ARBs, respectively. However, despite these treatments, there remains a significant residual risk for cardiorenal morbidity and mortality among patients with CKD and T2D (41-44). Use of a treatment with a different mode of action offers the potential for further improvements in risk reduction of cardiorenal morbidities in CKD in T2D. The pivotal phase 3 study (FIDELIO-DKD) provides clinical evidence of the success of this novel treatment approach, demonstrating clinically significant renal and CV benefits with finerenone in patients with CKD and T2D already on background guideline-directed therapy, plus well-controlled glycated haemoglobin and blood pressure levels (9, 85).

The proposed dose of finerenone (10mg or 20mg o.d.) and the dose-titration regimen based on serum potassium and eGFR levels are aligned with FIDELIO-DKD, although it is recommended in the draft SPC that all patients are initiated on a 10mg dose.

Relevance of the outcomes assessed in clinical trials to clinical benefits experienced by patients in routine clinical practice

The mix of renal and CV endpoints in the study reflects the major morbidities experienced by patients with CKD in T2D.

The renal composite and individual endpoints in FIDELIO-DKD align with current recommendations for appropriate assessment of kidney failure / progression of CKD in clinical trials (32). Renal failure, kidney transplantation, initiation of maintenance dialysis, and death from kidney failure are realities faced by patients with CKD and T2D in clinical practice and routine laboratory measurement of eGFR and UACR for predicting progression to kidney failure is an established practice (see Table 5). Benefits of a clinically meaningful preservation of kidney function could, as an example, delay the necessity for (or progression to) renal replacement therapy, which is costly and has a negative impact on quality of life (26).

There were an estimated 7,000 extra strokes and 12,000 extra myocardial infarctions in people with CKD in 2009–2010, relative to the expected number in people of the same age and sex without CKD (14). The cost to the NHS of health care related to these strokes and MIs is estimated at £174–178 million (14). Thus, cardiovascular risk and the reduction thereof is extremely relevant to patients, clinicians and the broader NHS and country's economic perspective.

Assessment of all outcomes followed standard diagnostic / monitoring procedures as used within the NHS.

It is considered, from the review of evidence in this submission, that the clinical evidence from FIDELIO-DKD is both relevant and applicable to routine clinical practice in England. Study results demonstrate a positive benefit in the slowing of CKD progression and reducing the risk of major CV events, in adding finerenone to current standard of care including ACEIs / ARBs in patients with CKD and T2D with well-controlled glycated haemoglobin and blood pressure levels.

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

To ensure all relevant cost-effectiveness models available for CKD were captured, an SLR was conducted.

The methodology of the SLR followed the NICE and CRD guidelines and it was organised according to the following phases: search strategy, selection of articles, data extraction & quality control, data synthesis.

The searches were run on the 15th of April 2020 in the following databases: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R), Embase, Health Technology Assessment (HTA), NHS Economic Evaluation Database (NHS EED), and the Database of Abstracts of Reviews of Effects (DARE), and an update of this search was then performed on the 5th of March 2021. Medline and Embase databases were accessed via the OVID interface while the HTA, NHS EED and DARE databases were accessed via the crd.york website. Additionally, in December 2020 and March 2021, manual searches of the following HTA agencies' websites were conducted: The National Institute for Health and Care Excellence (NICE), the Scottish Medicines Consortium (SMC), the Haute Autorité de Santé (HAS), the Canadian Agency for Drugs and Technologies in Health (CADTH) and the Institute for Clinical and Economic Review (ICER).

The search strategy included keywords for the population and its synonyms, combined with relevant keywords for health economic models, as recommended by NICE. The search strategy is presented in Appendix G.

Overall, 16,363 hits were identified in the selected databases (15,194 from the initial search and 1,169 during the update), 47 of them were duplicates which were removed. After title and abstracts screening, 15,568 records were excluded. 748 references proceeded to the full-text review phase and 61 publications were included after that stage. Additionally, after searching the HTA databases, 7 more reports were included (6 from the initial search and one from the review update). After full-text screening, the data from 68 studies was extracted.

All economic models considering a population of patients with CKD, irrespective of the form of economic evaluation used, were included. Although the target population for finerenone is CKD in T2D, a broader approach was adopted to extend this SLR to patients with CKD regardless of diabetes status, based on experts' opinion.

The results of the SLR were analysed separately for three subgroups: models based on CKD patients, models based on CKD and associated diseases (e.g., diabetes, anaemia, heart failure, hyperkalaemia, secondary hyperparathyroidism) and models based on CKD screening.

The searches identified:

- 34 CKD models, with CKD modelled through the full spectrum of condition severity, as a single disease,
- 25 models considering CKD and associated diseases,
- 9 models focusing on CKD screening.

No cost-effectiveness studies of finerenone were retrieved.

Details for all cost-effectiveness studies included in the SLR are summarised in Appendix G. The most relevant studies in the context of development of the CE model for finerenone have been presented in the tables below (Table 36 presents models among patients with CKD, Table 37 presents models among patients with CKD and associated diseases, Table 38 presents models on CKD screening). The tables below include all models which are referenced later in the submission as well as all identified models focused on the UK, considered most relevant to decision making in England.

Table 36. Summary list of key cost-effectiveness studies - models among patients with CKD

Author, year, country	Study population	Patients age (SD)	Summary of model	Incremental costs	Incremental QALYs	ICER (Cost/QALY)
Evans 2019 (92), UK	Cohort of CKD stage 3a patients	60	• Type: Patient-level simulation model • Time horizon: Lifetime • Cycle length: 1 month • Perspective: UK healthcare payer	Ongoing RAASi vs no RAASi: (per patient) Discounted: -£3135 • RRT: -£14,143 • CKD management: +£8091 • Arrhythmia: +£327 • Hospitalisation: +£2129	Ongoing RAASi vs no RAASi: <u>Incremental QALY</u>: • Discounted: 1.02	Ongoing RAASi vs no RAASi • Undiscounted: -£24.48 per QALY gained • Discounted: -£3073.53 per QALY gained
Schlackow 2017 (93), UK	Moderate-to-advanced CKD participants	62 (12)	• Type: Markov • Time horizon: Lifetime • Cycle length: 1 year • Perspective: NR	NR	NR	NR
Mihaylova 2016 (94), UK	Patients 40 years or older with CKD but without known coronary heart disease were eligible if they were receiving maintenance dialysis or had serum or plasma creatinine levels of at least 150 mmol/L (1.7 mg/dL) in men or 130 mmol/L (1.5 mg/dL) in women	62 (12)	• Type: No model provided • Time horizon: median follow-up was 4.9 years • Cycle length: NR • Perspective: Healthcare system	Simvastatin 20 mg plus ezetimibe 10mg daily vs placebo: • All patients: £1142 • 5-year risk of cardiovascular disease at randomisation - <10%: £1492 - 10% -20%: £1239 - ≥20%: £893 • CKD stage at randomisation - CKD3: £1341 - CKD4: £1276 - CKD5 not on dialysis: £1028 - on dialysis: £1021	<u>Incremental QALY</u>: Simvastatin 20mg plus ezetimibe 10mg daily vs placebo: • 5-year risk of cardiovascular disease at randomisation - <10%: 0.06 - 10% -20%:0.08 - ≥20%: 0.05 • CKD stage at randomisation - CKD3: 0.13 - CKD4: 0.11 - CKD5 not on dialysis: 0.04 - on dialysis: 0.05	NR

Author, year, country	Study population	Patients age (SD)	Summary of model	Incremental costs	Incremental QALYs	ICER (Cost/QALY)
Thompson 2013 (95), UK	NDD-CKD patients, ≥18 years old, stage 3-4 CKD	57.9	• Type: Markov model • Time horizon: Lifetime • Cycle length: 1 month • Perspective: Healthcare system	Sevelamer vs calcium carbonate (per patient): £37,282	Sevelamer vs calcium carbonate (per patient): Incremental QALY: 1.5613	Sevelamer vs calcium carbonate: £23,878 per QALY gained
Vegter 2011 (96), UK	Predialysis CKD population and Incident dialysis population	NR	• Type: Decision analytical structure and Markov model • Time horizon: Lifetime (40 years) • Cycle length: 1 year • Perspective: Healthcare system	Additional drug costs, second line LC vs CB alone, £ (90% PI) • Pre-dialysis population: 387 (333–451) • Dialysis population: 386 (338–446) Dialysis costs, second line LC vs CB alone, £ (90% PI) • Pre-dialysis population: -726 (-1020–509) • Dialysis population: NA Total costs, second line LC vs CB alone, £ (90% PI): • Pre-dialysis population: -339 (-634 to 129) • Dialysis population: 386 (338–446)	Total clinical benefit of second-line LC treatment, QALYs (90% PI): Incremental QALY: • Pre-dialysis population: 44.1 (34.1–54.2) • Dialysis population: 55.8 (42.6–72.3)	Second-line LC vs. CB alone: • Pre-dialysis population: Dominating • Dialysis population: £6900 per QALY gained (90% PI £5500–£8800 per QALY gained)
Black 2010 (97), UK	A cohort of individuals with non-diabetic CKD	72	• Type: Markov • Time horizon: 35 years • Cycle length: NR • Perspective: Healthcare system	• Refer at CKD 3a vs Standard practice (referral upon transit to CKD stage 5): £1691 • Refer at CKD 3b vs Standard practice (referral upon transit to CKD stage 5): £1012 • Refer at CKD 4 vs Standard practice (referral upon transit to CKD stage 5): £332 • Refer ACR 30–299 mg/g vs standard practice (referral upon transit to CKD stage 5): £800 • Refer ACR ≥ 300 mg/g vs standard practice (referral upon transit to CKD stage 5): £512	Incremental QALYs: • Refer at CKD 3a vs Standard practice: 0.413 • Refer at CKD 3b vs Standard practice: 0.232 • Refer at CKD 4 vs Standard practice: 0.056 • Refer ACR 30–299 mg/g vs standard practice: 0.154 • Refer ACR ≥ 300 mg/g vs Standard practice: 0.049 • Refer at CKD 3b or ACR ≥ 30 mg/g vs Standard practice: 0.291 • Refer at CKD 3b or ACR ≥ 300 mg/g vs Standard practice: 0.248	• Refer at CKD 3a vs Standard practice: £4091 per QALY gained • Refer at CKD 3b vs Standard practice: £4352 per QALY gained • Refer at CKD 4 vs Standard practice: £5923 per QALY gained • Refer ACR 30–299 mg/g vs standard practice: £5194 per QALY gained • Refer ACR ≥ 300 mg/g vs Standard practice: Dominated

Author, year, country	Study population	Patients age (SD)	Summary of model	Incremental costs	Incremental QALYs	ICER (Cost/QALY)
				• Refer at CKD 3b or ACR ≥ 30 mg/g vs standard practice (referral upon transit to CKD stage 5): £1255 • Refer at CKD 3b or ACR ≥ 300 mg/g vs standard practice (referral upon transit to CKD stage 5): £1118		• Refer at CKD 3b or ACR ≥ 30 mg/g vs Standard practice: £4313 per QALY gained • Refer at CKD 3b or ACR ≥ 300 mg/g vs Standard practice: £4508 per QALY gained
Ludbrook 1981 (98), UK	Patients with chronic renal insufficiency	NR	• Type: Markov • Time horizon: NR • Cycle length: 1 month • Perspective: NR	NR	NR	NR

Abbreviations: ACR - Albumin-to-creatinine ratio; CB – Calcium-based binder; CKD – chronic kidney disease; ICER – incremental cost-effectiveness ratio; LC – Lanthanum carbonate; NDD – non–dialysis-dependent; NA – not applicable; NR – not reported; QALY – quality adjusted life year; PI – probbaility interval; RAASi - Renin-angiotensin aldosterone system inhibitor; RRT – Renal replacement therapy; SD – standard deviation

Table 37. Summary list of key cost-effectiveness studies - models among patients with CKD and associated diseases

Author, year, country	**Study population**	**Patients age (SD)**	**Summary of model**	**Incremental costs**	**Incremental QALYs/**	**ICER (Cost/QALY)**
Witham 2020 (99), UK	Older patients with advanced CKD (stage 4 or 5, not on dialysis) and mild acidosis (serum bicarbonate concentration of <22 mmol/l)	Bicarbonate: 73.9 (7.6), Placebo: 74 (6.6)	• Type: NR • Time horizon: 2 years • Cycle length: NR • Perspective: -Healthcare system -Societal	Sodium bicarbonate vs. placebo (95% CI): • Complete cases over 12 months' follow-up: £563.74 (88.18 to 1154.18) • Complete cases over 24 months' follow-up: £591.00 (166.29 to 1078.36) • Complete cases over 24 months' follow-up and all participants starting RRT during the trial: £808.93 (–4124.71 to 5411.89)	Sodium bicarbonate vs. placebo (95% CI): Incremental QALY: • Complete cases over 12 months' follow-up: -0.047 (–0.078 to –0.015) • Complete cases over 24 months' follow-up: -0.083 (–0.166 to –0.005) • Complete cases over 24 months' follow-up and all participants starting RRT during the trial: -0.074 (–0.151 to –0.003)	Sodium bicarbonate vs. placebo: • Complete cases over 12 months' follow-up: Dominated • Complete cases over 24 months' follow-up: Dominated • Complete cases over 24 months' follow-up and all participants starting RRT during the trial: Dominated

Author, year, country	Study population	Patients age (SD)	Summary of model	Incremental costs	Incremental QALYs/	ICER (Cost/QALY)
Javanbakht 2020 (100), UK	Hypothetical cohort of patients with CKD stage 3–4 undergoing DAG and/or PCI	72	• Type: Decision analytical structure and Markov model • Time horizon: - Decision tree: 3 months - Markov: Lifetime • Cycle: 3 months • Perspective: NHS and PSS	DyeVert™ PLUS EZ system vs current practice: − £448 per patient: Total long-term cost results (£): • Cost of procedure (DAG and/or PCI): 0 • Cost of DyeVert™ PLUS EZ system: £15,897,192 • Cost of CI-AKI and related complications (first 3 months): −£6,808,389 • Cost of subsequent disease management: −£28,850,398 • Total costs: −£19,761,595	Incremental QALY: DyeVert™ PLUS EZ system vs current practice: 0.028 QALY	DyeVert™ PLUS EZ system vs Current practice: Dominant
SMC 2020 (sodium zirconium) (101), Scotland	Patients with HK (defined as a serum potassium of >6.0mmol/L) with CKD stage 3b to 5 and/or HF, who would otherwise need to down-titrate or discontinue their RAASi therapy to maintain a clinically acceptable serum potassium level (normokalaemia)	NR	• Type: Patient-level simulation model • Time horizon: Lifetime (80 years) • Cycle: NR • Perspective: Healthcare system (assumed)	Sodium zirconium cyclosilicate vs SoC: £4,103	Incremental QALY: Sodium zirconium cyclosilicate vs SoC: 0.435	Sodium zirconium cyclosilicate vs SoC: £9,438 per QALY gained
SMC 2020 (patiromer) (102) Scotland	Adult patients with CKD stage 3 or 4 with or without HF, with a serum potassium level of >6.0mmol/L who are receiving or RAASi	Up to 80 years of age	• Type: Markov • Time horizon: Lifetime (35 years) • Cycle: 1 month • Perspective: NHS and Social Care	Patiromer vs. SoC: £377	Patiromer vs. SoC: Incremental QALY: 0.0287	Patiromer vs. SoC: £13,154 per QALY gained
NICE 2019 (patiromer) (103), UK	• Patients with stage 3-4 CKD and HF comorbidity (CKD HF+) with a serum	Starting age: 65	• Type: Markov • Time horizon: Lifetime (35 years) • Cycle: 1 month	Patiromer vs No Patiromer: £3,289	Patiromer vs No Patiromer: Incremental QALY: 0.17406	Patiromer vs No Patiromer: £18,893 per QALY gained

Author, year, country	Study population	Patients age (SD)	Summary of model	Incremental costs	Incremental QALYs/	ICER (Cost/QALY)
	potassium of ≥5.5 mmol/L at baseline • Patients with stage 3-4 CKD without HF comorbidity (CKD [no HF]) with a serum potassium level of >6.0 mmol/L		• Perspective: NHS and PSS			
SMC 2018 (patiromer) (104), Scotland	Patients with stage 3 or 4 CKD on stable doses of at least one RAASi treatment who develop HK	65	• Type: Markov • Time horizon: 35 years • Cycle: 1 month • Perspective: Healthcare system (assumed)	NR	NR	Patiromer vs no patiromer strategy: £13,264 per QALY gained
NICE 2015 (tolvaptan) (105), UK	ADPKD in adults with CKD stages 1 to 3 at initiation of treatment	38.7 years (18–50 years), CKD stages 2 and 3: 44	• Type: Patient-level simulation model • Time horizon: Lifetime (80 years) • Cycle: 1 year • Perspective: NHS and PSS	Tolvaptan vs Soc (with the patient access scheme): • Company's base case (after correcting a model code error): £31,838 • Company's base case using CKD-EPI as an approximation for eGFR (after correcting a model code error): £36,411 • ERG's preferred base case: £33,015 • ERG's preferred base case using CKD-EPI as an approximation for eGFR: £37,956 • ERG's worst-case scenario exploratory analyses using CKD-EPI as an approximation for eGFR: £32,095	Incremental QALYs: Tolvaptan vs standard care : •Company's base case (after correcting a model code error): 0.92 • Company's base case using CKD-EPI as an approximation for eGFR (after correcting a model code error): 0.72 • ERG's preferred base case: 0.76 • ERG's preferred base case using CKD-EPI as an approximation for eGFR: 0.59 • ERG's worst-case scenario exploratory analyses using CKD-EPI as an approximation for eGFR: 0.44	Tolvaptan vs Soc (with the patient access scheme): •Company's base case (after correcting a model code error): £34,733 per QALY gained • Company's base case using CKD-EPI as an approximation for estimated eGFR (after correcting a model code error): £50,524 per QALY gained • ERG's preferred base case: £43,280 per QALY gained • ERG's preferred base case using CKD-EPI as an approximation for eGFR: £64,515 per QALY gained • ERG's worst-case scenario exploratory analyses using CKD-

Author, year, country	Study population	Patients age (SD)	Summary of model	Incremental costs	Incremental QALYs/	ICER (Cost/QALY)
						EPI as an approximation for eGFR: £72,705 per QALY gained • ERG's revised base case: £43,514 per QALY gained (intention-to-treat population)
SMC 2015 (tolvaptan) (106), Scotland	ADPKD in adults with CKD stages 1 to 3 at initiation of treatment	Age 18 to 50 years	• Type: Patient-level simulation model • Time horizon: Lifetime • Cycle: NR • Perspective: Healthcare system**	Tolvaptan vs Soc (with the patient access scheme): £11,614	Incremental QALY: Tolvaptan vs SoC : 0.92	Tolvaptan vs Soc (with the patient access scheme): £12,563 per QALY gained
McEwan 2021 (107), UK	Adults with T2D at increased risk of CV disease as represented by DECLARE-TIMI 58	63.80	• Type: Patient-level fixed-time increment Monte Carlo simulation (Cardiff T2D) • Time horizon: Lifetime • Cycle length: NR • Perspective: UK healthcare payer	Dapagliflozin vs. Placebo: • Overall: -£2,552 • MRF: -£1,752 • eCVD: -£2,831 • No Prior HF: -£2,018 • Prior HF: -£4,150	Incremental QALY: Dapagliflozin vs Control: • Overall: 0.06 • MRF: 0.07 • eCVD: 0.09 • No Prior HF: 0.07 • Prior HF: 0.11	Dapagliflozin vs Placebol: • Overall: Dominant • MRF: Dominant • eCVD: Dominant • No Prior HF: Dominant • Prior HF: Dominant
Willis 2021 (108), UK	People with T2DM and DKD as represented by CREDENCE trial	63.0 (9.2)	• Type: Microsimulation • Time horizon: -10 years (Base case) -5, 20 and 40 years (SA) • Cycle length: NR • Perspective: NHS perspective	Canagliflozin vs. SoC: -£4,706	Canagliflozin vs. SoC: Incremental QALY: 0.279	Canagliflozin vs. SoC: Dominant
Erickson 2013 (109), USA	Patients with mild-to-moderate CKD and moderate hypertension but with no other traditional CV risk factors	NR	• Type: Markov • Time horizon: Lifetime • Cycle: 3 months • Perspective: - Base case: NR	Increased costs ($): • 50-year-old men: 1,700 • 50-year-old women: 1,700 • 55-year-old men: 1,800 • 55-year-old women: 1,800 • 60-year-old men: 1,800	Statins vs no statins Incremental QALY (discounted): • 50-year-old men: 0.09 • 50-year-old women: 0.03 • 55-year-old men: 0.09	• 50-year-old men: $20,500 per QALY gained • 50-year-old women: $56,800 per QALY gained

Author, year, country	Study population	Patients age (SD)	Summary of model	Incremental costs	Incremental QALYs/	ICER (Cost/QALY)
			- PSA: Societal	• 60-year-old women: 1,900 • 65-year-old men: 1,800 • 65-year-old women: 1,900 • 70-year-old men: 1,500 • 70-year-old women: 1,700 • 75-year-old men: 1,300 • 75-year-old women: 1,400 • 80-year-old men: 900 • 80-year-old women: 1,100 • 85-year-old men: 600 • 85-year-old women: 700	• 55-year-old women: 0.04 • 60-year-old men: 0.10 • 60-year-old women: 0.05 • 65-year-old men: 0.10 • 65-year-old women: 0.06 • 70-year-old men: 0.09 • 70-year-old women: 0.06 • 75-year-old men: 0.08 • 75-year-old women: 0.06 • 80-year-old men: 0.06 • 80-year-old women: 0.05 • 85-year-old men: 0.04 • 85-year-old women: 0.04	• 55-year-old men: $19,600 per QALY gained • 55-year-old women: $46,200 per QALY gained • 60-year-old men: $18,900 per QALY gained • 60-year-old women: $39,200 per QALY gained • 65-year-old men: $18,000 per QALY gained • 65-year-old women: $33,400 per QALY gained • 70-year-old men: $16,900 per QALY gained • 70-year-old women: $29,300 per QALY gained • 75-year-old men: $16,300 per QALY gained • 75-year-old women: $25,000 per QALY gained • 80-year-old men: $16,100 per QALY gained • 80-year-old women: $21,300 per QALY gained • 85-year-old men: $15,400 per QALY gained

Author, year, country	Study population	Patients age (SD)	Summary of model	Incremental costs	Incremental QALYs/	ICER (Cost/QALY)
						• 85-year-old women: $19,800 per QALY gained
Nuijten 2010 (110), UK	Hypothetical cohort of patients diagnosed with CKD with SHPT	NR	• Type: Markov • Time horizon: - Reference case analysis: 10 years - Scenario analysis: lifetime • Cycle: 1 year • Perspective: Healthcare system	Paricalcitol vs VDR activator: 3224 (£) ($US5970)	Incremental QALY: Paricalcitol vs VDR activator: 0.465	Paricalcitol vs VDR activator: • From the primary perspective of the UK NHS: £6933 ($12,840) per QALY gained • From the perspective of society after inclusion of indirect costs: £6815 ($12,620) per QALY gained
Abbreviations: ADPKD - autosomal dominant polycystic kidney disease; CI – confidence interval; CI-AKI – contrast-induced acute kidney injury; CKD – chronic kidney disease; CKD–EPI – Chronic Kidney Disease Epidemiology Collaboration; CV – cardiovascular disease; DAG - diagnostic coronary angiography; DKD - Diabetic kidney disease; eGFR - estimated glomerular filtration rate; ERG - Evidence Review Group; HF – heart failure; HK – hyperkalaemia; ICER – incremental cost-effectiveness ratio; MRF – multiple risk factor; NHS - National Health Service; NR – not reported ; PCI - percutaneous coronary intervention; PSA – probabilistic sensitivity analysis; PSS - Personal Social Services; QALY – quality-adjusted life years; RAASi - Renin-angiotensin aldosterone; RRT - Renal replacement therapy; SD – standard deviation; SHPT – secondary hyperparathyroidism; SMC - Scottish Medicines Consortium ; SoC – standard of care; T2D - Type 2 diabetes ; VDR - Vitamin D receptor						

Table 38. Summary list of key cost-effectiveness studies - models on CKD screening

Author, year, country	Study population	Patients age (SD)	Summary of model	Incremental costs	Incremental QALYs	ICER (Cost/QALY)
Go 2019 (111), Korea	Patients with progressing CKD	20-120	• Type: Markov • Time horizon: Lifetime • Cycle length: 1 year • Perspective: Societal	Current vs. No screening: $144.55	Incremental QALY: Current vs. No screening: 0.00216 QALY	Current vs. No screening: $66,874.29 per QALY gained
Abbreviations: CKD – chronic kidney disease; ICER – incremental cost-effectiveness ratio; KT – kidney transplantation; LYG – life years gained; NICE – National Institute for Health and Care Excellence; QALY – quality-adjusted life years; SMC – Scottish Medicines Consortium;						

B.3.2 Economic analysis

The main points of interest relating to the results of the performed review of existing economic evaluations in CKD are summarised below:

- In total, 34 health economic models conducted among patients with CKD were identified, 25 among the population with CKD and other diseases, and 9 CUAs studying screening for CKD.
- Among the included cost-utility analysis (CUAs) and cost-effectiveness analysis (CEAs) (n=66), there were Markov or semi-Markov models (n=41), decision trees together with Markov models (n=7), patient-level simulation models (n=5), discrete event simulation models (n=3), individual studies used patient-level fixed-time Monte Carlo simulation (n=1), microsimulation (n=1), or non-specified decision analytic model (n=1), and in the remaining studies, the model type was not provided (n=7). The SLR also identified two cost-benefit analysis (CBAs). The most common cycle length among the models identified in the SLR was 1 year (n=25)
- The most frequent timeframe was a lifetime horizon (n=41). Otherwise, the time horizon ranged between 1 year and 10 years.
- Most of the studies adopted a health care system perspective (n=29).
- The health states were mainly related to CKD progression (n=59).
- Efficacy measures were primarily quality adjusted life year (QALY) (n=59) and life year gained (LYG) (n=26).

Four analyses included in the SLR were considered particularly relevant in terms of the structure of the proposed model for finerenone: Schlackow 2017 (based on SHARP CKD-CVD outcomes model) (93, 112), Erickson 2013 (109), Black 2010 (97), and Go 2019 (111). All of them were Markov models, with health states based on the stages of CKD as defined by the Kidney Disease: Improving Global Outcomes (KDIGO) organization (113). In addition to the core CKD states, the incidence of cardiovascular events was also tracked.

Of note, a systematic review (Sugrue 2019 (114)) of CE models in kidney disease was identified. Authors of this review concluded that frameworks of future CKD models

should be informed by clinical rationale and data availability, to ensure validity of model results.

Development of a de novo model was deemed necessary in order to fully incorporate the FIDELIO-DKD trial results, however, a new model should be consistent with best practices of economic modelling in CKD.

3.2.1 Patient population

Based on the submission to EMA, it is expected that finerenone will be indicated to delay the progression of kidney disease and to reduce the risk of cardiovascular mortality and morbidity in adults with chronic kidney disease (stage 3 and 4 with albuminuria) and T2D. It is likely that caution will be advised for initiation in those patients with an eGFR below 25ml/min/1.73m^2 due to limited clinical data. Therefore, the data presented in this submission is for patients from the FIDELIO-DKD trial with an eGFR≥ 25 to < 60ml/min/1.73m^2. The modelled population reflects the majority of FIDELIO-DKD trial patients (~86%). We also present the full analysis set (FAS) data.

3.2.2 Model structure

The model health states are defined according to the stage of kidney disease and history of CV events and represent key outcomes of the FIDELIO-DKD trial. Four stages of CKD progression are considered: CKD 1/2, CKD 3, CKD 4, CKD 5 without RRT and 2 stages for end stage renal disease (ESRD) patients: dialysis and transplant. Transitions between all CKD stages are possible. The model also allows patients to start dialysis again after transplant, to reflect the risk of graft failure.

Patients start the model in one of the CKD stages without CV events i.e., before the occurrence of the first CV event within the model. Patients can remain in the same CKD stage, or move to a more/less advanced CKD stage, and/or experience a first modelled CV event (non-fatal MI, non-fatal stroke, hospitalisation for heart failure (HF)), or death. This structure reflects the progressive character of CKD, however, technically the model allows for transitions between any two CKD health states based on observations in the FIDELIO-DKD trial.

The model considers 6 corresponding health states for patients after the first CV event within the model (e.g., CKD 1/2 post-CV event, CKD 3 post-CV event). Once patients

experience a first CV event, they move to the post-CV event health state and are not able to move back to the health state without CV events. Patients can transition between CKD stage and experience a first CV event at the same time (e.g., a patient from CKD 3 can move to CKD 4 post-CV event). At any point in the model, patients can experience death.

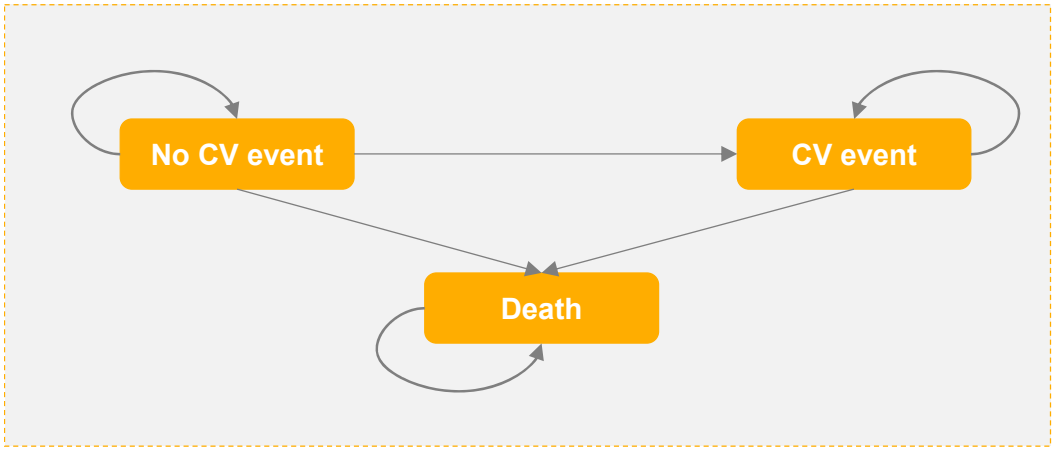
In summary, the model health states are defined according to the stage of kidney disease and history of CV events and include:

1. 4 stages of CKD progression
   - CKD 1/2,
   - CKD 3,
   - CKD 4,
   - CKD 5 w/o RRT
2. 2 states for patients with ESRD
   - dialysis,
   - post-transplant.
3. 6 corresponding states for patients after the first CV event observed within the model, i.e.
   - CKD 1/2 post-CV event,
   - CKD 3 post-CV event,
   - CKD 4 post-CV event,
   - CKD 5 w/o RRT post-CV event,
   - dialysis post-CV event,
   - post-transplant and CV event.
4. An absorbing death health state.

In addition to the health states presented above, other ***health events*** are incorporated in the model. They are defined as clinical outcomes that patients may experience within each health state, which do not affect the risk of subsequent renal events, CV events, or survival in this model. This is a simplifying assumption for the model and was explored with UK clinical experts (see section 3.10.2). These events include subsequent CV events, new onset of an atrial fibrillation/atrial flutter, hyperkalaemia (HK) and a sustained decrease of eGFR ≥40% from the baseline and are described further below.

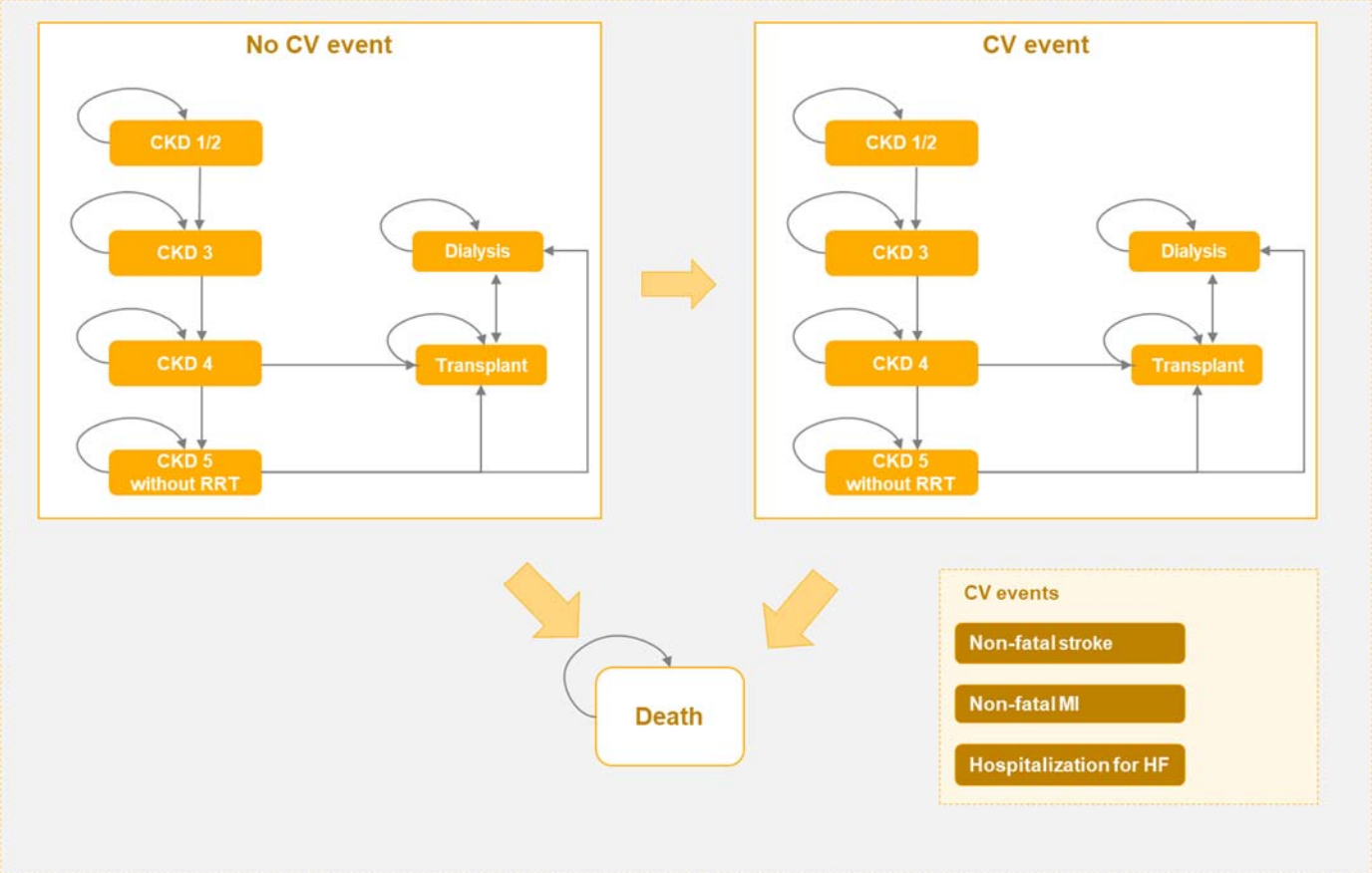
A top-level schematic of the overall concept of the model is presented in Figure 24, with a more detailed structure with essential transition probabilities shown in Figure 25.

Figure 24. Model diagram – overall concept



CV - Cardiovascular

Figure 25. Model diagram - details



CKD - Chronic Kidney Disease; MI - Myocardial Infraction; HF - Heart Failure; CV - Cardiovascular; RRT - Renal Replacement Therapy

Each health state in the model was defined by the following aspects:

- Probabilities:
  - Probability of transition to health state with CV event, for patients without CV events – dependent on treatment strategy, CKD stage, history of CV events and age;
  - Probabilities of progression to each stage of CKD or to dialysis – dependent on the treatment strategy and CKD stage;
  - Probabilities of transition to a kidney transplant – was assumed to be the same for each treatment strategy, as it is dependent rather on donor availability than treatment (treatment, however, may delay the CKD progression and indirectly move in time the necessity of a transplant);
  - Probability of health events, dependent on treatment strategy, history of CV events;

- Mortality – dependent on CKD stage, RRT, renal failure (including renal death), occurrence of CV events (including CV death), age, sex.

- Outcomes:
  - Costs – dependent on treatment, CKD stage, need for any kind of RRT and the occurrence of CV events and health events;
  - Utilities – dependent on age, CKD stage, need for and kind of RRT, the occurrence of CV events and health events.

The model structure was developed in conjunction with advice from health economic and clinical experts – please see section 3.10.1. Important assumptions were also validated with UK clinical experts – see section 3.10.2.

Cardiovascular events

Post-CV event states are divided into 2 periods (acute and post-acute), accounting for the impact of short-term consequences of CV events on costs and disutility in the first period following the event. The duration of the first (acute) period is adopted as 1 model cycle. Following transition through the temporary acute state, assuming no mortality in the interim, patients move to a chronic post-acute health state. They remain in that state in the absence of death or other transitions.

An average type of CV event is defined considering events included in the key secondary endpoint in the FIDELIO-DKD trial, i.e. non-fatal MI, non-fatal stroke, or hospitalisation for HF.

Due to the limited amount of data, and restrictions in terms of model complexity, health states for the subsequent CV events are not distinguished. Subsequent CV events occur at a low frequency in a 4-month period in practice; hence they were not observed frequently in the clinical trial. Table 39 presents the average number of subsequent CV events reported in the FIDELIO-DKD trial, for both arms (FAS population) per 4-month period.

Table 39. Average number of CV events per 4 months period, pooled arms, FAS population

Description	No. of subjects with events	No. of subjects	Probability
Subsequent CV event (fatal or not fatal MI, stroke or hospitalisation due to HF) after the first CV event experienced in the trial.	[redacted]	[redacted]	[redacted]

Abbreviations: CV – Cardiovascular, no. – Number, FAS – Full analysis set, HF – Heart failure, MI – Myocardial infarction,

Even though separate health states are not considered for the subsequent CV events, they are included in the model within the post-CV event health states. The risk of subsequent CV events is differentiated by treatment strategy. No limitation of the number of subsequent CV events is applied in the model, although an assumption is applied that there will be only one main event in any 4-month cycle.

This assumption was validated with health economic and clinical experts at a global level as well as with UK clinical experts. Experts agreed that separate health states for subsequent CV events would be too complex, and the way they are accounted for in the model is appropriate (see section B.3.10.2).

CKD and ESRD related health states

CKD-related health states are differentiated based on eGFR level (CKD 1/2, CKD3, CKD 4, CKD 5 without RRT). Due to the progressive character of CKD, patients might reach ESRD and require RRT (i.e., dialysis or a kidney transplant). Each of these states have specific costs and utilities as well as transition probabilities, including probability of mortality.

In the model, patients requiring dialysis or transplantation move to the corresponding health state (with or without CV event). For these patients, the model considers 2 periods: acute and post-acute. This allows for the model to account for different utility and costs in the first period after dialysis / transplant, until a chronic state is reached.

Death

The death health state is an absorbing state. Once patients enter this health state, they remain there until the end of the model. Patients may die in any health state in

the model. In line with the FIDELIO-DKD trial protocol, different causes of deaths are accounted for and implemented in the model. These comprise of renal death and cardiovascular death.

In line with FIDELIO-DKD, renal death is considered in the model only in the case of patients with eGFR<15 (before RRT).

As a part of the key secondary endpoint in FIDELIO-DKD, the time to first occurrence of CV death was evaluated. In line with this, the risk of acute CV death is considered only for the 1st CV event in the model.

In addition to the causes of death described above, background mortality is also considered. For each age, an average “per cycle” probability of death is computed, accounting for the ratio of males to females in the population. In each cycle, the appropriate probability of death is applied to each health state, according to the current age of the patients.

To avoid double counting, the proportions of deaths that are attributable to cardiovascular disease and renal death are removed from this background mortality using UK data or appropriate assumptions.

The background mortality also increases with CKD stage, as well as after transplant and starting dialysis. Moreover, the background mortality is assumed to increase following the first CV event. This is accounted for by using the HR for death due to MI, stroke and HF hospitalisation, sourced from Erickson 2013 (109).

It might be expected that the risk of death after second, third and any subsequent CV event might be higher, nevertheless it was not included in the model. It requires detailed clinical data which are limited and this would also have an impact on model complexity. In the model we used the simplifying assumption that the subsequent CV event is a “health event” and therefore does not affect the risk of subsequent renal events, CV events or survival in the model. This was discussed with health economic and clinical experts – please see section 3.10.1 and 3.10.2.

Model health events

Health events are defined by the following aspects:

- additional disutility due to the occurrence of the health event,
- resources and costs associated with the event,
- an assumed duration to apply the associated disutility and costs.

The events from the FIDELIO-DKD trial are presented in Table 40 describing the rationale for inclusion or non-inclusion in the model.

Table 40. List of events of interest considered for potential inclusion as health events in the model

Event	Retrieved in the SLR	Available in the FIDELIO-DKD trial	Included in model	Rationale
Subsequent CV event	✓	✓	✓	- Commonly used in other CE models - Significantly higher risk of subsequent CV event with BT compared to FIN + BT in FIDELIO-DKD - Impact on costs and QALYs with expected benefit for finerenone
First cardiovascular hospitalisation (other than HF hospitalisation)	✓	✓	✗	- Conservative assumption as higher risk of first CV hospitalisation (other than HF hospitalisation) found for BT in FIDELIO-DKD - Nevertheless, no significant difference between arms in FIDELIO-DKD
Non-CV hospitalisations	✗	✓	✗	
New onset of heart failure	✓	✓	✗	- Not included due to possible double counting with hospitalisation due to heart failure
New onset of atrial fibrillation/atrial flutter	✓	✓	✓	- Significantly lower risk of new onset of atrial fibrillation/atrial flutter with FIN + BT compared to BT in FIDELIO-DKD - Impact on costs and QALYs

Event	Retrieved in the SLR	Available in the FIDELIO-DKD trial	Included in model	Rationale
Eye disorders	✗	✓	✗	- Conservative assumption as higher risk for eye disorders found for BT in FIDELIO-DKD - The definition of the event was too vague to allow for allocation of costs and a utility decrement
Ear and labyrinth disorders	✗	✓	✗	- The definition of the event was too vague to allow for allocation of costs and utility decrements - These events are usually short-term, not costly to manage and with a minimal impact on quality of life, hence, their impact on the model results would be negligible - No significant difference between arms in FIDELIO-DKD
Flu syndrome	✗	✓	✗	
Infections and infestations	✗	✓	✗	
Hyperkalaemia (blood potassium increased)	✓	✓	✓	- Significantly higher risk of hyperkalaemia with FIN + BT compared to BT in FIDELIO-DKD - Impact on costs and QALYs
Sustained decrease of eGFR ≥40% from baseline	✓*	✓	✓	- Component of FIDELIO-DKD primary endpoint - Significantly higher risk for BT compared to FIN + BT in FIDELIO-DKD - Impact on QALYs

Abbreviations: BT - Background therapy; CE - Cost-effectiveness; CV - Cardiovascular; DKD - Diabetic kidney disease; eGFR - Estimated glomerular filtration rate; HF - Heart failure; FIN - Finerenone; QALY - Quality-adjusted life years; SLR - Systematic literature review

*as a component of a composite endpoint

Events are included if significant differences were observed in the FIDELIO-DKD trial and where a non-negligible impact on costs/QALYs existed. On this basis, the following health events are accounted for in the economic model: subsequent CV event, new onset of atrial fibrillation/atrial flutter, hyperkalaemia, and sustained

decrease of eGFR ≥40% from the baseline. The health events do not constitute health states in the model. They act as a way to count the number of events and their associated cost and utility impacts that are not captured elsewhere.

Persistence

In the base case patients discontinue the treatment with finerenone at the rate observed in FIDELIO-DKD. It is assumed that patients discontinuing FIN+BT receive BT alone. The cost of finerenone is only applied to patients remaining on treatment. Patients who discontinue, accrue the costs and efficacy of the BT arm.

Cycle length

A model cycle length should reflect a good compromise between accuracy and model simplicity. Each cycle represents the shortest time that could be captured by the model, meaning that a further breakdown of the cycle would not be possible. Therefore, it is best practice to define the model cycle length according to the shortest duration that captures both the health state transitions and the occurrence of acute events, while also ensuring the model is neither overly complex nor that it requires superfluous computational power.

The most common cycle length among the models identified in the SLR was 1 year, but the assessment of endpoints occurred every 4 months in the FIDELIO-DKD trial. Therefore, in the model, to reflect the disease progression more accurately, a 4-month cycle length was used. With a 4-month cycle, all costs, utility decrements and CV risks are captured appropriately within a single cycle.

In order to reduce the difference between real-world and the simulated costs and QALYs, a half-cycle correction is applied in the model.

Time horizon

The model simulates patients' trajectories over a lifetime horizon (up to 100 years old), thereby accounting for the chronic nature of CKD in T2D, and its associated impact on costs and outcomes. The mean age is taken from the FIDELIO-DKD trial (65.6 years) so in the base case, the time horizon is 33.4 years.

The most frequent timeframe of the models identified in the SLR was a lifetime horizon. It is important to consider a lifetime horizon since CV risks and renal progression are relevant for the duration of a patient's life.

Discount rate

The model allows the user to modify the discount rates for costs and outcomes separately. It is aligned with NICE recommendations in the base case.

Comparison with models evaluated by NICE

The single technology appraisal - tolvaptan for treating autosomal dominant polycystic kidney disease (ADPKD) (TA358) was identified through the systematic literature review [16].

Key features of the economic analysis in comparison to the previous NICE appraisal are outlined in Table 41, whilst recognising that ADPKD is a very specific form of CKD.

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Table 41. Features of the economic analysis

Factor	Previous NICE appraisal	Current appraisal	
	Tolvaptan (TA358)(105)	**Chosen values**	**Justification**
Discount rate (cost and health outcomes)	3.5%	3.5%	NICE guidelines (1)
Type of model	Type: Patient-level simulation model	Markov model	The model structure is influenced by the results of SLR on models conducted by Bayer and by the review of Sugrue 2019 (114).
Time horizon	Lifetime (80 years)	Lifetime (33.4 years)	The time horizon is selected so that the proportion of survivors in the last cycle would be negligible, and all potential costs and benefits are captured.
Cycle length	1 year	4 months	The assessment of endpoints occurred every 4 months in the FIDELIO-DKD trial. With a 4-month cycle, all costs, utility decrements, disease progression, as well as CV risks, are captured appropriately within a single cycle.
Treatment waning effect?	No	No	Treatment effects are considered constant over time. No modelling of a time-varying hazard ratio is implemented as there is no evidence of non-proportionality (details are in Appendix L).

Factor		Previous NICE appraisal	Current appraisal	
		Tolvaptan (TA358)(105)	**Chosen values**	**Justification**
Health states		- CKD stages 1 to 4 -a significant pain health state -CKD stage 5 pre-dialysis, -Haemodialysis -Peritoneal dialysis -Transplant -Death.	- CKD1/2 - CKD3 - CKD4 - CKD 5 without dialysis - Dialysis (HD and PD) - Transplant - Death All above health states were differentiated depending on the incidence of the first CV event in the model.	The model is developed to evaluate the impact of finerenone on both CKD progression and CV event occurrence. The health states are consistent with existing models for CKD.
Health events	Adverse events	Clinically significant pain	Hyperkalaemia	Hyperkalaemia is included in the model as it is the only adverse event for which finerenone shows a statistically significant impact vs BT (9, 114). Two types of events are considered depending on the need for hospitalisation.
	Other	-	- New onset of Atrial fibrillation/Atrial flutter, - Sustained decrease of eGFR ≥40% from baseline - Subsequent CV event	Table 40 presents the rationale for the health events considered. Events are included if significant differences were observed in the FIDELIO-DKD trial and where a non-negligible impact on costs/QALYs existed.

Factor	Previous NICE appraisal	Current appraisal	
	Tolvaptan (TA358)(105)	**Chosen values**	**Justification**
Source of utilities	The following studies identified through the systematic literature review conducted by the company: - Gorodetskaya et al. (2005) - Lee et al. (2005) - Dolan et al. (1997)	EQ-5D from FIDELIO trial	EQ-5D-5L data are obtained from the FIDELIO-DKD trial and used in the model as the preferred instrument to capture the impact of treatment on quality of life for CE analysis. According to NICE recommendations, utility values were mapped from the 5L into the 3L value set. Utility data from the literature is used in a scenario analysis.
Source of costs	• NICE guideline on chronic kidney disease and values were based on clinical expert opinion. • NICE guideline on peritoneal dialysis • Unit Costs of Health and Social Care (Curtis, 2014) and NHS Reference Costs 2012–13. • HRG code • Literature • Kerr et al. (2012) and NICE technology appraisal guidance on immunosuppressive therapy for renal transplantation in adults •NHS Blood and Transplant Organ Donation and Transplantation Activity Report 2013–14.	- Tolvaptan (TA358) (105) submission for CKD management costs - Literature (Alva 2015[115]) for the CV events costs - NICE guideline on chronic kidney disease (draft) for kidney transplant and dialysis costs (116) - National schedule of reference costs for the modelled health events - National tariff of drugs for medication costs	Nationally published costs were used where available, supplemented with sources identified as being most relevant to the UK from literature reviews.

Factor	Previous NICE appraisal	Current appraisal	
	Tolvaptan (TA358)(105)	Chosen values	Justification
Abbreviations: BT - Background therapy; CE - Cost-effectiveness; CKD - Chronic kidney disease; CV - Cardiovascular; DKD - Diabetic kidney disease; eGFR - Estimated glomerular filtration rate; EQ-5D - EuroQol 5 dimensions; HRG - Healthcare Resource Group; NHS - National Health Service; NICE - The National Institute for Health and Care Excellence; SLR - Systematic literature review			

3.2.3 Intervention technology and comparators

Finerenone (BAY 94-8862) is the intervention technology considered in the cost-effectiveness analysis. It is a novel, nonsteroidal, selective antagonist of the mineralocorticoid receptor (MR). In the FIDELIO-DKD study, finerenone demonstrated clinically meaningful effects in patients with CKD and T2D when added to standard of care, both in slowing CKD progression and in reducing CV morbidity and mortality.

The comparator for finerenone is standard of care established in clinical practice referred to further in this section of the submission as background therapy (BT) and reflects the placebo comparator arm of the FIDELIO-DKD study.

Two regimens were evaluated in the FIDELIO-DKD study:

- Finerenone + standard of care background therapy (called the FIN+BT arm in the economic model)
- Placebo + standard of care background therapy (called the BT arm in the economic model).

CKD in T2D is currently managed by lifestyle modifications and pharmacologic agents that target risk factors of the metabolic pathway (e.g. hyperglycaemia) and haemodynamic pathway (factors stimulated by RAAS and affecting blood pressure) (117).

The metabolic pathway is targeted with glucose-lowering agents to maintain the glycosylated haemoglobin level <7% (118). The haemodynamic pathway is targeted by RAS inhibitors and antihypertensive agents.

Other pathways that are important are the inflammatory and fibrotic pathways. There are a lack of agents targeting inflammatory and fibrotic pathways approved for the treatment of patients CKD and T2D (e.g. those activated by the MR). Thus, there is a high residual risk of developing end-organ damage in patients with CKD and T2D (18).

RAS inhibitors, including ACEIs or ARBs used in the management of blood pressure are first-line treatment options, and can also be used in combination with other strategies (119). For patients with CKD who have hypertension and an ACR over 30mg/mmol, the recently published NICE guidelines (3) recommend offering ACEI or

ARB (titrated to the highest licensed dose that the person can tolerate). For adults with CKD and diabetes and related persistent proteinuria if ACR is 3 mg/mmol or more, these guidelines also recommend offering an ACEI or ARB (titrated to the highest licensed dose that the person can tolerate).

Patients in the FIDELIO-DKD trial were prescribed an optimised dose of ACE/ARB at study entry. This is in line with the recommendations in the recently published NICE clinical guideline (3).

B.3.3 Clinical parameters and variables

The main source of clinical parameters in this analysis is the FIDELIO-DKD trial as described in section B.2. Additionally, a targeted literature review (TLR) was performed for epidemiological data. The summary of this review is presented in Appendix M.

3.3.1 Population characteristics and baseline distribution of patients

The base case population for the model consists of patients with a baseline eGFR between 25 and 60 (25 ≤ eGFR <60) which corresponds to CKD 3 and CKD 4, and albuminuria. This population described further as the proposed label population represents the population for which an indication has been sought in EMA.

3.3.2 Transition probabilities

The FIDELIO-DKD trial was designed and powered to make conclusions based on composite endpoints. Such outcomes are difficult to include in an economic evaluation, as each component has a different impact on costs, quality of life and, importantly, modelled events. Moreover, one of the components, namely the percentage decline in the eGFR from baseline is a relative measure that makes it less useful for the model in assessing the absolute benefits of treatments (both FIN and BT). For modelling 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. In terms of the 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.

The transition probabilities for both arms are derived from statistical analysis of patient-level data from the FIDELIO-DKD trial. At each 4-month interval, corresponding to the model cycle length, patients were assigned to one of the CKD health states, focusing on the CKD progression. This classification resulted in a set of transition probabilities between all health states in consecutive cycles. The transition probabilities for both arms (BT and FIN + BT) used in the model were calculated as the average probabilities over the four years available from FIDELIO-DKD. It is assumed in the model that the progression to the next CKD stage is dependent only on the current stage. Hence, the transition probabilities do not change over time. This simplifying assumption was validated with UK clinical experts (see section 3.10.2).

The number of kidney transplants recorded in FIDELIO-DKD was low, so it was investigated whether the study results reflect UK clinical practice. Based on experts' opinion (section 3.10.2), conducting a kidney transplant is dependent on donor availability rather than the treatments considered in the model. Experts highlighted that patients with T2D are often ineligible for transplantation due to their numerous comorbidities (see Appendix M). The following data were identified in a TLR and discussed with clinical experts (Table 42).

Table 42. Risk of kidney transplant

Author, year	Outcome	Value
Tolvaptan (TA358)(105)	Transition from CKD 5 or dialysis to kidney transplant	7.5% annually
Schlackow 2020(120)	Transition from dialysis to kidney transplant	6.1% annually
UKRR Report(121)	Transition from HD and PD to kidney transplant	4.93% annually
FIDELIO-DKD (BT arm)	Transition from CKD 5 or dialysis to kidney transplant	[redacted] annually

Experts suggested that even the lowest probability from all sources gathered could be considered an overestimate for patients with CKD and T2D. In line with the feedback, the data from FIDELIO-DKD were implemented.

Furthermore, in the model based on clinical opinion the same risks of progression to kidney transplant are applied for both arms i.e., FIN +BT and BT. These risks were assumed to be the same as the risk in the BT arm in FIDELIO-DKD trial.

The transition probabilities for both arms (BT and FIN + BT) are presented in the tables below (Table 43, Table 44).

The efficacy of FIN+BT in terms of delaying CKD progression is reflected by the health states transition probabilities reported in Table 44. In the case of the remaining health outcomes, the efficacy of FIN+BT was modelled based on HRs from the FIDELIO-DKD trial (see section B.3.3.7).

Table 43. 4-monthly CKD transition probabilities, FIDELIO-DKD patient-level data, BT arm

From \ To	CKD1/2	CKD3	CKD4	CKD5 without dialysis	Dialysis (acute)	Dialysis (post-acute)	Kidney Transplant (acute)	Kidney Transplant (post-acute)
CKD1/2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CKD3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CKD4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CKD5 without dialysis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dialysis (acute)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dialysis (post-acute)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Kidney Transplant (acute)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Kidney Transplant (post-acute)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 44. 4-monthly CKD transition probabilities, FIDELIO-DKD patient-level data, FIN + BT arm

From \ To	CKD1/2	CKD3	CKD4	CKD5 without dialysis	Dialysis (acute)	Dialysis (post-acute)	Kidney Transplant (acute)	Kidney Transplant (post-acute)
CKD1/2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CKD3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CKD4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CKD5 without dialysis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dialysis (acute)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dialysis (post-acute)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Kidney Transplant (acute)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Kidney Transplant (post-acute)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

3.3.3 Risk of first CV event

In each cycle, patients in health states without CV events can experience a first modelled CV event and move to a post-CV health state in the subsequent cycle.

Additional analyses of the FIDELIO-DKD trial patient-level data provided the first CV event risks at different points of time (e.g. events in each 4-month interval) for patients in each CKD and ESRD stage. The risk of the first CV event, which is used in the model, was calculated for the BT arm as an average rate over the four years available from the FIDELIO-DKD trial.

CV probabilities were obtained for an average CV event among patients without prior CV events within the FIDELIO-DKD follow-up; these probabilities are presented in Table 45. Only a few patients experienced a CV event after starting dialysis and no CV events were observed in transplanted patients. To ensure the data was representative of UK practice, a TLR was conducted (see details in Appendix M) although no credible sources were identified. 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. These assumptions were validated with UK clinical experts (section 3.10.2).

An average CV event was defined to avoid over-complexity of the model programming and owing to a lack of robust data to calculate the necessary transitions. The definition of this average CV event was based on events included in the key secondary endpoint of the FIDELIO-DKD trial: non-fatal MI, non-fatal stroke, and hospitalisations for HF. This simplified approach was validated with UK clinical experts (see section B.3.10.2).

The distribution of events is presented in Table 46. This distribution is used in the model to assess the impact of an average CV event on costs and utilities.

Table 45. 4-monthly probabilities of first CV event, FIDELIO-DKD patient-level data, BT arm

Outcome	CKD 1/2	CKD 3	CKD 4	CKD 5 without RRT	Dialysis	Transplant
Any CV event probability	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations : CKD - Chronic kidney disease; CV – cardiovascular; RRT - Renal replacement therapy

Table 46. CV events distribution, FIDELIO-DKD patient-level data based on both study arms

Outcome	MI	IS stroke	ICH stroke	HF hospitalisation
% of patients experienced event	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: CV – Cardiovascular; DKD - Diabetic kidney disease; HF - Heart failure; ICH - Intracerebral haemorrhage; IS - Ischaemic stroke; MI - Myocardial infarction				

3.3.4 Risk of other health events

The process of selection of these events is reported in Table 40. Based on the FIDELIO-DKD results, there were differences in probabilities of occurrence of health events between patients without a CV event and those after the 1st CV event. These differences were accounted for in the model.

Table 47 presents the health events probabilities for the BT arm, retrieved from the FIDELIO-DKD trial patient-level data, depending on the CV event status.

Table 47. 4-month health events probabilities, FIDELIO patient-level data, BT arm

Health event	Patients with no-CV event	Patients post-CV event
Subsequent CV event	NA	7.61%
Hyperkalaemia leading to hospitalisation	[redacted]	[redacted]
Hyperkalaemia not leading to hospitalisation	[redacted]	[redacted]
Sustained decrease in eGFR ≥40% from baseline (over at least 4 weeks)	[redacted]	[redacted]
New onset of atrial fibrillation / atrial flutter	[redacted]	[redacted]
Abbreviations: BT - Background therapy; CV – Cardiovascular, eGFR - Estimated glomerular filtration rate		

3.3.5 Duration of other health events

The duration of a health event was defined as the time during which consequences of its occurrence are accounted for.

Consequences of subsequent CV events are included in the model only in one cycle (4-months), assuming the long-term consequences are already considered after the first CV event. This approach avoids double counting of CV event consequences in the model.

It is assumed that duration of new onset of atrial fibrillation / atrial flutter and hyperkalaemia is also one cycle.

As per the event definition, a sustained decrease in eGFR by more than 40% from the baseline is assumed to last until the end of the time horizon.

Table 48 presents the duration of health events considered in the model. The duration is assumed to be similar for patients without CV events and patients in post-CV events health states.

Table 48. Duration of Health events

Health event	Event duration
Subsequent CV event	1 cycle (4 months)
Hyperkalaemia leading to hospitalisation	1 cycle (4 months)
Hyperkalaemia not leading to hospitalisation	1 cycle (4 months)
Sustained decrease in eGFR >=40% from baseline (over at least 4 weeks)	Lifetime (34.30 years)
New onset of atrial fibrillation / atrial flutter	1 cycle (4 months)
Abbreviations : CV – cardiovascular ; eGFR - Estimated glomerular filtration rate	

3.3.6 Mortality

In the model, mortality is divided into CV death, renal death, and remaining background mortality.

The average risk of CV death for the BT arm was retrieved from the FIDELIO-DKD trial and implemented for each cycle in the model for patients without CV events.

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). The transition probabilities between CKD 5 without RRT and renal death for BT were based on the FIDELIO-DKD trial results considering one component of the primary endpoint (renal death).

CV death and renal death probabilities from the FIDELIO-DKD trial, for the BT arm, are presented in Table 49. In the FIDELIO-DKD trial there were no transplanted patients who died due to a CV event. To ensure the data was representative of UK practice, a TLR was conducted (see details in Appendix M) although no credible sources were identified. In the model it is assumed that the risk of CV death for transplanted patients is the same as for CKD 4 based on the opinion of the UK clinical experts (see section B.3.10.2).

Table 49. 4-monthly probabilities of CV and renal death, BT

Outcome	CKD 1/2	CKD 3	CKD 4	CKD 5 without RRT	Dialysis	Transplant
CV death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations : BT - Background therapy; CKD - Chronic kidney disease; CV – Cardiovascular; RRT - Renal replacement therapy

In addition to the causes of death described above, background mortality is also considered in the model. The general underlying risk of death is estimated using the life tables (by age and sex) from the Office for National Statistics for years 2016-2018 (122). To avoid double counting, the proportions of deaths that are attributable to cardiovascular disease and renal death is removed from this background mortality using UK data from the Office for National Statistics (122).

Background mortality increases in the model with CKD progression as is common in other models e.g. Go 2019, Schlackow 2020, Erickson 2013 (109, 111, 120). The inputs reflecting this increase were identified in the TLR (see details in Appendix M).

In this TLR, a number of potentially relevant publications, including the publication by Darlington 2021(123) were identified. Darlington 2021 was selected as the most robust

source as it was the most up to date publication assessing the risk of death in patients with CKD and presented data for patients with diabetes. This study presented the associations between baseline comorbidity (i.e., diabetes, hypertension, MI, stroke), CKD stage (from CKD 2 to CKD 5) and all-cause mortality for CKD patients, based on evidence from a systematic literature review. The hazard ratios presented in Darlington 2021(123) were derived from 323 studies that met the inclusion criteria and reported associations between CKD stage and all-cause mortality. The results for the population with diabetes as a baseline comorbidity was included in the model (Table 50).

In the Darlington 2021(123) publication, no data for RRT patients was reported. The HRs in prevalent RRT patients were calculated based on data reported in the UKRR report 2018, also identified through the TLR and considered a robust source (121). HR for dialysis was calculated comparing the death rate in a prevalent RRT population with the death rate in the general population as they were presented in UKRR 22nd Annual Report for people aged 65-69. HR for kidney transplant was then derived taking into account ratio of deaths 5 years after kidney transplant to deaths occurring 5 years after dialysis. UKRR data for adult patients incident to transplant, haemodialysis and peritoneal dialysis were used in calculations. Moreover, frequency of haemodialysis compared to peritoneal dialysis as analysed in the model was preserved by weighting.

Table 50. Increased mortality, HRs due to CKD stage.

Health state	HR	Reference
CKD 1/2	1.14	Darlington 2021(123) (calculated as the average of HRs for CKD 1 and CKD 2. Weighting with FIDELIO data not possible - % of patients in CKD 1 unknown)
CKD 3	1.33	Darlington 2021 (calculated as the average of HRs for CKD 3A and 3B and weighted by the % of CKD 3A and 3B patients from FIDELIO)
CKD 4	6.42	Darlington 2021(123)
CKD 5 w/o RRT	9.49	Darlington 2021(123)
Dialysis, acute	10.04	UKRR Annual Report 2018(121)
Dialysis, post-acute	10.04	UKRR Annual Report 2018(121)
Transplant, acute	1.55	UKRR Annual Report 2018(121)

Transplant, post-acute	1.55	UKRR Annual Report 2018(121)
Abbreviations: CKD - Chronic kidney disease; DKD - Diabetic kidney disease; HR - Hazard ratio; RRT - Renal replacement therapy; UKRR - UK Renal Registry		

Increased mortality following the first CV event was also considered in the model and follows the approach in other CE models. Apart from CV death, which is the immediate effect of a CV event, mortality was assumed to increase in the cycles following the first CV event. The HRs based on the CE analysis by Erickson 2013 (109) were applied for patients in each cycle post-CV event, as presented below (Table 15). The Erickson 2013 (109) publication was found in the SLR conducted on economic models in CKD. In this paper the definition of increased mortality after CV events reflects the model requirements. Erickson 2013 (109) presented the long-term increase in mortality after MI and stroke for patients who survived the acute event. Due to lack of data for hospitalisation due to HF the same HR as for MI was included in the analysis. This assumption was validated with UK clinical experts (see section B.3.10.2) who said that undoubtedly the treatments for HF have markedly reduced mortality over recent years. At the same time the death from MI has also dropped substantially due to the use of percutaneous coronary intervention. Experts agreed that it is reasonable to assume that the increased mortality due to HF hospitalisation is the same as for MI, based on Erickson 2013 (109).

Table 51. Increased mortality, HRs due to CV event

Description	HR	Reference
HR due to MI	1.40	Erickson 2013 (109)
HR due to stroke	2.30	Erickson 2013 (109)
HR due to hospitalisation for HF	1.40	Assumption, the same as for MI (UK clinical expert validation)
Abbreviations: CV - Cardiovascular; HF - Heart failure; HR - Hazard ratio; MI - Myocardial infarction		

3.3.7 Treatment efficacy

The efficacy of FIN+BT in terms of delaying CKD progression is reflected by the health states transition probabilities reported in the section B.3.3.2. In the case of the remaining health outcomes, the efficacy of FIN+BT was modelled based on HRs from the FIDELIO-DKD trial.

Table 52 presents the HRs for the Main CV/ Renal Events which were implemented in the model for FIN + BT.

Table 52. HRs for Main CV / Renal Events for FIN + BT vs BT – proposed label population

Outcome	HR FIN + BT vs BT (95%CI)
CV death	[redacted]
Renal death, CKD 5 without RRT	[redacted]
First CV event	[redacted]
Abbreviations: BT - Background therapy; CI – confidence interval; CKD - Chronic kidney disease; CV - Cardiovascular; FIN - Finerenone; HR - Hazard ratio; RRT Renal replacement therapy	

Table 53 presents the HRs for other health events which were implemented in the model for FIN + BT.

Table 53. HRs for health events for FIN + BT

Outcome	Label population
Subsequent CV event	[redacted]
Hyperkalaemia not leading to hospitalisation	[redacted]
Hyperkalaemia leading to hospitaliation	[redacted]
Sustained decrease in eGFR ≥40% from baseline (over at least 4 weeks)	[redacted]
New onset of atrial fibrillation / atrial flutter	[redacted]
Abbreviations: BT - Background therapy; CV - Cardiovascular; eGFR - Estimated glomerular filtration rate; FIN - Finerenone; HR - Hazard ratio;	

Several assumptions were considered in terms of HRs used in the model:

- HRs were considered constant over time without an efficacy waning approach (analysis presented in Appendix L demonstrates that there was no strong evidence against the proportional hazards assumption).
- HRs were applied independently of significance level; ISPOR (124) recommends that all known data should be incorporated for key parameters, including those that fall short of the conventional thresholds of statistical significance.

3.3.8 Persistence

Table 54 shows the premature permanent discontinuation of therapy in FIDELIO-DKD. 40.30% of FIN +BT patients discontinued treatment over the course of the study. It is assumed that patients discontinuing FIN +BT receive BT alone. The cost of FIN +BT is only applied to patients remaining on treatment. Patients who discontinue FIN +BT accrue the costs and efficacy of the BT arm.

Two scenarios are further tested:

- the discontinuation is not considered at all,
- the discontinuation is applied as in base case in line with the FIDELIO-DKD trial but only has an impact on costs, i.e. patients discontinuing FIN +BT receive BT alone and account for BT costs, but the discontinuation does not have an impact on efficacy.

HRs obtained from FIDELIO-DKD are based on the intention to treat analysis, so the discontinuation of the study drug is already reflected in the value of obtained HRs. Hence, waning the FIN efficacy just after its discontinuation in the model can be considered as a conservative approach. The aim of the scenario analysis is to show the maximum level of the underestimation of FIN+BT benefits in this regard in the base case.

Table 54. Non-persistence rates from the FIDELIO-DKD trial

Strategy	Rate
FIN + BT – 4-year rate	[redacted]
FIN + BT – 4-month rate	[redacted]
Abbreviations: BT - Background therapy; DKD - Diabetic kidney disease; FIN - Finerenone	

3.3.9 Extrapolation over a longer horizon

The results from the FIDELIO-DKD trial were used through the lifetime horizon as the transition probabilities to a more advanced CKD stage (based on eGFR decrease) as well as to ESRD for BT did not vary over time.

In the context of CV risk, it was assumed that CV risk increases with age. Therefore, to extrapolate the CV probabilities to a lifetime horizon, a HR for increased CV risk was used.

We performed a targeted literature review (TLR) to find a credible source to assess this impact. During this review, Wilson 2012(125) was found and determined to be an appropriate source. This study was based on the well reported Reduction of Atherothrombosis for Continued Health (REACH) registry. The REACH population includes patients ≥ 45 years with established coronary artery disease, cardiovascular, or peripheral arterial disease. In this study, cardiovascular prediction models were estimated from the 2-year follow-up data of 49,689 participants from around the world. Risk analyses were performed using Cox proportional hazard regression. Model development included clinical judgment and careful consideration of well-accepted traditional variables for vascular disease risk assessment.

The HR for the increase in risk with each year of age was 1.03 [95%CI 1.03-1.04] and it was applied to the baseline risks.

B.3.4 Measurement and valuation of health effects

3.4.1 Health-related quality-of-life data from FIDELIO-DKD

Although the FIDELIO-DKD trial was not designed nor powered to make conclusions based on quality of life, post hoc analyses on the EQ-5D questionnaire were conducted in preparation of the economic model. The EQ-5D utilities were assessed for health states as well as health events. The statistical evaluation was performed by using the software package SAS release 9.2 or higher (SAS Institute Inc., Cary, NC, USA).

The baseline data from the FIDELIO-DKD trial was considered to inform the utility of CKD1/2, without CV event health state.

In the next step, the results of a multivariate regression (multilevel mixed repeated measurements) model were used to estimate utility values for the remaining health states, as well as health events included in the model. The approach allows estimation of the EQ-5D values and utilities depending on patient characteristics as well as the

presence of different events of interest. This multivariate model is conducted only on the overall population (FAS population), to minimise potential bias due to low number of events.

For each outcome, a dummy variable was calculated for each EQ-5D assessment, including the information on whether the respective health event occurred in the given time prior to the EQ-5D assessment (1=event occurred, 0=event did not occur). This variable was forwarded into a repeated measure model to evaluate the effect of the health event on the EQ-5D health state.

The repeated measure regression models for the post baseline EQ-5D utility scores were calculated and included multiple factors (Table 57).

In the multivariate analysis, if no improvement in EQ-5D is observed with finerenone, the effect of finerenone is assumed negligible and all treatment arms are pooled together. Both age and baseline EQ-5D were adjusted for their respective mean (i.e., mean adjusted age = age – mean[age] and mean adjusted baseline EQ-5D = baseline EQ-5D – mean [baseline EQ-5D]).

The repeated measurements were recorded at several visits at which the EQ-5D questionnaires were handed out. A repeated measure mixed model was used in order to model the covariance structure considering the visit structure. The SAS procedure PROC MIXED was used modelling an unstructured covariance between the visits. PROC MIXED has been used estimating covariance patterns with the maximum likelihood method.

Results

An overview on the number of EQ-5D assessments per visit is presented in Table 55.

Table 55. Number of EQ-5D assessments per visit

Visit	# of EQ-5D assessments
Visit 5	[redacted]
Visit 8	[redacted]
Visit 11	[redacted]

Visit	# of EQ-5D assessments
Visit 14	[redacted]
Premature discontinuation	[redacted]
End of Study Visit	[redacted]

The mean utility from FIDELIO-DKD for patients in CKD 1/2 at the baseline was [redacted] Details are presented in Table 56.

Table 56. The baseline CKD 1/2 utility

Treatment group	N	Mean utility for CKD 1/2	SD
Finerenone	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]
Finerenone or Placebo	[redacted]	[redacted]	[redacted]
Abbreviations : CKD – Chronic kidney disease; SD - Standard deviation			

Multivariate analysis

The results of a multivariate analysis (multilevel mixed repeated measurements model) are presented in Table 57.

The estimate of the intercept can be interpreted as the utility associated with an event-free health state, among males at the mean age of the overall FIDELIO-DKD study population. The other estimates can be interpreted as the decrements/increments in health state utility for the respective event.

Initially, in the multivariate analysis acute MI, acute stroke, acute hospitalisation for HF (where acute indicates that the event was experienced in the last 4-months before a given visit) and post-MI, post-stroke and post hospitalisation for HF were investigated separately. Nevertheless, the obtained results were counterintuitive as the utility decrement in post-acute phases were higher than in the acute ones. The reason behind this is probably the low number of EQ-5D assessments for acute phases. Hence, it was considered more relevant to model acute and post-acute phases combined.

Table 57. Parameter estimates of the multilevel mixed repeated measurements model for EQ-5D total score

Effect	Estimate	Standard Error	t Value	Pr > |t|
Intercept	[redacted]	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]	[redacted]
Age - mean[Age]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline EQ-5D – mean [Baseline EQ-5D]	[redacted]	[redacted]	[redacted]	[redacted]
CKD stage based on Fidelio=3vs1/2	[redacted]	[redacted]	[redacted]	[redacted]
CKD stage based on Fidelio=4vs1/2	[redacted]	[redacted]	[redacted]	[redacted]
CKD stage based on Fidelio=5vs1/2	[redacted]	[redacted]	[redacted]	[redacted]
Any prior MI=yes	[redacted]	[redacted]	[redacted]	[redacted]
Any prior stroke=yes	[redacted]	[redacted]	[redacted]	[redacted]
Any prior Hospitalisation for HF=yes	[redacted]	[redacted]	[redacted]	[redacted]
Acute new onset of atrial fibrillation/ atrial flutter (in the last 4 months)=yes	[redacted]	[redacted]	[redacted]	[redacted]
Acute Hyperkalemia or blood potassium increased leading to hospitalisation (in the last 4 months)=yes	[redacted]	[redacted]	[redacted]	[redacted]
Acute dialysis (in the last 4 months)=yes	[redacted]	[redacted]	[redacted]	[redacted]
Post dialysis (in the previous months excluding the last 4)=yes	[redacted]	[redacted]	[redacted]	[redacted]
Acute transplant (in the last 4 months)=yes	[redacted]	[redacted]	[redacted]	[redacted]
Post transplant (in the previous months excluding the last 4)=yes	[redacted]	[redacted]	[redacted]	[redacted]
Sustained eGFR decrease <=40% =yes	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CKD - Chronic kidney disease; eGFR - Estimated glomerular filtration rate; EQ-5D - EuroQol 5 dimensions; HF - Heart failure; MI - Myocardial infarction;

All but one estimate was associated with plausible values: the new onset of atrial fibrillation/atrial flutter (in the last 4 months) was shown to increase patients QoL by [redacted]. This was considered unrealistic and the value of 0 was used in the model. The disutility for atrial fibrillation/atrial flutter was searched for in the utilities SLR (see results in Appendix H) and is tested in the scenario analysis. All remaining results are

used as a primary source for utility data in the base case analysis. The details are presented in Table 62.

3.4.2 Mapping

The health-related quality of life data was gathered in FIDELIO-DKD with EQ-5D-5L. According to NICE recommendations, utility values were mapped from the 5L into the 3L value set. The mapping was conducted based on van Hout 2012(126).

3.4.3 Health-related quality-of-life studies

Details of the SLR on utilities are provided in Appendix H.

QoL has been shown to decline mainly because of CKD burden and while the decline in QoL is small in CKD 3, it becomes more significant as CKD advances.

Table 58 presents the disutility values associated with health states and events used in scenario analysis. They were derived from the most relevant publications identified in the SLR.

The disutilities for CKD health states with and without RRT were sourced from the Tolvaptan NICE appraisal (TA358)(105), and were based on the SLR conducted by the submitting company. This source was selected as it reported all of the utilities needed for the CKD health states and had been previously accepted by NICE. The ERG only commented on the disutility value (0.06) applied for haemodialysis and peritoneal dialysis complications observing these as exaggerated and favouring the tolvaptan arm. The ERG explored applying a lower disutility (0.02) for haemodialysis and peritoneal dialysis complications instead. We have included in the scenario analysis the disutility suggested by the ERG (0.02).

In terms of CV events, Meads 2014 (127) was selected as the most appropriate source. The utility values were based on UK studies (using the EQ-5D instrument), focusing on both MI and stroke and with inclusion of short- and long-term impact. Disutility in the first year after an event was almost twice as high as in the subsequent years. Disutility due to hospitalisation for HF was based on the CE analysis, McEwan 2020(128), where utility decrements were derived from a pooled analysis of individual patient-level EQ-5D-5L data from the Dapagliflozin And Prevention of

Adverse-outcomes in Heart Failure trial (DAPA-HF). The set of disutility values obtained from published literature are presented in Table 58.

Table 58. Published literature, disutility values for health states – scenario analysis

Health state	Disutility	Source
CKD 1/2 without CV event	-	
CKD 3 without CV event	-0.030	Tolvaptan (TA358)(105)
CKD 4 without CV event	-0.050	Tolvaptan (TA358)(105)
CKD 5 w/o RRT without CV event	-0.222	Tolvaptan (TA358)(105)
Haemodialysis (HD)	-0.352	Tolvaptan (TA358)(105)
Peritoneal dialysis (PD)	-0.262	Tolvaptan (TA358)(105)
Disutility associated with HD complications	-0.02	Tolvaptan (TA358)(105)
Disutility associated with PD complications	-0.02	Tolvaptan (TA358)(105)
Transplant, acute	-0.148	Tolvaptan (TA358)(105)
Transplant, post-acute	-0.082	Tolvaptan (TA358)(105)
MI, acute	-0.139	Meads 2014(127)
MI, post-acute	-0.070	Meads 2014(127)
Stroke, acute	-0.160	Meads 2014(127)
Stroke, post-acute	-0.080	Meads 2014(127)
Hospitalisation for HF, acute	-0.321	McEwan 2020(128)
Hospitalisation for HF, post-acute	-0.025	McEwan 2020(128)

Abbreviations: CKD - Chronic kidney disease; CV - Cardiovascular; HF - Heart failure; MI - Myocardial infarction; RRT - Renal replacement therapy

*CV events defined as coronary death, non-fatal myocardial infarction, any arterial revascularisation procedure, or stroke

3.4.4 Adverse reactions

Only hyperkalaemia is included in the model, within the health events, see section B.3.2.2. Disutility due to hyperkalaemia was sourced from Palaka 2020(129). In this study, identified in the SLR on utilities, data from the 2015 and 2018 Adelphi CKD Disease Specific Programmes, collected across EU-5, China and USA, were analysed to determine the association between HK and health state utilities measured by the

EQ-5D score among CKD non-dialysis patients, adjusting for age, sex, eGFR level, and presence of heart failure and diabetes.

Table 59. Published literature, disutility values for hyperkalaemia – scenario analysis

Health state	Disutility	Source
Hyperkalemia (leading to hospitalisation and not)	-0.030	Palaka 2020

3.4.5 Other health events

New onset of AF, sustained decrease of eGFR ≥40% from baseline and subsequent CV events are included in the model, within the health events, see section B.3.2.2.

Utility decrement due to AF was based on Rinciog 2019(130) identified in the SLR on utilities. In this paper, the CE model detecting AF in patients at high risk of stroke was described.

The disutility due to a subsequent CV event used the same values as associated with the acute phase of an MI/stroke/hospitalisation due to HF. This is applied as a one off (additive) disutility and is applied in the cycle in which the event occurred. There were no additional sources to test the disutility due to sustained decrease of eGFR ≥40% from baseline identified in the SLR, therefore the value from FIDELIO-DKD was used (Table 60).

Table 60. Published literature, disutility values for other health events – scenario analysis

Health state	Disutility	Source
Subsequent CV event	-0.246	Weighted average from acute MI (-0.139, Meads 2014(127)), acute stroke (-0.160, Meads 2014(127)) and HF hospitalisation acute (-0.321, McEwan 2020(128)) with CV event distribution from FIDELIO-DKD.
Atrial fibrillation/Atrial flutter (AF)	-0.014	Rinciog 2019(130)
Sustained decrease of eGFR ≥40% from baseline	-0.010	FIDELIO-DKD

3.4.6 Age-adjustment

An age-adjustment, applying a multiplier to the utility value, was considered appropriate in the base case analysis, to account for the impact of age on utility based on the UK norms for EQ-5D (131). The values used are presented in Table 61.

Table 61. EQ-5D index population norms (UK-specific TTO value sets) according to age

18-24	25-34	35-44	45-54	55-64	65-74	75+	Total
0.940	0.927	0.911	0.847	0.799	0.779	0.726	0.856

Given that patients in FIDELIO-DKD are aged 65.6 at entry of the model, a multiplier is set in the following way:

- a multiplier of 1.0 for all ages until 74y
- 0.932 thereafter (0.726/0.779 = 0.932)

3.4.7 Health-related quality-of-life data used in the cost-effectiveness analysis

Currently, the EQ-5D is the most frequently applied generic questionnaire that measures health-related quality of life. It is also preferred by NICE. Although the FIDELIO-DKD trial was not designed nor powered to make conclusions based on quality of life, the EQ-5D questionnaires were collected in the FIDELIO-DKD trial, which allows for post hoc analyses to be conducted. This allows for the utilities which originated directly from the clinical trial for finerenone to be used in the cost-effectiveness model.

In the case of the 1st CV event, the event distribution (MI, stroke, HF hospitalization) from FIDELIO-DKD was used to calculate an average utility decrement due to 1st CV event. This utility was used for both acute and post-acute phase of CV event as counterintuitive results were observed in the multivariate analysis when the acute and post-acute phases were analysed separately (see section 3.4.1).

The disutility due to a subsequent CV event used the same values as associated with the acute phase of an MI/stroke/hospitalisation due to HF. This is applied as a one off (additive) disutility and is applied in the cycle in which the event occurred.

Table 62. Summary of utility values for cost-effectiveness analysis

Health state / Health event	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
Health states utilities				
CKD 1/2 without CV event	[redacted]	[redacted]	B.3.4 Measurement and valuation of health effects (pages 162- and 171)	EQ-5D-5L utility directly from FIDELIO-DKD
CKD 3 without CV event	[redacted]	[redacted]		Multivariate analyses on EQ-5D-5L based on FIDELIO-DKD
CKD 4 without CV event	[redacted]	[redacted]		
CKD 5 w/o RRT without CV event	[redacted]	[redacted]		
Dialysis without CV event	[redacted]	[redacted]		
Post-dialysis without CV event	[redacted]	[redacted]		
Transplant without CV event	[redacted]	[redacted]		
Post-transplant without CV event	[redacted]	[redacted]		
Utility decrement due to event				
MI, acute	[redacted]	[redacted]	B.3.4 Measurement and valuation of health effects (pages 162- and 171)	Multivariate analyses on EQ-5D-5L based on FIDELIO-DKD
MI, post-acute	[redacted]	[redacted]		
Stroke, acute	[redacted]	[redacted]		
Stroke, post-acute	[redacted]	[redacted]		
Hospitalisation for HF, acute	[redacted]	[redacted]		
Hospitalisation for HF, post-acute	[redacted]	[redacted]		
New onset of Atrial fibrillation/ Atrial flutter*	[redacted]	[redacted]		No disutility assumed.
Hyperkalaemia leading to hospitalisation**	[redacted]	[redacted]		Multivariate analyses on EQ-

Health state / Health event	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
Hyperkalaemia not leading to hospitalisation**	[redacted]	[redacted]		5D-5L based on FIDELIO-DKD
Sustained decrease in eGFR >=40% from baseline (over at least 4 weeks)	[redacted]	[redacted]		
Subsequent CV event	[redacted]	[redacted]		Weighted average of MI, stroke and HF hospitalization from multivariate analysis with weights based on CV event distribution from the FIDELIO-DKD
Abbreviations: CKD – Chronic kidney disease; CV – Cardiovascular; MI – Myocardial infarction; HF – Heart failure; eGFR – Estimated glomerular filtration rate				

* The new onset of atrial fibrillation/atrial flutter (in the last 4 months) was shown to increase patients QoL by 0.009. This was considered unrealistic and the value of 0 was used in the model.
**The disutility due to hyperkalaemia were based on all hyperkalaemia events in the trial

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

A TLR was performed for costs and resource use to be used in the analysis. The summary of this review, with further details on the search strategy and results, is presented in Appendix I. The three most important sources identified in the TLR were:

- Tolvaptan NICE appraisal (TA358)(105),
- NICE CG 2021 (in development) (116),
- Alva 2015(115).

These sources were considered as most important as they were validated or developed by NICE (Tolvaptan NICE appraisal (TA358) (105), and NICE CG 2021 (in development) (116)) and presented detailed input data based on a long-term UK study (UKPDS study on T2D-related complications - Alva 2015(115).

Unit costs were taken from established UK sources, including the NHS dictionary of medicines and devices, NHS schedule of reference costs and the PSSRU Unit Costs of Health and Social Care, as per the NICE reference case (1). If available, the FIDELIO data were also used (e.g., the proportion of patients who use each type of BT drugs, CV events distribution) to inform cost calculations.

As recommended by NICE, the perspective of the National Health Service and Personal Social Services was adopted (1).

In the model only direct costs were considered. The following type of costs were included:

- Medication costs
    - Finerenone
    - Background therapy
- Health states costs
    - CKD 1/2, CKD 3, CKD 4 and CKD 5 without dialysis management
    - Initiation of dialysis
    - Maintenance dialysis
    - Transplantation
    - Post-transplant management
    - MI, stroke, HF hospitalisation (acute and post-acute)
    - Death costs (CV death, renal death)
- Health events costs
    - Hyperkalaemia
    - Subsequent CV event
    - New onset of atrial fibrillation / atrial flutter

The model assigns medication costs to each patient, and a cost to each health state. These costs were combined with the number of patients in that health state over the time horizon. Costs of health events are applied to the proportion of patients

experiencing those events to calculate the total average costs over the time horizon of the model.

Costs presented below have been taken from literature. Where appropriate, costs were inflated to the 2020 UK prices, using the cost inflation index from the Personal Social Services Research Unit (132). No inflation was applied to the inpatient costs that were sourced from the National Schedule of Reference Costs (133). These were taken directly from the most up to date document.

3.5.1 Intervention and comparators' costs and resource use

Finerenone

Finerenone will be available in 10 mg and 20 mg tablets with the same price regardless of the dose.

The indicative NHS list price of finerenone is £1.84 per day (Table 63).

Table 63. Daily medication costs, Finerenone

Item	Daily cost	Source
Finerenone10 mg / 20 mg	£1.84	NHS indicative list price for Finerenone (Bayer plc)

Background therapy

As a background therapy, all commonly used therapies in CKD patients with diabetes in England were included:

- ACEIs
- ARBs
- Beta-blockers
- Diuretics
- Calcium antagonists
- Statins
- Platelet aggregation inhibitors
- Glucose-lowering therapies

To estimate the daily cost, a representative drug has been chosen for each class of drug. It was the most common drug from a given class used in the FIDELIO-DKD trial. The costs of drugs were based on the NHS Dictionary of medicines and devices. The proportion of patients who use each class of drugs was calculated based on FIDELIO-DKD, more precisely the average values from the whole study follow up was considered. Note - these values differ from the ones presented in the clinical section as these percentages relate to average values from the whole study follow up.

In terms of insulin intake, due to the fact that the dose regimen should be individually adjusted for patients, the daily cost was based on Eibich 2017 (134). This paper was identified during the TLR review on costs and resource use. Authors aimed to assess costs of medication for people with T2D in the UK, their variability, and changes over time. Prescription and biomarker data for 7,159 people with type 2 diabetes were extracted from the GoDARTS cohort study, covering the period 1989-2013. Average follow-up was 10 years. This source was considered as most relevant for this appraisal as it focused on medication therapy costs in a large number of patients (19,269 prescription blocks for 7,159 individuals) with T2D in UK.

The cost of BT was the sum of all treatments comprising BT weighted by % of patients who use each therapy in FIDELIO-DKD (Table 64).

Table 64. Daily medication costs, Background therapy

Drug Class	Example used	Daily dose	Pack size	Pack price	Daily cost	% use
ACEIs	Ramipril	5 mg	28 tablets 5 mg	£ 1.55	£0.06	[redacted]
ARBs	Losartan	50 mg	28 tablets 50 mg	£ 1.71	£0.06	[redacted]
Beta-blockers	Carvedilol	12.5 mg	28 tablets 12.5 mg	£ 1.72	£0.06	[redacted]
Diuretics	Furosemide	40 mg	28 tablets 20 mg	£ 0.82	£0.06	[redacted]
Calcium antagonists	Amlodipine	5 mg	28 tablets 5 mg	£ 0.89	£0.03	[redacted]
Statins	Atorvastatin	10 mg	28 tablets 10 mg	£ 0.93	£0.03	[redacted]

Drug Class	Example used	Daily dose	Pack size	Pack price	Daily cost	% use
Platelet aggregation inhibitors	Acetylsalicylic acid (Aspirin)	75 mg	28 tablets 75 mg	£ 1.38	£0.05	[redacted]
Glucose-lowering therapies						
Insulin	Insulin glargine	-	-	-	£2.72	[redacted]
Metformin	Metformin	1,500mg	28 tablets 500 mg	£ 1.61	£0.17	[redacted]
Acarbose	Acarbose 50 mg Tablets	150 mg	90 tablets 50 mg	£ 14.58	£0.49	[redacted]
Sulfonylurea	Gliclazide	40 mg	28 tablets 40 mg	£ 1.56	£0.06	[redacted]
DPP-4 inhibitors	Linagliptin	5 mg	28 tablets 5 mg	£33.26	£1.19	[redacted]
GLP-1 agonists	Liraglutide	1.2 mg	2 pre-filled pens 18 mg / 3 ml	£78.48	£2.62	[redacted]
SGLT2	Canagliflozin	100 mg	30 tablets 5 mg	£39.2	£1.31	[redacted]
Average BT cost	-	**-**	-	**-**	**£ 2.56**	-

Abbreviations: ACEi - Angiotensin-converting-enzyme inhibitors; ARBs - Angiotensin receptor blockers; BT - Background therapy; DPP - Dipeptidyl peptidase; GLP - Glucagon-like peptide; SGLT - Sodium-glucose Cotransporter

3.5.2 Health-state unit costs and resource use

In the model, the unit cost per cycle for each health state is calculated.

CKD management costs for model health states CKD 1 to CKD 5 without RRT are based on the Tolvaptan NICE appraisal for treating autosomal dominant polycystic kidney disease (APCKD) (TA358)(105), which was identified in the SLR and TLR. The management costs used in that appraisal were not APCKD specific but referred to management of CKD patients in general.

Other sources were considered after identification in a TLR (see Appendix I), but the tolvaptan NICE appraisal was considered the most appropriate source based on consultation with UK experts (see section 3.10.2).

For patients in CKD 1 and CKD 2 the costs used were based on the following resource use (per year): 1 nephrology visit, 1 specialist nurse, 1 biochemistry test, 1 haematology test, 1 phlebotomy. The resource use was based on clinical opinion leading to an annual cost of £171.89.

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.

Originally this cost was sourced from the NICE CG182 (35) where it refers to CKD 3 and CKD 4 patients, without any differentiation. However, in the Tolvaptan appraisal (TA358)(105) the cost for CKD 3 was adjusted using the ratio from a medical record abstraction study and equated to £1,436.16 per year. The ERG questioned this approach and recommended using the same costs for CKD 3 and CKD 4.

At the time of development of this dossier, the updated NICE CG 2021 (116) was prepared with a draft version available in the public domain. However, only the outpatient visits are considered in this document for CKD management. It was confirmed by clinical experts that taking into account other costs such as inpatient stays and outpatients' visits (as it was done in the previous version of the NICE CG) is important to reflect the real burden of the disease. At the same time, the new guidelines suggest differentiation in the management of CKD 3 and CKD 4 patients. The need for such differentiation was also raised by the UK clinical experts. It was stated by experts that CKD 3 patients experienced a lower number of admissions then CKD 4 patients (see section 3.10.2).

Taking into account the clinical opinion as well as the difference in the outpatient visits suggested in the update of the NICE CG, we have included different costs of CKD management between CKD 3 and CKD 4 using a consistent approach to the Tolvaptan submission (TA358)(105) (i.e. £1,436.16).

For patients in CKD 5 the costs (£5,238.59 per year) were also based on the Tolvaptan NICE appraisal (TA358)(105) and included inpatient stays, nephrology outpatient visits, antihypertensive drugs, and GP visits.

All the costs for CKD 1/2 to CKD 5 without RRT were inflated to the 2020 UK prices, using the cost inflation index from the Personal Social Services Research Unit (132).

Dialysis costs were calculated separately for haemodialysis and peritoneal dialysis based on the latest draft of NICE CG 2021(116), which was identified in the TLR. In the guidance, for each type of dialysis: home HD, hospital HD, satellite HD and continuous ambulatory or automated PD, the number of sessions as well as cost per session was calculated. For a proportion of patients who receive hospital and satellite HD the transport costs were also accounted for (the transport cost was taken from the renal replacement therapy guideline). 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. For consistency, the distribution of HD (88%) and PD (12%) was taken from the same source.

Kidney transplant costs were also based on the draft NICE CG 2021(116). In the source, both deceased and living donor transplants were included and the unit costs were based on NHS reference costs 2018/2019. Since NHS reference costs 2019/2020 have been published, the costs for the model were updated accordingly.

CKD management costs were updated to 2020 using the NHS cost inflation index from the Personal Social Services Research Unit (132). NHS reference costs were not inflated.

Table 65. Details of cost items per health state – CKD related health states

Health state	Cost per cycle	Reference
CKD 1/2	£64	Tolvaptan (TA358)(105), updated to UK 2020
CKD 3	£538	Tolvaptan (TA358)(105), updated to UK 2020
CKD 4	£1,259	Tolvaptan (TA358)(105), updated to UK 2020
CKD 5 w/o RRT	£1,964	Tolvaptan (TA358)(105), updated to UK 2020
Haemodialysis, acute	£8,927	NICE CG 2021(116) (draft which will be published in August 2021)

Health state	Cost per cycle	Reference
Haemodialysis, post-acute	£8,927	NICE CG 2021(116) (draft which will be published in August 2021)
Peritoneal dialysis, acute	£8,756	NICE CG 2021(116) (draft which will be published in August 2021)
Peritoneal dialysis, post-acute	£8,756	NICE CG 2021(116) (draft which will be published in August 2021)
Transplant, acute	£16,457	NICE CG 2021(116) (draft which will be published in August 2021), updated according to NHS 2019/2020
Transplant, post-acute	£2,777	NICE CG 2021(116) (draft which will be published in August 2021)
Abbreviations: CKD – Chronic kidney disease; w/o – Without; RRT – Renal replacement therapy		

The costs for CV events are presented in Table 66. They were sourced from Alva 2015(115), which was identified in the TLR. This paper presents the input data based on the long-term UK study (UKPDS study) on T2D-related complications which was considered a reliable source of data.

Alva 2015(115)aimed to assess immediate and long-term inpatient and non-inpatient costs for T2D-related complications. It considered a population of T2DM patients from the UK. Data included in the Alva 2015 study were taken from UKPDS (UK Prospective Diabetes Study) – a randomised trial of 5,102 patients in 23 centres in England, Scotland and Northern Ireland. The values from Alva 2015(115) were inflated to the 2020 UK prices, using the cost inflation index from the Personal Social Services Research Unit (132). The numbers are presented in Table 66.

Table 66. Cost of CV events

Description	Cost per cycle	Reference
Acute MI	£6,889	Alva 2015(115), updated to 2020
Post-acute MI	£684	Alva 2015(115), updated to 2020
Acute IS stroke	£7,470	Alva 2015(115), updated to 2020
Acute ICH stroke	£7,470	Alva 2015(115), updated to 2020
Post-acute IS stroke	£705	Alva 2015(115), updated to 2020

Description	Cost per cycle	Reference
Post-acute ICH stroke	£705	Alva 2015(115), updated to 2020
Acute hospitalisation for HF	£2,856	Alva 2015(115), updated to 2020
Post-acute hospitalisation for HF	£917	Alva 2015(115), updated to 2020
Abbreviations: CV – Cardiovascular; MI – Myocardial infarction; HF – Heart failure; IS – Ischaemic stroke; ICH – Intracerebral haemorrhage		

Table 67 presents the average cost of the first CV event for acute and post-acute phases (the CV events distribution was described in Table 46).

Table 67. Average cost of first CV event in the model

Description	Cost per cycle
Average cost of first CV event – acute phase	£4,763
Average cost of first CV event – post-acute phase	£819
Abbreviations: CV - Cardiovascular	

The model also accounts for death costs.

The cost of renal death was based on PSSRU 2020(132). In PSSRU (132) the cost of hospital and social care services by diagnostic group per decedent in the final year of life are reported. Renal failure and diabetes were diagnostic groups for which these average costs in the final year of life were presented. We used both to estimate a reliable cost for renal death for the model. From the average hospital care cost in the final year of life of renal failure patients, the costs incurred due to diabetes were subtracted.

As, there was no appropriate diagnostic group in the PSSRU corresponding to CV death, the literature was searched to obtain the cost of CV death. In the model, the value from Kent 2015 (135) was used. Authors provided the additional annual hospital care costs associated with vascular death in the year of the event. This source which was also used in the well-known SHARP CKD-CVD model (112) was considered as reliable.

In the model, it was assumed that other reasons for death do not account for any costs.

Table 68. Death costs

Description	Cost per cycle	Reference
Cardiovascular death	£1,306	Kent 2015(135), updated to UK 2020
Renal death	£1,553	PSSRU 2020 (132).
Non-CV & non-renal death	£0	Assumption
Abbreviations: CV – Cardiovascular		

3.5.3 Adverse reaction / health events unit costs and resource use

As set out in section 3.3.2, pages 141-3, hyperkalaemia was the only adverse reaction considered relevant to include in the health economic model.

Hyperkalaemia

The costs related to hyperkalaemia leading to hospitalisation were based on relevant HRG codes. Costs presented in the table are weighted average costs, based on non-elective long/short stay fluid or electrolyte disorders registered in the NHS reference costs 2019/2020.

The elective patients were not considered in these calculations as advised by UK clinical experts (see section B.3.10.2).

In the model it is considered that the hospitalisation costs are incurred in the cycle when the event occurred. Table 71 presents costs estimated over a 4-month period.

Table 69. Hyperkalaemia leading to hospitalisation cost over 4 months

Currency	Currency Description	Activity	Unit Cost
KC05G	Fluid or Electrolyte Disorders, with Interventions, with CC Score 5+	3653	£4,679
KC05H	Fluid or Electrolyte Disorders, with Interventions, with CC Score 0-4	229	£2,864

Currency	Currency Description	Activity	Unit Cost
KC05J	Fluid or Electrolyte Disorders, without Interventions, with CC Score 10+	27491	£2,103
KC05K	Fluid or Electrolyte Disorders, without Interventions, with CC Score 7-9	25079	£1,407
KC05L	Fluid or Electrolyte Disorders, without Interventions, with CC Score 4-6	29568	£1,032
KC05M	Fluid or Electrolyte Disorders, without Interventions, with CC Score 2-3	15270	£771
KC05N	Fluid or Electrolyte Disorders, without Interventions, with CC Score 0-1	6621	£536
Weighted average		-	£1,452

In the model, for patients who experienced hyperkalaemia not leading to hospitalisation, the following resource use and costs were considered based on UK clinical experts opinion:

- 2 extra blood tests (one to confirm the diagnosis and then another one during treatment to evaluate treatment response),
- 1 GP consultation,
- drug costs for potassium binders for the treatment duration,
- a consultation with a dietetic adviser (by phone).

In Table 70 the details of these costs are provided.

The assumption that all patients with hyperkalemia not leading to hospitalization incur all of these costs should be considered conservative.

Table 70. Hyperkalaemia not leading to hospitalisation cost over 4 months

Description	Source	Unit cost	Resource use	Cost
Integrated blood services (DAPS03)	NHS reference costs 2019/2020	£1.91	2	£3.82
GP visit: per patient contact lasting 9.22 minutes, including direct care staff costs, w/o qualification costs	PSSRU 2020(132)	£33.19	1	£33.19
Dietitian visit (band 4), cost per hour	PSSRU 2020(132)	£34.00	0.25 (15 minutes)	£8.50

Description	Source	Unit cost	Resource use	Cost
Potassium binders: Calcium Resonium, 45g per day	CG of acute HK in adults(136) NHS Dictionary of medicines and devices	£12.32	3 days	£17.25
Sum				£82.48
Abbreviations: CG – Clinical guidelines, GP – General practictioner, HK – Hyperkalaemia, NHS - National Health Service, w/o – Without, PSSRU - Personal Social Services Research Unit				

Subsequent CV event

In order not to double count the CV events costs, the cost for subsequent CV events is accounted for only in the cycle in which this event occurred. It is assumed to be the same as the cost of the acute phase of a CV event for the first CV event experienced in the model (Table 67). It is considered that the further management of the patient is covered by the post-acute phase cost of the first CV event and therefore no additional costs are accounted for.

New onset of atrial fibrillation / atrial flutter

The costs related to new onset of atrial fibrillation / atrial flutter were based on the relevant HRG. Costs presented in the table are weighted average costs, based on the events registered in the NHS reference costs 2019/2020.

Table 71 presents costs estimated over a 4-month period. As a conservative approach, no costs are considered after 4 months.

Table 71. New onset of atrial fibrillation / atrial flutter cost over 4 months

Currency	Currency Description	Activity	Unit Cost
EB07A	Arrhythmia or Conduction Disorders, with CC Score 13+	15538	£2,399
EB07B	Arrhythmia or Conduction Disorders, with CC Score 10-12	21846	£1,556
EB07C	Arrhythmia or Conduction Disorders, with CC Score 7-9	33623	£1,145
EB07D	Arrhythmia or Conduction Disorders, with CC Score 4-6	46999	£874
EB07E	Arrhythmia or Conduction Disorders, with CC Score 0-3	61690	£573
Weighted average		-	£1,036

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

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).

The summary of costs of health events included in the model is presented in the table below.

Table 72. Summary of costs for adverse reaction and health events

Adverse reaction / health event	Cost per event
Hyperkalaemia leading to hospitalisation	£1,452
Hyperkalaemia not leading to hospitalisation	£82.48
Subsequent CV event	£4,763
New onset of atrial fibrillation / atrial flutter	£1,036
Sustained decrease in eGFR ≥40% from the baseline (over at least 4 weeks)	£0
Abbreviations; CV – Cardiovascular; eGFR - Estimated glomerular filtration rate	

3.5.4 Miscellaneous unit costs and resource use

NA

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

3.6.1 Summary of base-case analysis inputs

Table 73. Summary of all inputs and variables of the cost-effectiveness analysis

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Mean age [years]	[redacted]	CI ([redacted]) Normal (μ,σ)	B.3.3 Clinical parameters and variables
Proportion of males	[redacted]	CI ([redacted]) Beta (α,β)	B.3.3 Clinical parameters and variables
Cumulative risk of premature discontinuation at 4 years, finerenone	[redacted]	CI ([redacted]) Beta (μ,σ)	B.3.3 Clinical parameters and variables
Baseline patients distribution: CKD1/2	[redacted]	Dirichlet (0,4301,559,0,0,0)	B.3.3 Clinical parameters and variables
Baseline patients distribution: CKD3	[redacted]	Dirichlet (0,4301,559,0,0,0)	
Baseline patients distribution: CKD4	[redacted]	Dirichlet (0,4301,559,0,0,0)	
Baseline patients distribution: CKD 5 w/o RRT	[redacted]	Dirichlet (0,4301,559,0,0,0)	
Baseline patients distribution: Dialysis	[redacted]	Dirichlet (0,4301,559,0,0,0)	
Baseline patients distribution: Kidney Transplant	[redacted]	Dirichlet (0,4301,559,0,0,0)	
Four-month risk of first CV event, CKD1/2	[redacted]	CI ([redacted]%) Beta (α,β)	
Four-month risk of first CV event, CKD3	[redacted]	CI ([redacted]%) Beta (α,β)	
Four-month risk of first CV event, CKD4	[redacted]	CI ([redacted]%) Beta (α,β)	
Four-month risk of first CV event, CKD 5 w/o RRT	[redacted]	CI ([redacted]%) Beta (α,β)	
Four-month risk of first CV event, Dialysis (acute)	[redacted]	CI ([redacted]%) Beta (α,β)	
Four-month risk of first CV event, Dialysis (post-acute)	[redacted]	CI ([redacted]%) Beta (α,β)	
Four-month risk of first CV event, Kidney Transplant (acute)	[redacted]	CI ([redacted]%) Beta (α,β)	
Four-month risk of first CV event, Kidney Transplant (post-acute)	[redacted]	CI ([redacted]%) Beta (α,β)	
Increased risk of first CV event, HR due to age	1.03	CI (1.03;1.03) LogNormalY (μ,σ)	
Time after which risk of first CV event is increased [years]	4.0	CI (3.6;4.43) LogNormalX (μ,σ)	
Four-month risk of hyperkalaemia leading to hospitalisation, no-CV event	[redacted]	CI ([redacted]%) Beta (α,β)	
Four-month risk of hyperkalaemia not leading to hospitalisation, no-CV event	[redacted]	CI ([redacted]%) Beta (α,β)	
Four-month risk of sustained decrease in eGFR >=40% from baseline, no-CV event	[redacted]	CI ([redacted]%) Beta (α,β)	
Four-month risk of new onset of atrial fibrillation / atrial flutter, no-CV event	[redacted]	CI ([redacted]%) Beta (α,β)	
Four-month risk of subsequent CV event, post-CV event	[redacted]	CI ([redacted]%) Beta (α,β)	
Four-month risk of hyperkalaemia leading to hospitalisation, post-CV event	[redacted]	CI ([redacted]%) Beta (α,β)	

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Four-month risk of hyperkalaemia not leading to hospitalisation, post-CV event	[redacted]	CI ([redacted]%) Beta (α,β)	
Four-month risk of sustained decrease in eGFR >=40% from baseline, post-CV event	[redacted]	CI ([redacted]%) Beta (α,β)	
Four-month risk of new onset of atrial fibrillation / atrial flutter, post-CV event	[redacted]	CI ([redacted]%) Beta (α,β)	
Duration of hyperkalaemia leading to hospitalisation [years]	0.33	CI (0.14;0.67) LogNormalX (μ,σ)	
Duration of hyperkalaemia not leading to hospitalisation [years]	0.33	CI (0.14;0.67) LogNormalX (μ,σ)	
Duration of sustained decrease in eGFR >=40% from baseline [years]	[redacted]	CI ([redacted]) LogNormalX (μ,σ)	
Duration of new onset of atrial fibrillation / atrial flutter [years]	0.33	CI (0.14;0.67) LogNormalX (μ,σ)	
Four-month CV death probability, CKD1/2	[redacted]	CI ([redacted] Beta (α,β)	
Four-month CV death probability, CKD3	[redacted]	CI ([redacted]%) Beta (α,β)	
Four-month CV death probability, CKD4	[redacted]	CI ([redacted]%) Beta (α,β)	
Four-month CV death probability, CKD5 w/o RRT	[redacted]	CI ([redacted]%) Beta (α,β)	
Four-month CV death probability, Dialysis (acute)	[redacted]	CI ([redacted]%) Beta (α,β)	
Four-month CV death probability, Dialysis (post-acute)	[redacted]	CI ([redacted]%) Beta (α,β)	
Four-month CV death probability, Kidney Transplant (acute)	[redacted]	CI ([redacted]%) Beta (α,β)	
Four-month CV death probability, Kidney Transplant (post-acute)	[redacted]	CI ([redacted]%) Beta (α,β)	
Four-month renal death probability, CKD5 w/o RRT	[redacted]	CI ([redacted]%) Beta (α,β)	
Increased mortality risk, HR due to CKD1/2	[redacted]	CI ([redacted]) LogNormalY (μ,σ)	
Increased mortality risk, HR due to CKD3	[redacted]	CI ([redacted]) LogNormalY (μ,σ)	
Increased mortality risk, HR due to CKD4	[redacted]	CI ([redacted]) LogNormalY (μ,σ)	
Increased mortality risk, HR due to CKD5 w/o RRT	[redacted]	CI ([redacted]) -	
Increased mortality risk, HR due to Dialysis (acute)	[redacted]	CI ([redacted]) LogNormalY (μ,σ)	
Increased mortality risk, HR due to Dialysis (post-acute)	[redacted]	CI ([redacted]) LogNormalY (μ,σ)	
Increased mortality risk, HR due to Kidney Transplant (acute)	[redacted]	CI ([redacted]) LogNormalY (μ,σ)	
Increased mortality risk, HR due to Kidney Transplant (post-acute)	[redacted]	CI ([redacted]) LogNormalY (μ,σ)	
Increased mortality risk, HR due to first MI	[redacted]	CI ([redacted]) LogNormalY (μ,σ)	
Increased mortality risk, HR due to first stroke	[redacted]	CI ([redacted]) LogNormalY (μ,σ)	
Increased mortality risk, HR due to first hospitalisation for HF	[redacted]	CI ([redacted]) LogNormalY (μ,σ)	
HR: CV death, FIN + BT vs BT	[redacted]	CI ([redacted]) LogNormalY (μ,σ)	
HR: Renal death, CKD 5 w/o RRT, FIN + BT vs BT	[redacted]	CI ([redacted]) LogNormalY (μ,σ)	

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
HR: First CV event, FIN + BT vs BT	[redacted]	CI ([redacted]) LogNormalY (μ,σ)	
HR: Subsequent CV event, FIN + BT vs BT	[redacted]	CI ([redacted]) LogNormalY (μ,σ)	
HR: Hyperkalaemia leading to hospitalisation, FIN + BT vs BT	[redacted]	CI ([redacted]) LogNormalY (μ,σ)	
HR: Hyperkalaemia not leading to hospitalisation, FIN + BT vs BT	[redacted]	CI ([redacted]) LogNormalY (μ,σ)	
HR: Sustained decrease in eGFR >=40% from baseline, FIN + BT vs BT	[redacted]	CI ([redacted]) LogNormalY (μ,σ)	
HR: New onset of atrial fibrillation / atrial flutter, FIN + BT vs BT	[redacted]	CI ([redacted]) LogNormalY (μ,σ)	
% of patients who use ACEIs	[redacted]	CI ([redacted]%) Beta (α,β)	B.3.5 Cost and healthcare resource use identification, measurement and valuation
% of patients who use ARBs	[redacted]	CI ([redacted]%) Beta (α,β)	
% of patients who use beta-blockers	[redacted]	CI ([redacted]%) Beta (α,β)	
% of patients who use diuretics	[redacted]	CI ([redacted]%) Beta (α,β)	
% of patients who use calcium antagonists	[redacted]	CI ([redacted]%) Beta (α,β)	
% of patients who use statins	[redacted]	CI ([redacted]%) Beta (α,β)	
% of patients who use platelet aggregation inhibitors	[redacted]	CI ([redacted]%) Beta (α,β)	
% of patients who use insulin	[redacted]	CI ([redacted]%) Beta (α,β)	
% of patients who use metformin	[redacted]	CI ([redacted]%) Beta (α,β)	
% of patients who use acarbose	[redacted]	CI ([redacted]%) Beta (α,β)	
% of patients who use sulfonylurea	[redacted]	CI ([redacted]%) Beta (α,β)	
% of patients who use DPP-4 inhibitors	[redacted]	CI ([redacted]%) Beta (α,β)	
% of patients who use GLP-1 agonists	[redacted]	CI ([redacted]%) Beta (α,β)	
% of patients who use SGLT2 inhibitors	[redacted]	CI ([redacted]%) Beta (α,β)	
Daily cost of ACEIs [£]	£0.06	CI (0.04;0.07) Gamma (μ,σ)	
Daily cost of ARBs [£]	£0.06	CI (0.04;0.08) Gamma (μ,σ)	
Daily cost of beta-blockers [£]	£0.06	CI (0.04;0.08) Gamma (μ,σ)	
Daily cost of diuretics [£]	£0.06	CI (0.04;0.08) Gamma (μ,σ)	
Daily cost of calcium antagonists [£]	£0.03	CI (0.02;0.04) Gamma (μ,σ)	
Daily cost of statins [£]	£0.03	CI (0.02;0.04) Gamma (μ,σ)	
Daily cost of platelet aggregation inhibitors [£]	£0.05	CI (0.04;0.07) Gamma (μ,σ)	
Daily cost of insulin [£]	£2.72	CI (1.9;3.68) Gamma (μ,σ)	
Daily cost of metformin [£]	£0.17	CI (0.12;0.23) Gamma (μ,σ)	
Daily cost of acarbose [£]	£0.49	CI (0.34;0.66) Gamma (μ,σ)	
Daily cost of sulfonylurea [£]	£0.06	CI (0.04;0.07) Gamma (μ,σ)	
Daily cost of DPP-4 inhibitors [£]	£1.19	CI (0.83;1.61) Gamma (μ,σ)	
Daily cost of GLP-1 agonists [£]	£2.62	CI (1.83;3.54) Gamma (μ,σ)	

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Daily cost of SGLT2 inhibitors [£]	£1.31	CI (0.92;1.77) Gamma (μ,σ)	
CKD1/2 management cost per cycle	£64	CI (47;85) Gamma (μ,σ)	
CKD3 management cost per cycle	£538	CI (392;708) Gamma (μ,σ)	
CKD4 management cost per cycle	£1,259	CI (916;1655) Gamma (μ,σ)	
CKD 5 w/o RRT management cost per cycle	£1,964	CI (1429;2582) Gamma (μ,σ)	
% of haemodialysis in all dialysis	87.6%	CI (85.5%;89.6%) Beta (α,β)	
Cost of haemodialysis (acute), per cycle	£8,927	CI (6249;12075) Gamma (μ,σ)	
Cost of haemodialysis (post-acute), per cycle	£8,927	CI (6249;12075) Gamma (μ,σ)	
Cost of peritoneal dialysis (acute), per cycle	£8,756	CI (6129;11844) Gamma (μ,σ)	
Cost of peritoneal dialysis (post-acute), per cycle	£8,756	CI (6129;11844) Gamma (μ,σ)	
Cost of kidney transplant (acute), per cycle	£16,457	CI (11520;22261) Gamma (μ,σ)	
Cost of kidney transplant (post-acute), per cycle	£2,777	CI (1944;3757) Gamma (μ,σ)	
First CV events distribution: MI	[redacted]	Dirichlet (157,148,17,409)	Patients in the FIDELIO-DKD trial were prescribed an optimised dose of ACE/ARB at study entry. This is in line with the recommendations in the recently published NICE clinical guideline (3). B.3.3 Clinical parameters and variables
First CV events distribution: IS stroke		Dirichlet (157,148,17,409)	
First CV events distribution: ICH stroke		Dirichlet (157,148,17,409)	
First CV events distribution: Hospitalisation for HF		Dirichlet (157,148,17,409)	
Cost of MI (acute)	£6,889	CI (4629;9591) Gamma (μ,σ)	B.3.5 Cost and healthcare resource use identification, measurement and valuation
Cost of MI (post-acute)	£684	CI (544;840) Gamma (μ,σ)	
Cost of IS stroke (acute)	£7,470	CI (4199;11667) Gamma (μ,σ)	
Cost of IS stroke (post-acute)	£705	CI (502;943) Gamma (μ,σ)	
Cost of ICH stroke (acute)	£7,470	CI (4199;11667) Gamma (μ,σ)	
Cost of ICH stroke (post-acute)	£705	CI (508;934) Gamma (μ,σ)	
Cost of hospitalisation for HF (acute)	£2,856	CI (1433;4761) Gamma (μ,σ)	

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Cost of hospitalisation for HF (post-acute)	£917	CI (625;1264) Gamma (μ,σ)	
Cost of CV death	£1,306	CI (539;2406) Gamma (μ,σ)	
Cost of renal death	£1,553	CI (1087;2101) Gamma (μ,σ)	
Cost of non-CV & non-renal death	£0	NA	
Cost of hyperkalaemia leading to hospitalisation	£1,452	CI (536;2817) Gamma (μ,σ)	
Cost of hyperkalaemia not leading to hospitalisation	£82	CI (58;112) Gamma (μ,σ)	
Cost of sustained decrease in eGFR >=40% from baseline	£0	NA	
Cost of new onset of atrial fibrillation / atrial flutter	£1,036	CI (573;1634) Gamma (μ,σ)	
CKD1/2 utility	0.771	CI (0.274; 0.997) Beta (μ,σ)	B.3.4 Measurement and valuation of health effects
CKD3 utility	0.773	CI (0.276; 0.997) Beta (μ,σ)	
CKD4 utility	0.762	CI (0.265; 0.997) Beta (μ,σ)	
CKD 5 w/o RRT utility	0.742	CI (0.245;0.995) Beta (μ,σ)	
Dialysis (acute) utility	0.711	CI (0.214;0.991) Beta (μ,σ)	
Dialysis (post-acute) utility	0.711	CI (0.214;0.991) Beta (μ,σ)	
Kidney Transplant (acute) utility	0.734	CI (0.237;0.994) Beta (μ,σ)	
Kidney Transplant (post-acute) utility	0.880	CI (0.383;1.000) Beta (μ,σ)	
Utility decrement associated with first MI (acute)	-0.039	CI (-0.017;-0.069) -Beta (μ,σ)	
Utility decrement associated with first MI (post-acute)	-0.039	CI (-0.017;-0.069) -Beta (μ,σ)	
Utility decrement associated with first stroke (acute)	-0.053	CI (-0.032;-0.078) -Beta (μ,σ)	
Utility decrement associated with first stroke (post-acute)	-0.053	CI (-0.032;-0.078) -Beta (μ,σ)	
Utility decrement associated with first hospitalisation for HF (acute)	-0.042	CI (-0.026;-0.062) -Beta (μ,σ)	
Utility decrement associated with first hospitalisation for HF (post-acute)	-0.042	CI (-0.026;-0.062) -Beta (μ,σ)	
Utility decrement associated with hyperkalaemia leading to hospitalisation	-0.008	CI (-0.001;-0.025) -Beta (μ,σ)	
Utility decrement associated with hyperkalaemia not leading to hospitalisation	-0.008	CI (-0.001;-0.025) -Beta (μ,σ)	
Utility decrement associated with sustained decrease in eGFR >=40% from baseline	-0.010	CI (-0.001;-0.027) -Beta (μ,σ)	
Utility decrement associated with new onset of atrial fibrillation / atrial flutter	0.000	NA	

3.6.2 Assumptions

Several conservative assumptions were used in the model:

- Patients may experience up to 1 Main CV Event within a 4-month cycle; it is possible for a patient to experience more than 1 Main CV Event in clinical practice,
- Health events do not affect the subsequent risk of CV events, CKD progression or survival; this is conservative for health events where finerenone shows a benefit,
- No treatment interruption; this may overestimate treatment costs,
- Constant efficacy of treatment; there is no evidence that the proportional hazard assumption was not met, so modelling of a time-varying hazard ratio was not performed (Appendix L).

Other assumptions and comments relating to how they are explored in sensitivity/scenario analyses (if at all) include:

- Memoryless assumption of Markov models; partly relaxed with composite health states tracking patients' history,
- Lifetime treatment duration; explored in a scenario,
- HRs applied independently of significance level; ISPOR (124) recommends that all known data should be incorporated for key parameters, including those that fall short of the conventional thresholds of statistical significance,
- Similar utility values for health states / health events in all treatment arms; no evidence to suggest that treatment choice has any impact on quality of life.

B.3.7 Base-case results

Base-case incremental cost-effectiveness analysis results

The deterministic results for the base case analysis are reported in Table 74. The results compare the incremental costs and benefits of FIN+BT versus BT for patients with a baseline eGFR between 25 and 60 and albuminuria, reflecting the proposed license population. The base case results are based on a lifelong time horizon.

The ICER for FIN + BT versus BT is £17,561 per QALY gained based on a lifelong time horizon and assuming the cost of finerenone as £1.84 per day.

Table 74. Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
FIN + BT	£51,983	8.25	6.11	£1,779	0.12	0.10	£17,552	£17,552
BT	£50,204	8.12	6.01					
Abbreviations: ICER - incremental cost-effectiveness ratio; LYG - life years gained; QALYs - quality-adjusted life years								

The clinical outcomes estimated in the model, the costs stratified by item and the utilities by health state in each arm are presented in Appendix J.

Importantly, there are aspects of health related quality of life that are not captured within the QALY calculation so these estimates may be considered conservative. One of the consequences of progressing to ESRD is chronic dialysis. Dialysis is an intervention that has a substantial impact on the life of patients and their family and/or caregivers. A treatment such as finerenone that can delay the progression to kidney failure and the need for dialysis will offer considerable benefits to ***both*** patients and their caregivers (for further information on this aspect of quality of life, see section B.2.12).

B.3.8 Sensitivity analyses

3.8.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analyses (PSA) were also performed. The model was run 1,000 times for each scenario. At the end of the simulation process, the joint statistical distribution for costs and effectiveness was represented as a cloud of points on the

cost-effectiveness plane (Figure B3. 2). It was then possible to generate a cost-effectiveness acceptability curve (CEAC), as displayed in Figure B3.

Detailed results of the PSA are presented below, with the mean PSA results, as well as the incremental cost-effectiveness plane and the cost-effectiveness acceptability curve.

Based on 1,000 simulations, the mean PSA ICER is £17,843 per QALY gained. The probability that FIN + BT is cost-effective against BT is approximately 60%, when considering a cost-effectiveness threshold of £20,000/QALY. At a cost-effectiveness threshold of £30,000/QALY, this probability is approximately 78%.

Table 75. Mean PSA results

Statistics	Incr. costs (£)	Incr. QALYs	ICER (£/QALYs)
Base Case	1,779	0.101	17,552
Mean	1,781	0.100	17,843
Probability(<£20,000 threshold)	-	-	60.4%
Probability (<£30,000 threshold)	-	-	78.1%

Figure 26. PSA results, incremental cost-effectiveness plane

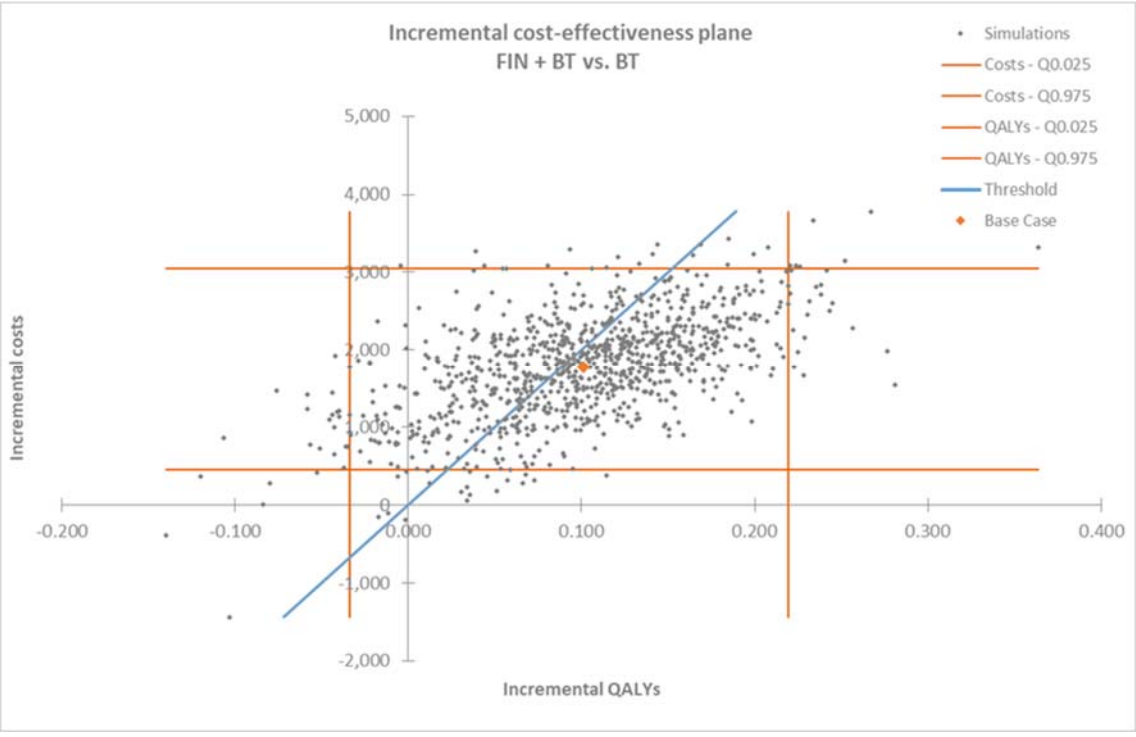
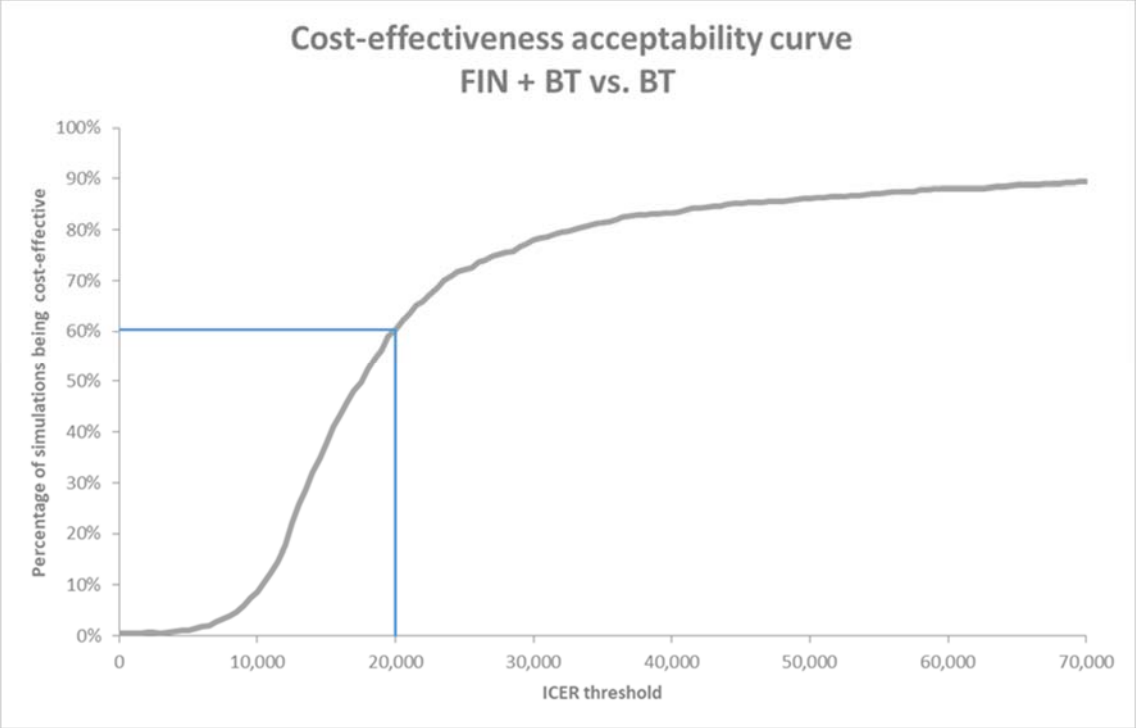


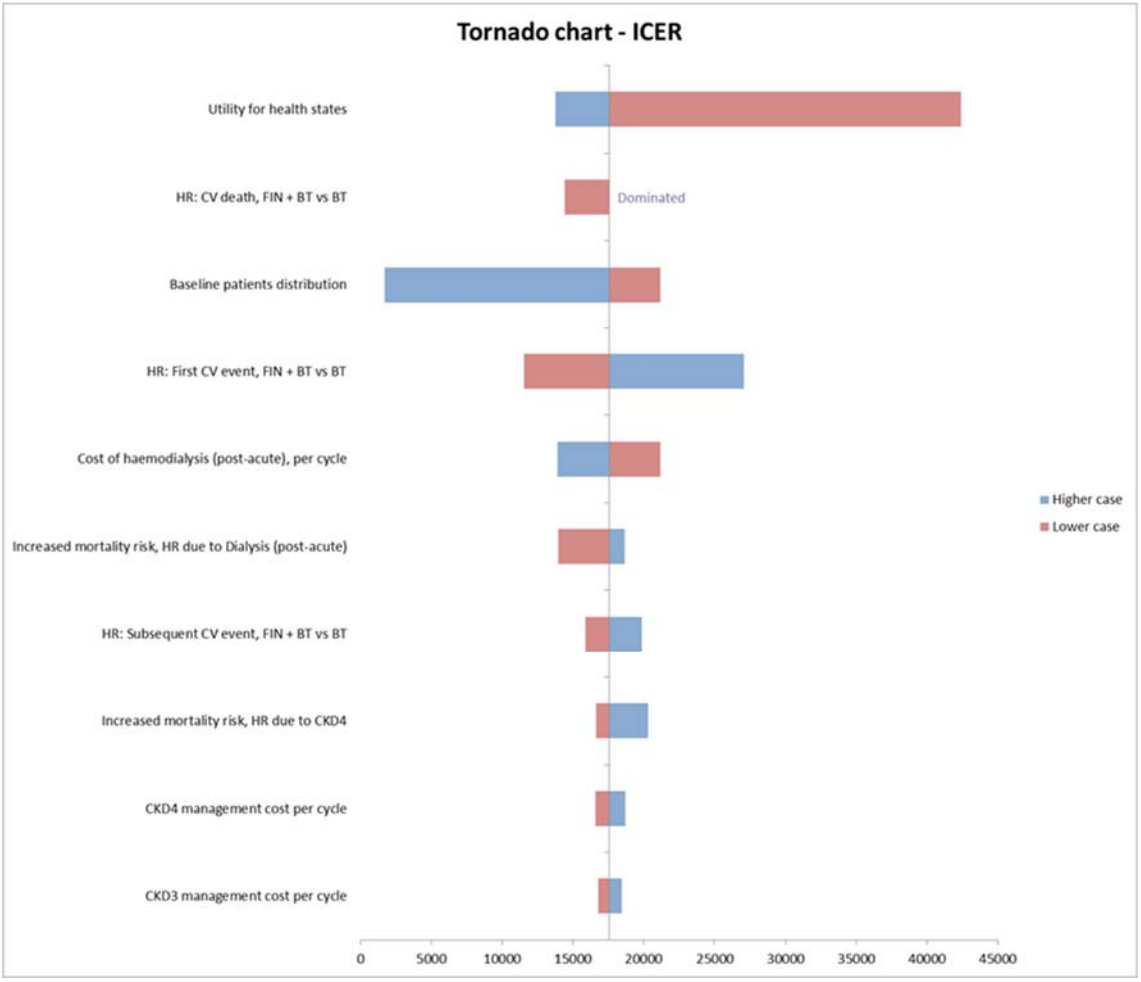
Figure 27. PSA results, cost-effectiveness acceptability curve



3.8.2 Deterministic sensitivity analysis

The sensitivity of the base case cost-effectiveness ratio to input parameters was explored by varying key parameters within ranges reflecting possible parameter values. The ranges applied in the current analysis are summarised in Table 73. This process helps to define the possible boundaries of the cost-effectiveness results and identify parameters that warrant further investigation. Results are presented in tornado diagrams (Figure 28).

Figure 28. DSA results, 10 first drivers on the ICER (£/QALY)



The DSA shows that the main ICER drivers include utility values for health states, HR: CV death, HR: CV event and baseline patient distribution.

Table 76. DSA results, 10 first drivers on the ICER (£/QALY)

Results driver	Lower case	Higher case
Utility for health states	42,410	13,734
HR: CV death, FIN + BT vs BT	14,400	Dominated
Baseline patient distribution	21,193	1,672
HR: First CV event, FIN + BT vs BT	11,521	27,082
Cost of haemodialysis (post-acute), per cycle	21,182	13,921
Increased mortality risk, HR due to Dialysis (post-acute)	13,939	18,665
HR: Subsequent CV event, FIN + BT vs BT	15,880	19,866
Increased mortality risk, HR due to CKD4	16,608	20,318

CKD4 management cost per cycle	16,571	18,685
CKD3 management cost per cycle	16,759	18,468

3.8.3 Scenario analysis

A comprehensive set of scenario analyses were conducted, considering alternative data sources for certain model parameters to investigate the robustness of the model to different assumptions – the scenarios investigated are outlined in Table 77 and the results are presented in Table 78.

Table 77. Scenario analyses – input parameters

Model input	Base Case	Rationale	Scenarios
Population	Proposed label population	The proposed label population represents the population for which the indication has been sought with EMA	FAS data set (presented in Appendix N)
Utilities inputs	FIDELIO-DKD data	Directly from FIDELIO-DKD trial	Literature data (see the inputs in sections B.3.4.3 and B.3.4.4.)
Treatment persistence	Treatment persistence : impact on costs and efficacy	Discontinuation as reported in FIDELIO-DKD trial is considered. Patients who discontinue FIN +BT accrue the costs and efficacy of the BT arm.	Treatment persistence: impact on costs only
			No persistence simulated
Time horizon	Lifetime	Consistent with licence	15 years
Delayed progression to dialysis (for 3 cycles)	Not considered	The same transition probabilities estimated over 4-years of FIDELIO-DKD trial	Delayed progression to dialysis (for 3 cycles), see explanation in Appendix J, supported by clinical data in section B.2.6 (text between Table 15 and Figure 5)
Treatment discontinuation in terms of RRT	Not considered	Consistant with indication	Finerenone is stopped after initiation of RRT, but BT is not
Discount rates	3.5%	NICE guidelines	0% for both cost and health outcomes
Discount rates	3.5%	NICE guidelines	5% for both cost and health outcomes

Table 78. Scenario analyses – results

Model input	Parameter value	Incremental costs	Incremental QALY	ICER
Base case	-	£1,179	0.10	£17,552 per QALY gained
Scenario 1: Population	FAS data set	£2,243	0.15	£15,125 per QALY gained
Scenario 2: Utilities	Literature data	£1,779	0.12	£14,966 per QALY gained
Scenario 3: Treatment persistence:	Impact on costs only	£964	0.16	£5,924 per QALY gained
Scenario 4: treatment persistence	No persistence simulated	£3,252	0.16	£19,982 per QALY gained
Scenario 5: Time horizon:	15 years	£1,638	0.08	£19,838 per QALY gained
Scenario 6: progression to dialysis	Delayed for 3 cycles	£1,828	0.10	£18,158 per QALY gained
Scenario 7: Discontinuation of therapy after initation of RRT	Finerenone is stopped after initiation of RRT, but BT is not	£1,531	0.10	£15,556 per QALY gained
Scenario 8: Discount rates	0% (cost and health outcomes)	£2,041	0.15	£13,893 per QALY gained
Scenario 9: Discount rates	5% (cost and health outcomes)	£1,696	0.09	£19,377 per QALY gained

3.8.4 Summary of sensitivity analyses results

In terms of DSA, the impact of utilities on the analysis results is significant due to the wide ranges for utilities obtained from the FIDELIO-DKD trial. These results should be analysed with caution; hence an additional scenario analysis was performed in which health states utilities have been based on the findings from a previously performed SLR. The results for this scenario are consistent with the base case confirming the findings from the model.

In terms of the impact of HR for CV death, this HR is 0.93 in the base case, but the CI interval is 0.71-1.20. Cost-effectiveness of FIN + BT was confirmed in the DSA for any

other model parameter as well as in all considered scenarios. Furthermore, the probabilistic and deterministic ICERs are consistent with high probability of FIN + BT being a cost-effective treatment in comparison to BT alone shown in the PSA.

B.3.9 Subgroup analysis

NA

B.3.10 Validation

3.10.1 Model structure validation

The model has undergone multiple levels of review from clinical and health economics experts.

Prior to model development, a literature review was conducted to evaluate other economic models in CKD. Models were assessed for structure, cycle length, assumptions etc and the information presented to the experts. During the model development the experts participated in teleconferences and email exchange.

Over a period of several months, input was sought from each advisor on the appropriate model structure and clinical assumptions e.g., treatment duration, persistence, hazard ratios, extrapolation beyond the trial, cycle length, time horizon etc. The final model structure was presented to the experts for review.

3.10.2 UK clinical experts' validation

During the process of adapting the global economic model for the NICE submission, further targeted literature reviews were conducted to address identified data gaps and to ensure maximum generalisability of the included parameters and associated analyses. For selected cardiovascular, renal, and epidemiological parameters some uncertainty remained regarding appropriate sources to use or assumptions made. Three UK clinical experts were identified based on their experience in CKD. Each was interviewed remotely to seek their advice on the applicability and suitability of various parameters and assumptions applied in the economic modelling. These areas of uncertainty included the following:

- CKD related health states costs

- Hyperkalaemia management
- Risk of 1st CV event and CV death for dialysis and kidney transplant patients
- CKD progression
- Increased risk of death following the 1st CV events
- QoL after dialysis
- Key model assumptions.

Based on the advice received, appropriate sources were selected, assumptions validated, and inputs updated to reflect UK clinical practice.

3.10.3 Results validation

The technical validity of the model was tested by two independent modelling agencies to ensure that calculations were correct and that the results were logical and consistent.

Apart from the technical validation, an external validation was performed to test the credibility of the model and check that the model results are in line with real-life data.

The patient level data from FIDELIO-DKD were compared with outputs of the CE model. The frequency of the following events observed in FIDELIO-DKD was compared with model predictions for the following: first CV event in the model, CV death, and number of patients undergoing dialysis.

The validity of the model outcomes in relation to those observed in the FIDELIO-DKD trial are presented in Appendix J and show the model accurately reflects the observed results.

B.3.11 Interpretation and conclusions of economic evidence

This economic evaluation was performed to assess the cost-effectiveness of finerenone added to BT in delaying CKD progression and reducing CV risks in patients with CKD and T2D. This cost-effectiveness model has been developed based on the clinical data available for finerenone, as well as findings from several SLRs performed to identify previous models and utility weights in the indication of interest. The development of the model specifications was presented to, discussed with, and

validated by a scientific committee of clinical and health economic experts. In general, the structure and assumptions of the current model are consistent with approaches in the existing literature of modelling both CKD progression and the incidence of CV events. Utilising the most used, and well-validated, model type and structure ensures transparency and reduces the uncertainty that would arise from an unnecessarily complex structure. Additionally, the model adequately allows for the inclusion of finerenone benefits demonstrated in the FIDELIO-DKD trial.

The model population reflects the FIDELIO-DKD patient population, i.e., patients with CKD and T2D. Hence, the simulated cohorts are characterised by a certain distribution of CKD stages at baseline to allow determination of CKD progression. Finerenone was shown to delay CKD progression and reduce the risk of renal events, including ESRD. Finerenone was also shown to confer a benefit in terms of CV risk, by reducing the risk of a patient meeting the criteria of the composite endpoint (time to first occurrence of CV death, non-fatal MI, non-fatal stroke or hospitalisation for HF).

Indeed, the clinical benefits of using finerenone in terms of delaying CKD progression were proven in the FIDELIO-DKD trial. However, the trial was designed and powered to make conclusions based on composite endpoints. Such outcomes are difficult to include in an economic evaluation, as each composite has a different impact on costs, quality of life and, importantly, modelled events. Moreover, one of the components, namely the percentage decline in the eGFR from baseline is a relative measure which makes it less useful for the model in assessing the absolute benefits of treatments (both FIN and BT). Therefore, it was necessary for the model to use patient level data from FIDELIO-DKD trial in order to obtain transition probabilities reflecting the CKD progression and the impact of finerenone.

In terms of the other health outcomes considered in the economic evaluation it was possible to model clinical benefits of finerenone by using relative measures obtained within the trial applied to the absolute estimates for BT. According to ISPOR recommendations, all known data should be incorporated for key parameters, including those that fall short of the conventional thresholds of statistical significance. We have followed this recommendation in order to adequately reflect the benefits of using finerenone shown in FIDELIO-DKD. Confidence intervals of all hazard ratios

considered in the model were tested in the PSA, showing consistent results with the deterministic analysis. According to model results, finerenone is a cost-effective treatment in comparison to BT and the probability of cost-effectiveness is approximately 60% when the willingness-to-pay threshold is set at £20,000 per QALY gained. This probability increases to 78% considering a threshold of £30,000 per QALY gained.

Finerenone's cost-effectiveness has been shown despite the application of several conservative assumptions. Importantly, there are aspects of health related quality of life that are not captured within the QALY calculation. One of the consequences of progressing to ESRD is chronic dialysis. Dialysis is an intervention that has a substantial impact on the life of patients and their family and/or caregivers. A treatment such as finerenone that can delay the progression to kidney failure and the need for dialysis will offer considerable benefits to ***both*** patients and their caregivers (for further information on this aspect of quality of life, see section B.2.12).

The estimates generated by the model correspond well with the FIDELIO-DKD results, as shown in the external validation that was undertaken and so we believe that this model allows for a reliable assessment of both the benefits and costs related to the use of finerenone in patients with CKD and T2D in the UK.

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B.5 Appendices

All Appendices saved as stand-alone files.

Appendix C: Summary of product characteristics (SmPC)

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analysis

Appendix F: Adverse reactions

Appendix G: Published cost-effectiveness studies

Appendix H: Health-related quality-of-life studies

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

Appendix J: Clinical outcomes and disaggregated results from the model

Appendix K: Checklist of confidential information

Appendix L: Proportional hazards assumption justification

Appendix M: Epidemiology inputs identification and valuation

Appendix N: FAS population data set

Appendix O: Cardiovascular endpoint definitions (9)

Appendix P: Additional analyses of endpoints in FIDELIO-DKD

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

Clarification questions

October 2021

[UPDATED CONFIDENTIAL MARKING APRIL 2022]

File name	Version	Contains confidential information	Date
ID3773 finerenone ERG clarification_Bayer response_ACIC	1	**Y**	6 October 2021

Notes for company

Highlighting in the template

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Section A: Clarification on effectiveness data

Literature searches

A1. The literature searches in Appendix D do not include search terms for angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) as comparators (current standard of care). Please clarify why these drugs were not included in searches.

As mentioned in section B.1.3 of Document B, ACEIs and ARBs are recommended for patients with CKD and T2D and constitute the current standard of care according to many CKD / T2D guidelines including those from KDIGO, ADA, NICE and joint guidelines from ESC and EASD. They are however one component of standard of care (see figure 1 in Document B). Alongside dietary and lifestyle interventions, proven pharmacological strategies for CKD prevention and treatment in T2D patients are to reduce the rate of progression of CKD by optimisation of blood pressure control, lipid levels (using statins), and glycaemic control (using anti-diabetics).

The FIDELIO study protocol specified that all patients should be treated with the individual maximum tolerated labelled dose of either an ACEI or an ARB. It also specified that antihypertensive therapy for renal and CVD protection will be administered according to local

guidelines. Further, that advice was given to follow the recommendations of local guidelines for the management of CVD and CKD, the use of statins, anti-platelets and beta-blockers, and guidelines for glycaemic control.

Considering ACE/ARB explicitly in the search strategy would have led to identification of multiple RCTs comparing ACEs and/or ARBs to other ACEs and/or ARBs. Such RCTs would not be relevant for evaluating the cost-effectiveness of finerenone, as:

(1) finerenone is an add-on therapy to standard of care including ACEi/ARB, and

(2) the comparator in the cost-effectiveness model is standard of care established in clinical practice, reflected by the placebo comparator arm of the FIDELIO-DKD study.

Therefore, we concluded that considering ACE/ARB explicitly in the search strategy would not add value in this case.

A2. Appendix D states that "In total, the search yielded 4548 records". The original and update database searches of Medline/Embase/CENTRAL retrieved 3763 records. Please clarify the source of the additional records.

Bayer apologises for not making this clearer. We can confirm that the original and update database searches of Medline/Embase and CENTRAL retrieved 3763 records. Additional records (n=785) were retrieved from clinical trials registries.

Decision problem

A3. Please confirm that the intention is to focus on the population aligned with the proposed indication under review by EMA.

Bayer can confirm, that whilst the proposed indication is still under review by EMA, that it is our intention to be appraised according to this proposed indication. Detailed further analysis of the

FIDELIO-DKD data was conducted in line with the proposed indication to support the submission, referred to as “label population” throughout the submission documents.

Bayer presented the Full Analysis Set (FAS) data from the trial in parallel for completeness, but understood from the methods guide (section 2.2.3) that NICE would only make recommendations on the population addressed in the final marketing authorisation, or subgroups of this population.

A4. The company submission states that SGLT2 inhibitors are not relevant comparators, noting that market share data indicates that “*the market share by volume of SGLT2 inhibitors at less than [redacted]% as compared against oral and parenteral hypoglycaemics*” Although the percentage is low, please explain which people are currently receiving SGLT2 inhibitors in clinical practice. If people receiving SGLT2 inhibitors will not be excluded, include SGLT2 inhibitors as a comparator.

Thank you for giving us further clarity on this question during the call on the 28th September.

In the time available, Bayer was unable to clarify this directly with a representative body of UK clinicians and so Bayer does not currently have specific information on the characteristics of patients currently prescribed SGLT2is in UK clinical practice. However usage should be according to the respective marketing authorisations of the different SGLT2i.

The marketing authorisations for these drugs were, until recently, for the management of blood glucose levels along with diet and exercise in patients with type 2 diabetes (T2D). Changes to the marketing authorisations referring to cardiovascular benefits followed and only since mid-2020 have marketing authorisations started to refer to renal benefits. Indeed, the change to the marketing authorisation for dapagliflozin was made as recently as August 2021, around the time of the finerenone NICE submission (1).

As such, Bayer consider that up until very recently, the SGLT2is have been used primarily for glycaemic control. Indeed, it is well recognised that chronic kidney disease (CKD) in T2D is under-diagnosed/ recognised (2-4) so it would seem to be a large and unsupported assumption that this use is related to the recent cardiovascular and renal outcome studies. Whilst usage may increase as a result of the recent changes in marketing authorisation, Bayer contend that the SGLT2is are

not embedded within clinical practice in the UK for the management of CKD. As such, they are not a relevant comparator in this appraisal.

As set out in our response to the draft scope and also during the decision problem discussion, Bayer consider that the SGLT2is do not meet the definition of a comparator according to the NICE methods guide. Consultee feedback on the draft scope also confirmed that SGLT2is should not be considered a comparator as they are not part of standard of care.

Clinical effectiveness

A5. Please provide evidence of the generalisability of the clinical trial population to the UK population e.g. relevance of baseline characteristics from the trial vs UK data.

Bayer have conducted a thorough interrogation of published epidemiological literature relating to the UK population with type 2 diabetes and chronic kidney disease. A pragmatic literature search of the pubmed database has been conducted and complimented by desk research. Priority was given to the retrieval of high-quality, UK specific, published sources of evidence. However, for particular parameters, no such source could be retrieved. In this instance, Bayer has relied upon an analysis of data from the Clinical Practice Research Datalink. This approach has also been taken when answering question A6.

The FIDELIO-DKD study was a randomised, double-blind, placebo-controlled, parallel-group, multicentre, event-driven Phase 3 study designed to investigate the efficacy and safety of finerenone, in addition to standard of care, on the progression of kidney disease in subjects with type 2 diabetes mellitus and the clinical diagnosis of diabetic kidney disease (5-13).

Bayer recognise the FIDELIO-DKD study as having a high degree of external validity, being generalisable across a variety of key epidemiological characteristics with the equivalent population under consideration in the UK.

Background characteristics:

Bayer believe the recruitment into the FIDELIO-DKD trial is generalisable to the UK population across a variety of epidemiological factors, including: age, race and distribution of sex.

The mean age in the intervention arm of the clinical trial population is 65.4 years (comparator arm = 65.7 years). Similarly, for the intended label population the mean age is [redacted] years in the intervention arm (comparator arm = [redacted] years). Hill et al (2014) estimates the prevalence of CKD in a T2D population using the UK National Diabetes Audit (14). This publication presents a very similar mean age of 66 years for those patients with T2D and CKD.

The percentage of males in the intervention arm of the clinical trial population is 68.9 (comparator arm = 71.5). Similarly, for the intended label population the percentage of males in the intervention arm is [redacted] (comparator arm = [redacted].8%). Hill et al (2014) (14) reports that the proportion of males with T2D diabetes and CKD is 55.4%. Likewise, an analysis of CPRD data indicates that this same percentage is [redacted]%. Bayer propose that this discrepancy is, in part, related to the fact that clinical trials typically see higher rates of enrolment of male participants. It has been noted that this disparity in recruitment to clinical trials is even wider, favouring male recruitment, in a CKD population (15). Notwithstanding, there is no evidence from the FIDELIO-DKD trial to suggest the effectiveness of finerenone varies in accordance with patient sex with a non-significant p value in a test for heterogeneity (5).

The percentage of patients identifying as white in the intervention arm of the clinical trial population is 62.7 (comparator arm = 63.9). Similarly, for the intended label population the percentage of patients identifying as white in the intervention arm is [redacted] (comparator arm = [redacted]). Hill et al (2014) (14) criticise the recording of ethnicity within UK National Diabetes Audit data, at both the regional and national level (overall 42.9% patients with missing data). Another source, González-Pérez et al (2020) (16) reports the same lack of reporting of patient ethnicity when using The Health Improvement Network (THIN) to estimate the incidence of CKD in patients with newly diagnosed T2D. With this in mind, an analysis of Clinical Practice Research Datalink (CPRD) data (17) indicates that the ethnic diversity of the FIDELIO-DKD trial is reflective of real-world clinical practice in the UK. This is true, insofar as, this same proportion of white patients diagnosed with CKD and T2D is estimated to be [redacted]% in the UK. Likewise, the same can be said of the black population diagnosed with CKD and T2D. Black patients in the clinical trial population account for 4.9% of the intervention arm and 4.4% of the comparator arm. For the intended label

population, black patients represent [redacted]% of the intervention arm and [redacted]% of the comparator arm. CPRD data (17) illustrates that black patients account for [redacted]% of those diagnosed with CKD and T2D in the UK. Mathur et al (2013) (18) state that "the ethnic breakdown of the CPRD is comparable to the UK censuses". Likewise, they report that ethnicity is recorded to high levels within the database for patients registered since mid-2006 (78.3%).

Cardiovascular risk factors:

Bayer believe the FIDELIO-DKD trial to be generalisable to the UK population with T2D and CKD, across a variety of cardiovascular risk factors.

The proportion of patients in the clinical trial with a medical history including hypertension varies between 96.6% (intervention arm) and 97.4% (comparator arm). For the intended label population, these proportions change to [redacted]% and [redacted]%, respectively. A study at East Kent University Hospitals NHS Foundation Trust reported that between 2008-2010 that 89.4% of patients with CKD were hypertensive (19). According to CPRD data (17), the proportion of patients with T2D and CKD with hypertension is [redacted]%. It should be considered that real world data will include patients with earlier stages of CKD than found in FIDELIO-DKD which could lead to this slight difference observed.

The mean systolic blood pressure (mmHg) in the FIDELIO-DKD study population was 138.1 (intervention arm) and 138.0 (comparator arm). These mean blood pressures change to [redacted] mmHg and [redacted] mmHg, respectively, when considering the proposed label population. Hill et al (2014) (14), report a very similar systolic blood pressure of 134.9 mmHg for patients diagnosed with T2D and CKD in the UK.

Furthermore, the proportion of patients with a medical history including ischaemic stroke in the clinical trial population varies between 11.6% (intervention arm) and 12.7% (comparator arm). For the label population, these proportions change to [redacted]% and [redacted]%, respectively. According to CPRD data (17), the proportion of patients diagnosed with T2D and CKD with a medical history including stroke is [redacted]%, so these figures are similar

In conclusion, Bayer consider that the baseline characteristics of the FIDELIO-DKD trial are representative of the proposed label population in UK clinical practice.

A6. Please provide evidence as to how the comparator arm in the FIDELIO-DKD trial is reflective of clinical practice in the UK in terms of treatments received.

As mentioned in the response to clarification question A5, Bayer have conducted a thorough search for sources of real-world literature that could be used to assess the generalisability of FIDELIO-DKD to the equivalent population of T2D patients with CKD in the UK. Whilst sources of published literature have been retrieved, it has been noted that analyses of real-world data sources, consider patients with T2D across the entire spectrum of CKD disease severity. Analyses of real-world evidence, considering those patients with long-standing diabetes and advanced CKD, already pre-treated with optimised renin angiotensin blockade, has not been possible. This is an identified data gap and area for future research.

In the retrieved resources of real-world evidence, a high proportion of patients are in the early stages of CKD. They are, by extension, less likely to receive treatment for the associated co-morbidities related to the advanced stages of CKD (e.g. hypertension and poor glycaemic control). It should be noted, therefore, that if patients eligible for finerenone could be identified in the retrieved analyses of RWE, the percentages of patients taking insulin, calcium channel blockers and diuretics would be more aligned with FIDELIO-DKD.

Antihypertensive therapies:
Bayer believe the distribution of antihypertensive therapies received by patients in the FIDELIO-DKD trial to be reflective of the patients who would receive finerenone in real-world practice in the UK.

Angiotensin-receptor blockers (ARB) or angiotensin-converting enzyme inhibitors (ACEi) have been the mainstay of therapy for patients with CKD and T2D in the UK for several decades. This is reflected in NICE guideline CG182 (20) and the most recent update NG203 (21). According to an analysis of CPRD data (17), the proportion of patients with CKD and T2D prescribed an ACEi or ARB in the last 3 months (data cut December 31st 2019) is [redacted]% ([redacted]% ACEi, [redacted]% ARB).In the cost-effectiveness model the proportion of patients taking either an ACE or ARB is [redacted]% ([redacted]% ACE, [redacted]% ARB). As discussed above, real world data will include patients with earlier stages of CKD than found in FIDELIO-DKD which could lead to a difference in observed ACE/ARB

use. Further, in order to fully reflect guideline recommendations, the eligibility criteria of the FIDELIO-DKD trial (5-13) stipulated that trial participants must already be treated with renin-angiotensin system blockade at the maximum dose. This restriction is reflective of the intention for finerenone to be used to treat the residual risk of renal deterioration in patients with CKD and T2D currently taking ACEi/ARBs.

The proportion of patients receiving calcium antagonists in the submitted cost-effectiveness model, informed by the FIDELIO-DKD study is [redacted]%. An analysis of CPRD data (17) estimates that the proportion of patients prescribed calcium channel blockers in the T2D population with CKD is [redacted]%. Additionally, the proportion of patients receiving treatment with diuretics in the submitted cost-effectiveness model is [redacted]%. An analysis of CPRD data (17) estimates that the proportion of patients prescribed diuretics in the T2D population with CKD is [redacted]% in the UK. There was no specific protocol requirement for calcium channel blockers or diuretics, so usage in the study should be largely representative of the clinical setting.

As highlighted in the response to A5, the proportion of patients in the clinical trial with a medical history including hypertension varies between 96.6% (intervention arm) and 97.4% (comparator arm) and that this may be higher than reported in real world data which includes patients with less advanced DKD. Diuretics and calcium channel blockers are NICE guideline recommended therapies for the management of hypertension (NG136) (22). With progressing CKD, hypertension becomes more problematic and often multiple antihypertensives are needed; it is reasonable that the proportion of patients taking calcium channel blockers/diuretics is observed to be higher in FIDELIO-DKD compared to the analysis of CPRD data (17). This is true, insofar as, this source of real world data considers patients across the entire spectrum of CKD severity that a T2D patient may experience. A higher prevalence of patients is present in CPRD data of patients with earlier stages of CKD, who are less likely to receive therapies to address the complications associated with advanced disease, such as hypertension.

Lipid-lowering therapies:

Bayer believe the distribution of lipid-lowering therapies received by patients in the FIDELIO-DKD trial to be reflective of real-world practice in the UK.

According to the National Chronic Kidney Disease Audit (23) “69% of people with identified CKD were prescribed statin medication in accordance with NICE guidelines”. The proportion of patients taking statins in the submitted cost-effectiveness model, informed by the FIDELIO-DKD trial is 68.8%.

Glucose-lowering therapies:

Bayer believe the distribution of glucose-lowering therapies received by patients in the FIDELIO-DKD trial to be reflective of real-world practice in the UK.

A small proportion of patients were taking SGLT2 inhibitors in the FIDELIO-DKD trial, as a glucose-lowering therapy. The proportion of patients who were using SGLT2 inhibitors in the submitted cost-effectiveness model was [redacted]%. When considering an analysis of CPRD data, the proportion of patients with CKD and T2D who have been prescribed SGLT2 inhibitors is also [redacted]%.

Ruzafa et al (2015) (24) estimated the proportion of patients taking insulin in the incident population with T2D and CKD (stages 3a – 4) between 2006-2012 as ranging between 10.9% (stage 3a) and 23.3% (stage 4). In the submitted cost-effectiveness model, the proportion of patients taking insulin therapy is [redacted]%. The mean duration of diabetes for patients studied in Rufaza et al (2015) (24) is not reported. Kostev and Rathmann (2013) (25) conducted a retrospective database analysis to investigate the time to insulin initiation in T2D patients in the UK between 2005 and 2010. In 2010 they found the time to onset of insulin treatment in T2D patients to be 2061 days (~5.65 years). FIDELIO-DKD studied patients with long standing diabetes and advanced CKD. The mean duration of diabetes of patients in the FIDELIO-DKD clinical trial population was 16.6 years in both arms of the study. This much larger mean duration is likely responsible for a larger proportion of patients taking insulin in the FIDELIO-DKD population, compared to the T2D population with CKD studied in Rufaza et al (2015) (24). The use of insulin increases with worsening CKD as many oral anti-diabetics are less effective at lower kidney function and others are contraindicated in advanced CKD. Further to this, glycaemic control can become more challenging with more advanced CKD so titrated insulin is used more often in these patients. Lastly, there is no protocol requirement for the use of insulin in FIDELIO-DKD, thus, uptake in patients should be representative of the equivalent population in the UK.

In conclusion, Bayer consider that the proportion of patients who are eligible for finerenone in the UK, who are prescribed these medications, would align more closely with the FIDELIO-DKD study than the retrieved real world evidence studies. This is true, insofar as, such studies consider a high proportion of patients with T2D with early stage CKD. Such patients are less likely to receive treatment for the associated co-morbidities related to the advanced stages of CKD (e.g. hypertension and poor glycaemic control).

A7. The FIDELIO-DKD trial has a median follow up of 2.6 years. Crude incidence, incidence rate per 100 patient years and hazard ratios are presented at the end of the follow-up period. Please provide data to indicate these data are consistent over time aligned with the model cycles for the intention-to-treat (ITT) and label populations.

We present the KM curves for the outcomes from FIDELIO-DKD and the exponential distribution in our response to question A9. These curves indicate that this distribution fits well to the FIDELIO-DKD data. Hence, the use of constant rates in the CE model is justified.

A8. Please provide the Kaplan-Meier curves for all disaggregated endpoints for the FIDELIO-DKD trial for the ITT and label populations, including tests of proportional hazard assumptions.

Please find in the tables below the KM estimates for all disaggregated endpoints from the FIDELIO-DKD trial. The data for renal death has not been provided as there were too few patients experiencing renal death (4 events of renal death in the ITT population and therefore the analyses are not considered meaningful).

Please also find the tests for proportional hazard assumptions for each outcome. This links with the proportional hazard's assumption, the plausibility of which can be assessed by including a

time-treatment interaction term in the Cox model (time log transformed). The significance of the interaction is tested at the 5% type I error level. If the interaction is significant, the time-dependent hazard ratios are to be estimated within the model that includes the interaction term. **As can be seen below, the p-values for all the time-treatment interactions are non-significant.**

- ITT population: Time to onset of eGFR decrease of >=40% sustained over at least 4 weeks (days)

Table 1 Cumulative incidence probability of sustained decrease in eGFR >= 40%, ITT population

Months	Cumulative incidence probability	95% CI
4	[redacted]	[redacted]
8	[redacted]	[redacted]
12	[redacted]	[redacted]
16	[redacted]	[redacted]
20	[redacted]	[redacted]
24	[redacted]	[redacted]
28	[redacted]	[redacted]
32	[redacted]	[redacted]
36	[redacted]	[redacted]
40	[redacted]	[redacted]
44	[redacted]	[redacted]
48	[redacted]	[redacted]

[redacted]

- ITT population: Time to CV death

Table 2 Cumulative incidence probability of CV death, ITT population

Months	Cumulative incidence probability	95% CI
4	[redacted]	[redacted]
8	[redacted]	[redacted]
12	[redacted]	[redacted]
16	[redacted]	[redacted]
20	[redacted]	[redacted]
24	[redacted]	[redacted]
28	[redacted]	[redacted]
32	[redacted]	[redacted]
36	[redacted]	[redacted]
40	[redacted]	[redacted]
44	[redacted]	[redacted]
48	[redacted]	[redacted]
52	[redacted]	[redacted]

[redacted]

- ITT population: Time to 1st occurrence of MI

Table 3. Cumulative incidence probability of non-fatal MI, ITT population

Months	Cumulative incidence probability	95% CI
4	[redacted]	[redacted]
8	[redacted]	[redacted]
12	[redacted]	[redacted]
16	[redacted]	[redacted]
20	[redacted]	[redacted]
24	[redacted]	[redacted]
28	[redacted]	[redacted]
32	[redacted]	[redacted]
36	[redacted]	[redacted]
40	[redacted]	[redacted]
44	[redacted]	[redacted]
48	[redacted]	[redacted]
52	[redacted]	[redacted]

[redacted]

- ITT population: Time to 1st occurrence of non-fatal stroke

Table 4 Cumulative incidence probability of non-fatal stroke, ITT population

Months	Cumulative incidence probability	95% CI
4	[redacted]	[redacted]
8	[redacted]	[redacted]
12	[redacted]	[redacted]
16	[redacted]	[redacted]
20	[redacted]	[redacted]
24	[redacted]	[redacted]
28	[redacted]	[redacted]
32	[redacted]	[redacted]
36	[redacted]	[redacted]
40	[redacted]	[redacted]
44	[redacted]	[redacted]
48	[redacted]	[redacted]
52	[redacted]	[redacted]

[redacted]

- ITT population: Time to 1st occurrence of hospitalization due to heart failure

Table 5 Cumulative incidence probability of hospitalization due to heart failure, ITT population

Months	Cumulative incidence probability	95% CI
4	[redacted]	[redacted]
8	[redacted]	[redacted]
12	[redacted]	[redacted]
16	[redacted]	[redacted]
20	[redacted]	[redacted]
24	[redacted]	[redacted]
28	[redacted]	[redacted]
32	[redacted]	[redacted]
36	[redacted]	[redacted]
40	[redacted]	[redacted]
44	[redacted]	[redacted]
48	[redacted]	[redacted]
52	[redacted]	[redacted]

[redacted]

- ITT population: Time to first occurrence of HD or PD

Table 6. Cumulative incidence probability of dialysis, ITT population

Months	Cumulative incidence probability	95% CI
8	[redacted]	[redacted]
12	[redacted]	[redacted]
16	[redacted]	[redacted]
20	[redacted]	[redacted]
24	[redacted]	[redacted]
28	[redacted]	[redacted]
32	[redacted]	[redacted]
36	[redacted]	[redacted]
40	[redacted]	[redacted]
44	[redacted]	[redacted]
48	[redacted]	[redacted]
52	[redacted]	[redacted]

[redacted]

Please find below the KM curves for all disaggregated endpoints for FIDELIO-DKD for the label population.

- Label population: Time to onset of eGFR decrease of >=40% sustained over at least 4 weeks (days)

Table 7 Cumulative incidence probability of sustained decrease in egfr >= 40%, label population

Months	Cumulative incidence probability	95% CI
4	[redacted]	[redacted]
8	[redacted]	[redacted]
12	[redacted]	[redacted]
16	[redacted]	[redacted]
20	[redacted]	[redacted]
24	[redacted]	[redacted]
28	[redacted]	[redacted]
32	[redacted]	[redacted]
36	[redacted]	[redacted]
40	[redacted]	[redacted]
44	[redacted]	[redacted]
48	[redacted]	[redacted]

- Label population: Time to CV death

Table 8. Cumulative incidence probability of CV death, label population

Months	Cumulative incidence probability	95% CI
4	[redacted]	[redacted]
8	[redacted]	[redacted]
12	[redacted]	[redacted]
16	[redacted]	[redacted]
20	[redacted]	[redacted]
24	[redacted]	[redacted]
28	[redacted]	[redacted]
32	[redacted]	[redacted]
36	[redacted]	[redacted]
40	[redacted]	[redacted]
44	[redacted]	[redacted]
48	[redacted]	[redacted]
52	[redacted]	[redacted]

[redacted]

- Label population: Time to 1st occurrence of non-fatal MI

Table 9. Cumulative incidence probability of non-fatal MI, label population

Months	Cumulative incidence probability	95% CI
4	[redacted]	[redacted]
8	[redacted]	[redacted]
12	[redacted]	[redacted]
16	[redacted]	[redacted]
20	[redacted]	[redacted]
24	[redacted]	[redacted]
28	[redacted]	[redacted]
32	[redacted]	[redacted]
36	[redacted]	[redacted]
40	[redacted]	[redacted]
44	[redacted]	[redacted]
48	[redacted]	[redacted]
52	[redacted]	[redacted]

- Label population: Time to 1st occurrence of non-fatal stroke

Table 10. Cumulative incidence probability of non-fatal stroke, label population

Months	Cumulative incidence probability	95% CI
4	[redacted]	[redacted]
8	[redacted]	[redacted]
12	[redacted]	[redacted]
16	[redacted]	[redacted]
20	[redacted]	[redacted]
24	[redacted]	[redacted]
28	[redacted]	[redacted]
32	[redacted]	[redacted]
36	[redacted]	[redacted]
40	[redacted]	[redacted]
44	[redacted]	[redacted]
48	[redacted]	[redacted]
52	[redacted]	[redacted]

- Label population: Time to 1st occurrence of non-fatal hospitalisation due to HF

Table 11. Cumulative incidence probability of hospitalization due to heart failure, label population

Months	Cumulative incidence probability	95% CI
4	[redacted]	[redacted]
8	[redacted]	[redacted]
12	[redacted]	[redacted]
16	[redacted]	[redacted]
20	[redacted]	[redacted]
24	[redacted]	[redacted]
28	[redacted]	[redacted]
32	[redacted]	[redacted]
36	[redacted]	[redacted]
40	[redacted]	[redacted]
44	[redacted]	[redacted]
48	[redacted]	[redacted]
52	[redacted]	[redacted]

- Label population: Time to first occurrence of HD or PD

Table 12. Cumulative incidence probability of dialysis, label population

Months	Cumulative incidence probability	95% CI
8	[redacted]	[redacted]
12	[redacted]	[redacted]
16	[redacted]	[redacted]
20	[redacted]	[redacted]
24	[redacted]	[redacted]
28	[redacted]	[redacted]
32	[redacted]	[redacted]
36	[redacted]	[redacted]
40	[redacted]	[redacted]
44	[redacted]	[redacted]
48	[redacted]	[redacted]
52	[redacted]	[redacted]

[redacted]

A9. For all time-to-event outcomes, please provide visual comparisons of extrapolation against an exponential distribution to assess the suitability of time invariant rate assumptions.

Please find below Kaplan-Meier curves plotted against fitted exponential distributions for CV death, non-fatal CV event and dialysis. Graphs were not presented for renal death as too few of these events were observed in the trial. These curves indicate that this distribution fits well to the FIDELIO-DKD data. Hence, the use of constant rates in the CE model is justified.

Figure 1. Kaplan-Meier curve for CV death, ITT population, finerenone arm

Figure 2. Kaplan-Meier curve for non-fatal CV event, ITT population, finerenone arm

Figure 3. Kaplan-Meier curve for dialysis, ITT population, finerenone arm

* The graph starts after 12 months as there was no dialysis in the trial before.

Figure 4. Kaplan-Meier curve for CV death, label population, finerenone arm

Figure 5. Kaplan-Meier curve for non-fatal CV event, label population, finerenone arm

Figure 6. Kaplan-Meier curve for dialysis, label population, finerenone arm

* The graph starts after 12 months as there was no dialysis in the trial before.

The mechanism of action of finerenone taken together with the cumulative evidence of the role of the mineralocorticoid receptor and its overactivation in chronic pathophysiological processes that drive progressive organ dysfunction, indicates a strong biological plausibility of a sustained treatment effect of finerenone that is unlikely to attenuate over time. This is supported by clinical data from the FIDELIO-DKD study, whereby a sustained treatment benefit on kidney and

cardiovascular clinical outcomes was demonstrated with finerenone compared to placebo over the duration of the long-term study, as well a persistent reduction in urinary albumin-to-creatinine ratio and preservation of long-term estimated glomerular filtration decline over the course of the trial.

A10. Data from an interim analysis are used in the company submission. Please advise whether additional data from the FIDELIO-DKD trial will be available during the TA process.

Bayer apologise if it was not clear in the submission documents, but the data provided for FIDELIO-DKD was the final trial data and not an interim analysis. We discussed this further on the clarification call.

Section B: Clarification on cost-effectiveness data

Literature searches

B1. Please provide details of the search filter used to identify cost-effectiveness studies outlined in the searches in Appendix G.

A standard approach for the search filter was adapted: while searching the databases, keywords for disease were combined with all of the keywords related to economic evaluations (such as cost-effectiveness, cost-benefit, incremental cost, budgets, etc). When searching HTA agencies' websites, only keywords for disease were used. No other filters (such as search by date of publication, language, etc) were applied to the search strategy, except for a standard filter for duplicate removal.

B2. Search terms for cost-effectiveness studies have been combined with terms for people with CKD in the NHS Economic Evaluation Database (EED) reported in Appendix G. (As NHS EED is a database of economic evaluations, adding cost-effectiveness search terms may have narrowed searches unnecessarily). Please

explain any checks made to ensure relevant records from NHS EED were not missed through use of additional economic search terms.

NHS EED is an extensive database and contains not only publications on economic evaluations, but also publications focused on costs and resource use. Since those data were not of interest for the purpose of this review, we decided to include terms related to cost-effectiveness only in order to identify the most relevant studies. Moreover, since Medline and Embase databases were also searched, as well as HTA agencies' websites, the probability of non-retrieval of key literature was minimised.

Cost-effectiveness data and model structure

B3. PRIORITY QUESTION: The model adopts a Markovian state-transition structure, where transition probabilities are independent of event history and do not vary over time (with the exception of a fixed age-related increase in the risk of cardiovascular (CV) events). Please justify this approach to including CV event risks within its model, versus the use of other approaches (such as specifying risk equations and/or other methods of incorporating a time-varying risk of CV events).

We are not aware from our systematic review of the literature of any existing risk equations and/or other methods of incorporating a time-varying risk of CV events specifically for patients with CKD and T2D. Using risk equations for other populations would introduce uncertainty in terms of under/over estimation of the risk of CV events in the model. Both CKD and T2D are well known risk factors for CV events. Risk equations for a general population (e.g. Framingham risk equations) would need to be adjusted based on other sources and this would increase uncertainty. Using the clinical study data was deemed more appropriate and consistent with the applied relative effect of finerenone. The FIDELIO-DKD trial was considered sufficient to demonstrate the benefit of finerenone in terms of reducing the risk and overall incidence of CV events. However, this study was not built to be the basis for developing CV risk equations. It should be noted that the main risk factor i.e. CKD progression is taken into account in the way that CV event risks are included within the model. Indeed, the risk of CV events is different in

each CKD stage, hence, it varies over time while patients are transitioning between CKD model health states.

Applying constant transition probabilities between different CKD stages, is a common approach in the modelling of CKD (26-28). The de-novo economic model submitted is unique to some extent as it allows for back transitions reflecting the fluctuations of eGFR which can be seen in clinical practice. CKD progression in most of the existing models in the literature is handled in a more limited manner and based on the assumed constant eGFR decline associated with the progressive nature of CKD.

Bayer would like to highlight that the submitted model has been validated with clinical and health economist experts from the UK and other countries. Moreover, validation of the model estimates against FIDELIO-DKD data showed consistent results in terms of both CKD progression and CV events.

B4. In company submission Figure 25, a model schematic is presented which implies that people cannot transition from more advanced CKD stages (e.g., CKD 4) to less advanced CKD stages (e.g., CKD 1/2 or 3). Please confirm that backwards transitions are possible in the model, and provide a revised model diagram showing all possible transitions. In providing the revised model diagram, please align the health states included to those captured within the transition matrices, outlined in Tables 43 and 44 in the company submission.

Bayer confirms that backwards transitions are possible in the model. The model allows for transitions between any two CKD health states based on the FIDELIO-DKD data.

We described this on page 134 of Document B:

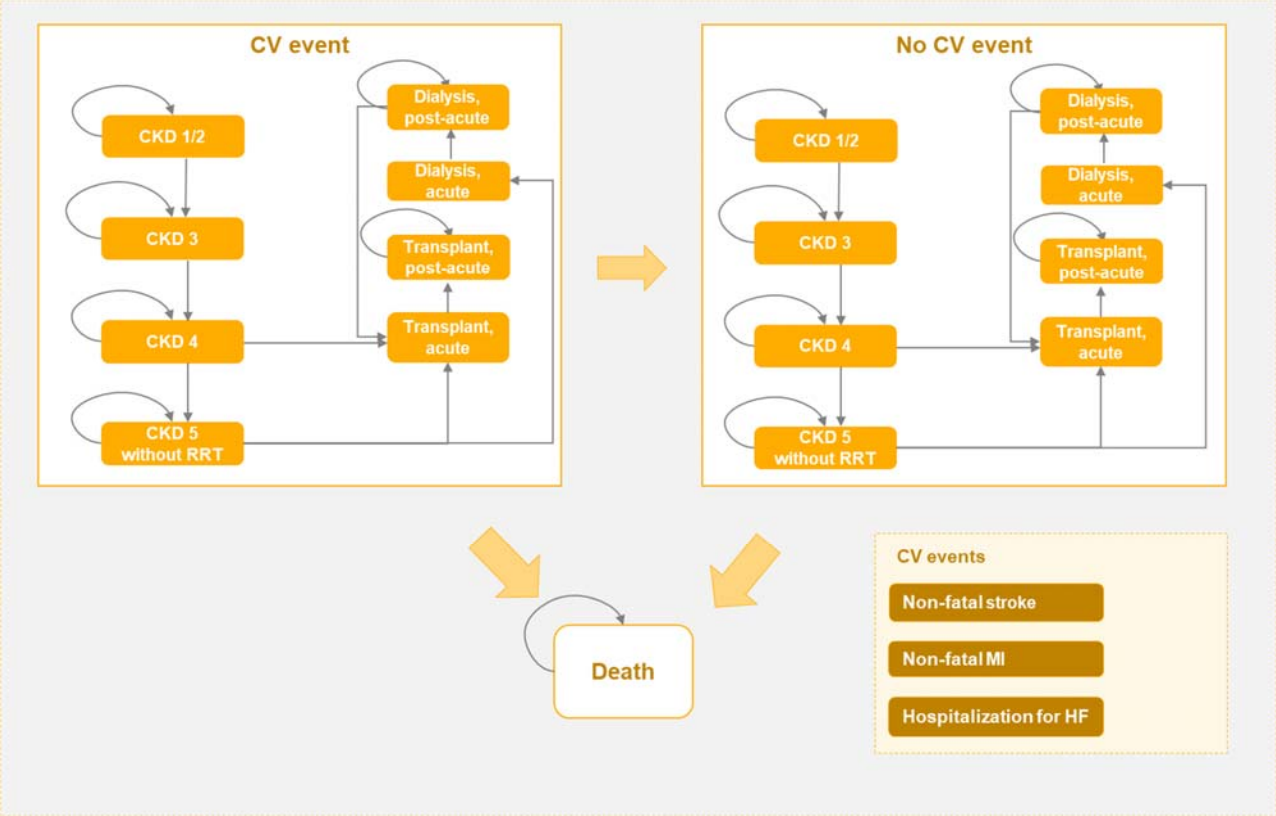
'This structure reflects the progressive character of CKD, however, technically the model allows for transitions between any two CKD health states based on observations in the FIDELIO-DKD trial'.

We apologise for not making this clear enough and agree that not all of the possible transitions are displayed on the somewhat simplified model diagram, nevertheless we believe that inclusion of the arrows from each health state to another would make the diagram unreadable.

However, we have revised the model diagram, as indeed not all states were included; Please find below the revised model with dialysis and transplant split into acute and post-acute phases. With the revised model structure diagram below it is important to mention that the model allows for transitions between any two CKD health states based on the FIDELIO-DKD data except that moving to 'dialysis post-acute' is only possible from 'dialysis acute' and moving to 'transplant post-acute' is only possible from 'transplant acute'.

As an extreme example, we confirm that in the model it is technically possible to move from CKD 5 without RRT to CKD 1/2.

Figure 7. Model diagram – details*



*The model structure reflects CKD progression. Technically the model allows for transitions between any two CKD health states based on the FIDELIO-DKD data (except that moving to dialysis post-acute is possible only from dialysis acute and moving to transplant post-acute is possible only from transplant acute)

B5. Please explain why the mean age value (65.8) in company submission Table 73 is not the same as the mean age specified earlier in the company submission (B.3.6.1, pg. 184) of 65.6?

Bayer apologies for this error and confusion.

In terms of the data presented in Table 10, page 50, 65.6 is the mean age in years in the finerenone arm of the proposed label population. The mean age for the placebo arm in this population is 65.9 years. We have used for the economic model the mean age from all patients. The mean age for the label population used in the model is 65.8 years and this is correctly reported in Table 73. Unfortunately, in the 2 other sections where 65.6 is mentioned (time horizon and below table 61) – these are typos and should read 65.8. Again, apologies for this error and any confusion caused.

B6. Please confirm the approach to half-cycle correcting costs and outcomes. More specifically, please comment on the decision to half-cycle correct the modelled discount rates.

There is no half-cycle correction for the modelled discount rates. Costs and health outcomes were discounted in line with the assumption that all costs and health outcomes are incurred in the half of each the cycle.

It should be noted that the half cycle correction is applied prior to the calculation of life years, QALYs, costs and discount rates.

The discount factor applies to half cycle adjusted values. Time within the discount function applies half-way through the cycle. The discount rate is applied to the column with data for which the half cycle correction has already been applied (i.e. all costs and health outcomes).

It should be noted that applying the discount rate at the end of the cycle instead of the middle by changing formulas in col. DC, HV in ‘BT Trace’ and col. GU, PF in ‘FIN Trace’ has a negligible impact on the model results – please see table below.

Table 13. Model results depending on the approach used to calculate discount factor

	Half-cycle discount factor	Full-cycle discount factor
Discounted incremental costs	£1,778.50	£1,768.33
Discounted incremental QALYs	0.1013	0.1008
Discounted incremental LYs	0.1245	0.1238
Cost / QALY	£17,551.51	£17,551.51*
Cost / LY	£14,285.79	£14,285.79

* Note, to demonstrate the difference in ICER, this would need to be presented to multiple decimal places

Transitions and efficacy

B7. PRIORITY QUESTION: The model includes transition probabilities based on statistical analysis of patient-level data from the FIDELIO-DKD trial.

Part A: Please confirm that transition probabilities applied in the model were estimated non-parametrically (i.e., the probabilities were estimated based on the observed numbers of people in each health state over 4-month intervals). If not, please provide further information concerning the derivation of the transition probabilities.

Yes, Bayer can confirm that the transition probabilities applied in the model were estimated non-parametrically. The probabilities were estimated based on the observed numbers of patients in each health state over 4-month intervals.

Part B: Assuming the probabilities were estimated non-parametrically, please provide further information concerning the following features of the analysis performed:

- **How missing data were handled within the analysis (for example, if somebody was lost to follow-up).**
- **How deaths were handled in the analysis.**

The analyses were performed based on the pre-specified statistical analysis plan (SAP). Deaths were included as a separate event, but finally mortality was modelled based on the UK life tables adjusted to each CKD stage based on published data. In case of missing data, the last available information was carried forward. Please find below relevant extracts from the SAP.

To document the CKD status transitions, several definitions were needed:

- A 4-month cycle was applied, starting with study day 1 to study day 120 for cycle 1, study day 121 to 240 for cycle 2 and so on. For each cycle, a transition status was assigned to a subject, always defined as “subject CKD status at cycle start → subject status at cycle end”.
- In each cycle, the subject could have the following status:
    - CKD 1/2, CKD 3, CKD 4 or CKD 5, based on KDIGO definition (LOCF approach if no eGFR assessment),
    - Dialysis defined as initiation or requirement of chronic haemodialysis (HD) or peritoneal dialysis (PD) which is necessary for at least 30 days,
    - Transplant related to kidney transplant only,
    - Death, the following deaths are considered: CV death, renal death and other death (as defined in the FIDELIO protocol).
- Subject CKD status at cycle start, or at cycle end, would be the last CKD status known:
    - If at the start of the cycle a patient was in CKD 2, then transitioned to CKD 3, and at the end of the cycle was in CKD 4, this should be taken into consideration as a transition from CKD 2 to CKD 4.

Table 14 presents how transitions were presented. Of note the column labels have the following definitions:

- Number of subjects with transition was defined as number of patients who transit from a given CKD stage to another CKD stage (or death) between start and end of the given cycle.

- Number of subjects was defined as the number of patients for whom a transition could be evaluated for the given cycle, from the given status at cycle start.
- Number of dropouts should include the number of subjects who discontinued the study follow up during the respective cycle. This could be either due to early termination as withdrawal of consent or lost to follow up, or due to regular study close out within the respective cycle. Subject death was not considered as a drop out, as subjects are presented for the transition to fatal events.
- Transition probability was calculated as the number of subjects with transition / number of subjects in cycle excluding the number of dropouts in the cycle.

Of note the transitions to other death were not taken for the model from this analysis. We include the general mortality as for the UK life tables and increased mortality due to each CKD stage.

Table 14. Transitions probabilities by CKD stage per cycle (ITT analysis set)

Transition	Cycle 1 (0 month - 4 months)				Cycle 2 (4 months - 8 months)				Etc.
	Nb subjects with transition	Nb of subjects in cycle	Nb dropouts in cycle	Transition probability	Nb subjects with transition	Nb of subjects in cycle	Nb dropouts in cycle	Transition probability	
CKD 1/2 → CKD 1/2									
CKD 1/2 → CKD 3									
CKD 1/2 → CKD 4									
CKD 1/2 → CKD 5									
CKD 1/2 → Dialysis									
CKD 1/2 → Transplant									
CKD 1/2 → CV death									
CKD 1/2 → Renal death									
CKD 1/2 → Other death									
CKD 3 → CKD 1/2									
CKD 3 → CKD 3									
CKD 3 → CKD 4									
CKD 3 → CKD 5									
CKD 3 → Dialysis									
CKD 3 → Transplant									
CKD 3 → CV death									

Transition	Cycle 1 (0 month - 4 months)				Cycle 2 (4 months - 8 months)				Etc.
	Nb subjects with transition	Nb of subjects in cycle	Nb dropouts in cycle	Transition probability	Nb subjects with transition	Nb of subjects in cycle	Nb dropouts in cycle	Transition probability	
CKD 3 → Renal death									
CKD 3 → Other death									
CKD 4 → CKD 1/2									
CKD 4 → CKD 3									
CKD 4 → CKD 4									
CKD 4 → CKD 5									
CKD 4 → Dialysis									
CKD 4 → Transplant									
CKD 4 → CV death									
CKD 4 → Renal death									
CKD 4 → Other death									
CKD 5 → CKD 1/2									
CKD 5 → CKD 3									
CKD 5 → CKD 4									
CKD 5 → CKD 5									
CKD 5 → Dialysis									
CKD 5 → Transplant									
CKD 5 → CV death									
CKD 5 → Renal death									
CKD 5→ Other death									
Dialysis → CKD 1/2									
Dialysis → CKD 3									
Dialysis → CKD 4									
Dialysis → CKD 5									
Dialysis → Dialysis									
Dialysis → Transplant									
Dialysis → CV death									
Dialysis → Renal death									
Dialysis → Other death									
Transplant → CKD 1/2									
Transplant → CKD 3									
Transplant → CKD 4									
Transplant → CKD 5									
Transplant → Dialysis									

Transition	Cycle 1 (0 month - 4 months)				Cycle 2 (4 months - 8 months)				Etc.
	Nb subjects with transition	Nb of subjects in cycle	Nb dropouts in cycle	Transition probability	Nb subjects with transition	Nb of subjects in cycle	Nb dropouts in cycle	Transition probability	
Transplant → Transplant									
Transplant → CV death									
Transplant → Renal death									
Transplant → Other death									

Note – the probability to move to post-acute health states is 100%, by definition.

Part C: Please comment on the differences in transition probabilities seen between the two treatment arms, which for some health states implies a negative treatment effect associated with finerenone (for example, the risk of progressing to dialysis from CKD5 for people taking background therapy (BT) patients is [redacted] versus [redacted] for people taking finerenone).

CKD progression is complex when all eGFR fluctuations are to be modelled but we are satisfied that the submitted model reflects clinical practice. It is important that CKD progression is considered based on all possible transitions, not selectively. For example, looking at all transitions from CKD5 it is apparent that more people taking finerenone are moving to less severe CKD stages in comparison to BT patients ([redacted]% vs [redacted]%). At the same time, a lower number of patients randomised to finerenone progress from CKD4 to CKD5 ([redacted]% vs [redacted]%). Moreover, there are more patients on BT starting dialysis in earlier CKD stages ([redacted]% vs [redacted]%). The model results are consistent with those from FIDELIO-DKD and confirm that finerenone delays CKD progression.

B8. The model includes a number of hazard ratios (HRs) to describe the effect of finerenone on the risk of 'health events', such as a subsequent cardiovascular event. Please comment on the directional effects seen in the estimation of some of these HRs, and provide context to whether or not the effects seen are likely to be a 'true' effect or potentially a consequence of the trial design, duration of follow-up, or other reason unrelated to the 'true' effect of finerenone. In response to this question, please provide any additional supportive evidence from the FIDELIO-DKD trial where relevant (such as number of events recorded, plots of event-free survival, etc.)

Bayer have interpreted that this question relates to the HRs presented in Table 53 of Document B and replicated below.

Table 15 (Table 53 in Document B) HRs for health events for FIN + BT

Outcome	Label population
Subsequent CV event	[redacted]
Hyperkalaemia not leading to hospitalisation	[redacted]
Hyperkalaemia leading to hospitalisation	[redacted]
Sustained decrease in eGFR ≥40% from baseline (over at least 4 weeks)	[redacted]
New onset of atrial fibrillation / atrial flutter	[redacted]
Abbreviations: BT - Background therapy; CV - Cardiovascular; eGFR - Estimated glomerular filtration rate; FIN - Finerenone; HR - Hazard ratio;	

We will answer your question taking each health event in turn.

Subsequent CV event

Having one CV event increases the risk of an individual having a subsequent CV event in clinical practice. Finerenone reduced the risk of a first CV event with a HR of 0.87 in the proposed label population (see Table 52 in Document B).It is therefore to be expected that if finerenone reduces the risk of a first CV event that it will follow that there is a reduction in subsequent CV events. This is supported by the HR reported in the table above. In terms of number of events, there were [redacted] ([redacted]%), (n=2437) second CV events after a first non-fatal CV event in the finerenone arm vs [redacted] ([redacted]%), (n=2423) in the placebo arm.

Hyperkalaemia

The risk of occurrence of hyperkalaemia in patients with CKD and T2D is naturally increased due to decreased potassium excretion by the kidney (29). According to clinical recommendations, hyperkalaemia risk can be managed by routine clinical monitoring (30). Due to the mode of action of finerenone, in the FIDELIO-DKD study finerenone led to a mean increase in serum potassium of 0.2 mmol/l, but this increase remained stable from Month 4 onwards to the end of the study (5). This increase was on a background of optimised ACE/ARB dosing which due to their effects of the renin-angiotensin-aldosterone system can also lead to elevated serum potassium levels. Whilst hyperkalaemia was increased in FIDELIO, the clinical impact of these events, as assessed by death, hospitalisation or permanent treatment discontinuation due to hyperkalaemia, was minimal. In terms of number of events of hyperkalaemia leading to hospitalisation, there were 47 (1.9%), (n=2437) in the finerenone arm vs 13 (0.5%), (n=2423) in the placebo arm.

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

The primary composite endpoint included 'a sustained decrease of eGFR ≥40% from baseline over at least 4 weeks' which is an established surrogate that predicts progression to kidney failure. Patients with an eGFR below 60 ml/min/1.73 m^2 who have a decline in the eGFR of ≥40% from baseline have a ten-fold higher risk of kidney failure over two years than those with a stable eGFR (31).

Finerenone demonstrated a significant reduction in this component of the primary efficacy endpoint. The reduction in decline of eGFR observed with finerenone demonstrates its efficacy in preventing progression of kidney disease towards the devastating and costly consequence of kidney failure.

New onset of atrial fibrillation/ flutter

Chronic kidney disease (CKD) and type 2 diabetes (T2D) are associated with increased risk of atrial fibrillation, and also higher morbidity and mortality associated with atrial fibrillation compared with patients without diabetes. Preclinical evidence suggests that aldosterone upregulation and

mineralocorticoid receptor overactivation are associated with structural cardiac remodeling and may also be involved in the pathophysiology of atrial fibrillation. In preclinical models, finerenone reduced mineralocorticoid receptor–mediated myocardial remodeling, including prevention of left atrial dilatation and left atrial fibrosis (32)

Effect on new-onset atrial fibrillation or flutter (AFF) was evaluated as a pre-specified outcome in FIDELIO-DKD adjudicated by an independent cardiologist committee. The results in the full analysis set (FAS) have recently been published (33) with the conclusion that in patients with CKD and T2D, finerenone reduced the risk of new-onset AFF.

In summary, all of the directional effects seen in the reported HRs are expected to be 'true' effects of finerenone based on its mechanism of action.

B9. The company submission explains that *"40.30% of FIN +BT patients discontinued treatment over the course of the study"* (Document B, Section 3.3.8). Please provide a figure illustrating the pattern of premature permanent discontinuation of therapy over time. Ideally, this would be presented as a Kaplan-Meier estimate, with the event defined as permanent discontinuation of treatment for any reason (including progression or death).

Please find below the Kaplan-Meier estimate, with the event defined as permanent discontinuation of treatment for any reason. These estimates were used in the model and do not include progression or death as they were modelled independently.

Table 16. Kaplan-Meier estimate for premature finerenone discontinuation

Time point	KM estimate
4 months	[redacted]
8 months	[redacted]
12 months	[redacted]
16 months	[redacted]
20 months	[redacted]
24 months	[redacted]
28 months	[redacted]
32 months	[redacted]
36 months	[redacted]
40 months	[redacted]
44 months	[redacted]
48 months	[redacted]

B10. The 4-monthly probabilities of CV and renal deaths are provided in Table 49 of the company submission. The ERG has some concerns with the values applied within the model, and their generalisability to clinical practice. Please provide sensitivity analyses for these estimates, based on the following:

Part A: The risk of CV/renal death is likely linked with CKD progression. In a scenario analysis, please edit the probabilities to ensure risks of CV/renal death by CKD stage are the same or higher for increasing disease progression (i.e., ensure that the risk of CV or renal death for any CKD stage is either equal or higher as CKD stage increases).

Please find below the assumptions and results generated for this scenario.

Table 17. Assumption for scenario analysis - B10 Part A

Event	CKD1/2	CKD3	CKD4	CKD 5 w/o RRT	Dialysis (acute)	Dialysis (post-acute)"	Kidney Transplant (acute)	Kidney Transplant (post-acute)
Base case								
CV death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Event	CKD1/2	CKD3	CKD4	CKD 5 w/o RRT	Dialysis (acute)	Dialysis (post-acute)"	Kidney Transplant (acute)	Kidney Transplant (post-acute)
Scenario 1								
CV death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 18. Results for scenario analysis on B10 Part A

Model input	Incremental costs	Incremental QALY	ICER
Base case	£1,779	0.10	£17,552 per QALY gained
Scenario 1	£1,758	0.10	£17,394 per QALY gained

Bayer note that this scenario analysis does not have a significant impact on the base case ICER, leading to a small improvement in favour of finerenone.

Part B: The definition of renal death in the FIDELO-DKD trial means that renal death can only occur in the 'CKD 5 without RRT' state ([redacted] per cycle). Given that this value is relatively small, affecting only one health state, and is linked directly to the definition of renal death specified in the FIDELO-DKD trial (which may not be reflective of the definition of renal death typically used in clinical practice); please disable the probability of renal death from the model entirely within a scenario analysis.

Please find below the assumptions and results generated for this scenario.

Table 19. Assumption for scenario analysis on B10 Part B

	CKD1/2	CKD3	CKD4	CKD 5 w/o RRT	Dialysis (acute)	"Dialysis	CKD1/2	CKD3
Base case								
Renal death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1								
Renal death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 20. Results for scenario analysis on B10 Part B

Model input	Incremental costs	Incremental QALY	ICER
Base case	£1,779	0.10	£17,552 per QALY gained
Scenario 2	£1,778	0.10	£17,550 per QALY gained

Bayer note that this scenario analysis does not have a significant impact on the base case ICER as anticipated.

Please provide comment on the requested scenarios, (for example, whether or not the points raised above are reasonable).

The requested scenarios are reasonable and show that the base case model is conservative. In the base case scenario, our intention was to replicate the trial results as far as possible.

B11. Based on the information presented in the clinical effectiveness section of the company submission and in Appendix J, it is unclear how the transition probabilities specific to progression to dialysis were obtained given the likely small number of people that progressed to dialysis across both arms from each health state. Please explain how these were derived. If possible, please provide specific number of people who progressed to dialysis by treatment arm and origin health state within the trial.

The transition probabilities for dialysis were derived in the same manner as for movements between other CKD stages. Bayer include a detailed description in the response to question B7B. The number of people who progressed to dialysis was [redacted] in the finerenone arm and [redacted] in the placebo arm. Please see below the number of patients who started dialysis during the FIDELIO-DKD study by CKD stage in the previous 4-month cycle (Table 21).

Table 21 Total number of patients who started dialysis during the study by CKD stage in the previous 4-month cycle.

Transition to dialysis from:	Finerenone arm	Placebo arm
CKD 1/2	[redacted]	[redacted]
CKD 3	[redacted]	[redacted]
CKD 4	[redacted]	[redacted]
CKD 5	[redacted]	[redacted]
Transplant	[redacted]	[redacted]

The incidence of dialysis was not analysed by the 'origin' health state within the trial but instead on the health state in the previous 4-month cycle.

B12. In a sensitivity analysis, the possibility of disabling transitions to dialysis by 1 year is explored, aligning with the time-to-dialysis data captured in the FIDELO-DKD trial (see Appendix J, Figures J8 and J9). Supporting text is also presented which states: *"…To mitigate these discrepancies and better reflect the FIDELIO-DKD results, an additional feature was implemented in the model. With this option, the transition to dialysis was not possible during the initial cycles, for a total period of up to one year."* (company submission Appendix J). However, it is unclear why the transitions were still permitted in the first year given that the sensitivity analysis appears to better reflect the experience of the FIDELO-DKD population. Please elaborate on the decision to not omit transitions to dialysis within the first year.

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.

B13. In company submission Section B.3.3.6, it states: *"To avoid double counting, the proportions of deaths that are attributable to cardiovascular disease and renal death is removed from this background mortality using UK data from the Office for National Statistics".* However, renal deaths were only possible to capture for people residing in the 'CKD 5 w/o RRT' state. Please explain how this combination of approaches to capture mortality appropriately reflects renal deaths. As a joint consequence of these two aspects of the model, renal deaths may be underrepresented by the model.

In the model apart from background mortality, CV and renal deaths are considered. We removed the proportions of deaths that are attributable to cardiovascular disease and renal death to avoid double counting. We believe this is a standard approach and without it we would overestimate the deaths.

According to the trial protocol, the death was considered as renal only if a patient dies and renal replacement therapy (RRT) has not been started although it is clinically indicated. That is why it was assumed in the model that renal deaths are possible only for people residing in the 'CKD 5 w/o RRT' state. Taken alone, Bayer could see how this could underestimate renal death. Further, this definition of renal death may differ from the one included in the Office for National Statistics. We believe, however, that this possible inconsistency in definition and related under-representation of the renal deaths by the model is negligible.

It is also important to mention that in the model, we include the increased mortality due to CKD stage as well as related to the RRT. These deaths were attributed to all-cause mortality. Finally, the approach for addressing mortality in the model was discussed and validated with the UK clinical experts.

Please find below 2 additional scenarios which are run to demonstrate the credibility of our assumptions.

Scenario 1: The renal deaths were not removed from the general mortality

Scenario 2: Without inclusion of renal deaths at all i.e., the risk of renal death = 0 and renal deaths were not removed from the general mortality

Table 22. Results for scenario analysis

Model input	Incremental costs	Incremental QALY	ICER
Base case	£1,779	0.10	£17,552 per QALY gained
Scenario 1	£1,780	0.10	£17,600 per QALY gained
Scenario 2	£1,780	0.10	£17,598 per QALY gained

In conclusion, if we change the how renal death is managed within the model, this has a minimal impact on the ICER.

Health-related quality of life

B14. Please confirm if the following features of the EQ-5D analysis performed on the FIDELIO-DKD trial data are correct.

Part A: The utility for 'CKD 1/2 without CV event' ([redacted], company submission Table 62) is equivalent to the baseline utility pooled by treatment arm ([redacted], company submission Table 56). However, at baseline in FIDELIO-DKD, [redacted] of people were CKD 3 and the remaining [redacted] of people were CKD 4 (company submission Table 73).

Bayer apologies for not making this clearer in the submission documents. The baseline patient distribution across CKD states as reported in Table 73 of Document B reflects the proposed label population with the split between stages 3 and 4 derived from the trial population. However, the utilities included in the model were derived from the multivariate analysis based on the whole trial population (FAS), which included approximately 11.6% of patients with stage 1 or 2 (see Table 10, on page 50 of Document B). 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. Patients in stage 1 and 2 without CV events were considered as a reference in the performed analysis.

In both tables (Table 62 and Table 56), utility represents the CKD 1/2 patients. The utility presented in the Table 56 was pooled by treatment arm but only for patients CKD1/2. The values in both tables should be equivalent as both concern the same patients. The utilities for patients CKD 3 and 4 were obtained by applying relevant decrements estimated for these health states in the multivariate analysis.

Part B: The decrements associated with CKD stages 3, 4, and 5 (as reported in company submission Table 57) were applied to the baseline utility value of [redacted] to obtain utility values for the other health states.

Bayer confirm that this is correct.

Part C: Please comment on the parameter estimate of +0.001 for "CKD stage based on Fidelio=3 vs 1/2" (i.e., an increase in utility when people progress from CKD 1/2 to CKD 3).

Bayer cannot explain this apparent anomaly in the data. The FIDELIO-DKD trial was not designed nor powered to make conclusions based on quality of life, but as the EQ-5D questionnaires were collected in the study, this allows for analyses to be conducted. It was considered that NICE would have a preference for Bayer to use the utilities which originated directly from the clinical trial in the cost-effectiveness model. However, to account for the limitations of the EQ-5D data collected in the FIDELIO-DKD study, it was decided to use literature based utility values in a scenario analysis. The impact of using the literature based utilities, derived from a SLR, was to improve the ICER from £17,552 in the base case to £14,966/QALY gained.

Part D: Please confirm the selection method for the variables included in the multivariate analysis.

The selection of the variables was made prior to any results being available from FIDELIO-DKD and pre-specified in the HEOR SAP. Ultimately more variables were considered in the multivariate analysis than were needed for the CE model. Please find information about the selection of health events to be considered in the model in Table 40 of Document B (page 141).

We included in the multivariate analysis all variables for which a utility decrement was potentially required in the cost-effectiveness model i.e.

- CKD stage at a given visit (including RRT)
- Any prior MI
- Any prior stroke
- Any prior Hospitalization for HF
- Cardiovascular Hospitalisation (other than HF hospitalisation) in the 4 months before a given visit
- Non-CV hospitalisations in the 4 months before a given visit
- New onset of Heart Failure in the 4 months before a given visit
- New onset of Atrial fibrillation/Atrial flutter in the 4 months before a given visit
- Ear and labyrinth disorders
- Eye disorders
- Flu syndrome in the 4 months before a given visit
- Infections and infestations in the 4 months before a given visit
- Hyperkalaemia or blood potassium increased in the 4 months before a given visit

and some additional ones, which were considered to be important to avoid bias as much as possible (i.e., gender, age, baseline EQ5D).

B15. PRIORITY QUESTION: The utility values reported in company submission Table 62 are misaligned with some values presented in the submitted cost-effectiveness model. For example, for 'CKD 3 without CV event', the company submission states a value of [redacted] is used, yet the model applies a value of [redacted]. Furthermore, similar discrepancies with some of the reported confidence interval (CI) limits have been identified. For example, the upper limits for the first three rows in company submission Table 62 is shown as [redacted], yet the model includes three different values for these upper limits (see 'DSA – Inputs', range I182:I184). Please confirm which utility values are correct, and update the model and/or relevant tables in the company submission accordingly.

Bayer apologies but there was a mistake in terms of the utility reported in the dossier. It affects the following tables (Table 62 and Table 57 in the Document B). Bayer confirms that all calculations and results are correct, as the mistake was only present in Document B and not in the CE model. Please see details in the table below (Table 23) and revised Tables 57 and 62.

We considered, two different multivariate analyses for utilities depending on the type of hyperkalaemia included. In one of them only the hyperkalaemia leading to hospitalization was analysed whereas all hyperkalaemia cases were included in the other. Results of the first analysis were presented in the submission. However, the obtained disutility due to hyperkalaemia leading to hospitalization was lower than the result for hyperkalaemia in general. Hence we decided to include the regression considering hyperkalaemia in general in the cost-effectiveness model. As finerenone is associated with a higher risk of hyperkalaemia, taking into account the higher disutility, the results are conservative.

We believe that the counter-intuitive results for utility decrements between hyperkalaemia in general and hyperkalaemia leading to hospitalization is caused by the low number of the latter observed in FIDELIO-DKD.

Table 23 Utilities values in the CE model and dossier – comparison

Parameter	Values in dossier	Values in model
CKD3 without CV event	[redacted]	[redacted]
CKD4 without CV event	[redacted]	[redacted]
CKD 5 w/o RRT, without CV event	[redacted]	[redacted]
Dialysis (acute), without CV event	[redacted]	[redacted]
Dialysis (post-acute), without CV event	[redacted]	[redacted]
Kidney Transplant (acute), without CV event	[redacted]	[redacted]
Kidney Transplant (post-acute), without CV event	[redacted]	[redacted]
MI (acute and post-acute)	[redacted]	[redacted]
Stroke (acute and post-acute)	[redacted]	[redacted]
Hospitalization for HF (acute and post-acute)	[redacted]	[redacted]
Hyperkalaemia leading to hospitalisation	[redacted]	[redacted]
Hyperkalaemia not leading to hospitalisation	[redacted]	[redacted]
Sustained decrease in eGFR ≥ 40% from baseline	[redacted]	[redacted]
Acute new onset of atrial fibrillation/ atrial flutter	[redacted]	[redacted]

*Leading to hospitalization only

Table 24 Parameter estimates of the multilevel mixed repeated measurements model for EQ-5D total score [Document B Table 57)

Effect	Estimate	Standard Error	t Value	Pr > |t|
Intercept	[redacted]	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]	[redacted]
Age - mean[Age]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline EQ-5D - mean[Baseline EQ-5D]	[redacted]	[redacted]	[redacted]	[redacted]
CKD stage based on Fidelio=3vs1/2	[redacted]	[redacted]	[redacted]	[redacted]
CKD stage based on Fidelio=4vs1/2	[redacted]	[redacted]	[redacted]	[redacted]
CKD stage based on Fidelio=5vs1/2	[redacted]	[redacted]	[redacted]	[redacted]
Any prior MI=yes	[redacted]	[redacted]	[redacted]	[redacted]
Any prior stroke=yes	[redacted]	[redacted]	[redacted]	[redacted]
Any prior Hospitalization for HF=yes	[redacted]	[redacted]	[redacted]	[redacted]
Acute new onset of Atrial fibrillation/ Atrial flutter (in the last 4 months)=yes	[redacted]	[redacted]	[redacted]	[redacted]
Acute Hyperkalemia or blood potassium increased (in the last 4 months)=yes	[redacted]	[redacted]	[redacted]	[redacted]
Acute dialysis (in the last 4 months)=yes	[redacted]	[redacted]	[redacted]	[redacted]

Effect	Estimate	Standard Error	t Value	Pr > |t|
Post dialysis (in the previous months excluding the last 4)=yes	[redacted]	[redacted]	[redacted]	[redacted]
Acute transplant (in the last 4 months)=yes	[redacted]	[redacted]	[redacted]	[redacted]
Post transplant (in the previous months excluding the last 4)=yes	[redacted]	[redacted]	[redacted]	[redacted]
Sustained eGFR decrease <=40% =yes	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: CKD - Chronic kidney disease; eGFR - Estimated glomerular filtration rate; EQ-5D - EuroQol 5 dimensions; HF - Heart failure; MI - Myocardial infarction;				

Table 25 Summary of utility values for cost-effectiveness analysis [Document B Table 62)

Health state / Health event	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
Health states utilities				
CKD 1/2 without CV event	[redacted]	[redacted]	**Error! Reference source not found.** (page 58 and 59)	EQ-5D-5L utility directly from FIDELIO-DKD
CKD 3 without CV event	[redacted]	[redacted]		Multivariate analyses on EQ-5D-5L based on FIDELIO-DKD
CKD 4 without CV event	[redacted]	[redacted]		
CKD 5 w/o RRT without CV event	[redacted]	[redacted]		
Dialysis without CV event	[redacted]	[redacted]		
Post-dialysis without CV event	[redacted]	[redacted]		
Transplant without CV event	[redacted]	[redacted]		
Post-transplant without CV event	[redacted]	[redacted]		
Utility decrement due to event				
MI, acute	[redacted]	[redacted]	**Error! Reference source not found.** (page 58 and 59)	Multivariate analyses on EQ-5D-5L based on FIDELIO-DKD
MI, post-acute	[redacted]	[redacted]		
Stroke, acute	[redacted]	[redacted]		
Stroke, post-acute	[redacted]	[redacted]		
Hospitalisation for HF, acute	[redacted]	[redacted]		
Hospitalisation for HF, post-acute	[redacted]	[redacted]		
New onset of Atrial fibrillation/ Atrial flutter*	[redacted]	[redacted]		No disutility assumed.
Hyperkalaemia leading to hospitalisation**	[redacted]	[redacted]		

Health state / Health event	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
Hyperkalaemia not leading to hospitalisation**	[redacted]	[redacted]		Multivariate analyses on EQ-5D-5L based on FIDELIO-DKD
Sustained decrease in eGFR >=40% from baseline (over at least 4 weeks)	[redacted]	[redacted]		
Subsequent CV event	[redacted]	[redacted]		Weighted average of MI, stroke and HF hospitalization from multivariate analysis with weights based on CV event distribution from the FIDELIO-DKD
Abbreviations: CKD – Chronic kidney disease; CV – Cardiovascular; MI – Myocardial infarction; HF – Heart failure; eGFR – Estimated glomerular filtration rate				

* The new onset of atrial fibrillation/atrial flutter (in the last 4 months) was shown to increase patients QoL by 0.009. This was considered unrealistic and the value of 0 was used in the model.
**The disutility due to hyperkalaemia were based on all hyperkalaemia events in the trial

Indeed, there are small differences in the confidence intervals included in the PSA and DSA. The reason is that SD was needed for all parameters to be randomized in the PSA as it is implemented in the model, whereas it was not always available from the original source. Hence, some calculations were needed between standard deviations, standard errors, and confidence intervals. These calculations resulted in some inconsistences most likely related to rounding. We believe that these inconsistences have negligible impact on the model results.

B16. The company submission 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."* (Document B, Section 3.5.2). Please confirm if the costs of antihypertensive drugs are double counted within the model as part of the health state costs, given the inclusion of BT costs, including the use of ACE inhibitors, beta blockers, ARBs, etc. Some adjustments were made to this cost, but it is unclear which elements comprise the final per-cycle cost of £538 which is applied within the model. Please also comment on the

costs for other health states (e.g., CKD 5) which also notes the use of antihypertensive medications.

The costs for CKD stage 4 were derived from TA358 (34) and inflated to 2020 UK prices. TA358 did not provide a breakdown of the components of this cost. However, as antihypertensive drugs are available as generic medicines, whilst there may be a small degree of double counting here, this would be minimal and would not be anticipated to have more than a negligible impact on the ICER. The same applies to the costing of the CKD 5 health state.

The step-by-step method to justify the £538 cost per cycle is included in the response to QB22 (please see the details in Table 27).

B17. In the multivariate analysis, "Acute new onset of atrial fibrillation/ atrial flutter (in the last 4 months)" is included in the table of parameter estimates (Table 57) but the value calculated from this analysis (0.009) was deemed unsuitable. Instead, a value of zero is used in the model. Please confirm whether this variable was excluded from the multivariate analysis to calculate the parameter estimates for the other variables.

Bayer can confirm that this variable was not excluded from the multivariate analysis to calculate the parameter estimates for the other variables. Here, we run the multivariate analysis with "Acute new onset of atrial fibrillation/ atrial flutter (in the last 4 months)" excluded to see if it has a significant impact on the results. We find that running this analysis generates the same parameter estimates for the other variables that are used in the model. Please see the values presented below.

Table 26 Parameter estimates of the multilevel mixed repeated measurements models for EQ-5D total score with acute and post CV events combined

Parameter	Analysis with "Acute new onset of AF" included	Analysis with "Acute new onset of AF" excluded
CKD3	[redacted]	[redacted]
CKD4	[redacted]	[redacted]
CKD 5 w/o RRT	[redacted]	[redacted]
Dialysis (acute)	[redacted]	[redacted]
"Dialysis	[redacted]	[redacted]
(post-acute)"	[redacted]	[redacted]
Kidney Transplant (acute)	[redacted]	[redacted]
Kidney Transplant (post-acute)	[redacted]	[redacted]
MI	[redacted]	[redacted]
Stroke	[redacted]	[redacted]
Hospitalization for HF	[redacted]	[redacted]
Hyperkalaemia	[redacted]	[redacted]
Sustained decrease in eGFR ≥ 40% from baseline	[redacted]	[redacted]
Acute new onset of atrial fibrillation/ atrial flutter	[redacted]	[redacted]

B18. The company submission's attempts to age-adjust utility values using published norms by Janssen *et al.*, (2014). However, a more specific set of population norms for the UK could be derived from an alternative study by Ara & Brazier, (2010), which provides the following equation for utility in the UK general population:

- **Utility = 0.9508566 + 0.0212126*male - 0.0002587*age - 0.0000332*age^2**

In this equation, 'male' is an indicator variable taking a value of 1 for males, and 0 for females. 'Age' is a continuous variable, based on the person's age. Using this equation, it is possible to consider a gradual loss of utility over time, which is not limited to the categories presented by Janssen *et al.*

Part A: Please update the application of age-adjusted utility values to align with this alternative equation.

We believe that the use of 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. We have however considered an alternative approach following your suggestion in our response to Part B below. We consider this to be a relevant way of applying age adjustment to utilities not limited to the categories presented by Janssen et al.

Part B: Given that the regression analysis included a covariate for age (company submission Table 57), please comment on the decision not to apply this age related decrement (which would be more specific to a CKD population) within its submitted model.

Please note that to inform the utility of CKD1/2 health state the mean utility value at baseline for CKD1/2 patients in both arms of the FIDELIO-DKD trial was used. This value already accounts for the average age of the study participants, therefore a covariate for age was not considered in the model.

Please see below how the inclusion of an age-related utility decrement from regression analysis (-0.001) instead of utility age-adjustment proposed by Janssen et al. (2014) impacts the model results. As can be seen from the results, this amendment has a minimal impact on the ICER.

	Utility age-adjustment by Janssen et al. (2014)	**Age-related utility decrement based on FIDELIO-DKD**
Incremental QALY, undiscounted	0.147	0.151
Incremental QALY, discounted	0.101	0.104
Cost / QALY, undiscounted	£13,893	£13,500
Cost / QALY, discounted	£17,552	£17,115

Costs and resource use

B19. PRIORITY QUESTION: Please confirm the pack size(s) in which finerenone is expected to be made available, along with the relevant costings. In addition, please explain how regularly treatment is anticipated to be dispensed in NHS practice if finerenone is made available via routine commissioning.

Finerenone will be available as 10mg tablets and 20mg tablets in the following pack sizes. The price is yet to be determined, but the indicative NHS list price is £1.84 per tablet.

Strength and form	Pack size	Indicative NHS list price per pack
10mg tablets	28	£51.52
20mg tablets	28	£51.52

If finerenone is made available via routine commissioning, it is expected 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.

B20. In the submitted model, the distribution of background therapy is independent of whether or not people receive finerenone, and limited information is presented concerning "commonly used" therapies.

> **Part A: Please explain the basis for this assumption made within the model, and if appropriate consider presenting a scenario analysis wherein arm-specific background therapy distributions are instead reflected within the model.**

The FIDELIO-DKD study protocol specified that all patients should be treated with the individual maximum tolerated labelled dose of either an ACEI or an ARB. It also specified that

antihypertensive therapy for renal and CVD protection will be administered according to local guidelines. Further, that advice was given to follow the recommendations of local guidelines for the management of CVD and CKD, the use of statins, anti-platelets and beta-blockers, and guidelines for glycaemic control. These are the standard therapies used in patients with T2D and CKD (please see Figure 1 in Document B – "Current management pathway for patients with CKD and T2D (adapted from NICE pathways: management of chronic kidney disease)).

Bayer considered that it was appropriate to consider the pooled background therapy distribution as the study was randomized and the distribution of medications was well balanced across the study arms.

To account for change in medication throughout the study, it was decided to use the pooled data from the whole study follow-up in the model. As this was background therapy and unlikely to be influenced by the use of finerenone, in that it would not have a significant impact on blood pressure, nor cholesterol levels or glycaemia, Bayer considers this to be a reasonable assumption.

We could consider arm specific therapy distributions, but this would not impact the efficacy findings as these come directly from the trial, but just the cost. As most of the medications are available in generic form, Bayer considers this would make a negligible impact on the ICER.

Part B: Which source(s) were used to determine the most commonly used background therapies for people with CKD, and please explain what defines "commonly used" in this context. (B.3.5.1, pg. 173)

The background therapies used in the model (drug classes) and proportion of patients prescribed these were sourced from the FIDELIO-DKD trial as described in section 3.5.1 of Document B. As described in this section of the submission, a representative drug was chosen for each class of drug which was the most common drug from a given class used in the FIDELIO-DKD trial. As discussed in response to question B6, Bayer consider that the FIDELIO-DKD trial and background therapies used, are representative of the UK population.

B21. In the company submission, section B.3.5.2, the approach taken to inform resource use estimates within the model is described. Please specify the literature source used to determine the 15% additional reference costs and how these were calculated.

In the model the dialysis costs were based on the CKD CG (draft version from March 2021) in which the following statement was noted: *'an additional 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'*. We did not apply a further increase in costs. Please also see the details in Table 28 in the response to QB22 below.

B22. Please detail how the following costs, reported in company submission Table 65, were derived:

- **CKD 1/2: £64**
- **CKD 3: £538**
- **CKD 4: £1,259**
- **CKD 5 w/o RRT: £1,964**
- **Haemodialysis (acute and post-acute): £8,927**
- **Peritoneal dialysis (acute and post-acute): £8,756**
- **Transplant, acute: £16,457**
- **Transplant, post-acute: £2,777**

More specifically, please specify which source unit costs were identified, which data/assumptions were made in terms of resource use, how costs were converted into a cost per 4 months, and how inflation indices were used (where applicable).

Please find below a table with the costs explained.

CKD management costs for model health states CKD 1 to CKD 5 without RRT were based on the Tolvaptan NICE appraisal for treating autosomal dominant polycystic kidney disease (APCKD) (TA358) (34). CKD management costs were updated to 2020 using the NHS cost inflation index from the Personal Social Services Research Unit (35).

Table 27. Cost for CKD stages

Cost in the dossier	Source value [Tolvaptan NICE appraisal (TA358)] – annual costs	Inflation applied at 112.46%	Cost per model cycle (4 months)*
CKD 1/2: £64	£171.89	£193.31	£64.44
CKD 3: £538	£1,436.16	£1,615.16	£538.39
CKD 4: £1,259	£3,357,65	£3,776.13	£1,258.71
CKD 5 w/o RRT: £1,964	£5,238.59	£5,891.50	£1,963.83

* Value in the “inflation” column divided by 3

For the cost of dialysis, we used the CKD CG (draft version March 2021) (36). Please find the details in the table below.

Table 28 Dialysis cost

Cost in the dossier	Source value [DRAFT NICE CG 2021]					Adjustments for the CE model	
	Cost item	Cost per session (£)	Number of sessions per 3-month cycle	Cost of 3-month cycle	Proportion receiving cost item	Weighted average cost of 3-months: HD and PD only	Adjustment per model cycle (4 months)
Haemodialysis (acute and post-acute): £8,927	Home HD	212.15	52	11031,52	4.80%	£6,695	£8,927
	Hospital HD	153.78	39	7095.7	32.30%		
	Satellite HD	153.27	39	7075.63	50.50%		
Peritoneal dialysis (acute and post-acute): £8,756	Continuous ambulatory PD	66.16	91.3	6040.81	5%	£6,567	£8,756
	Automated PD	75.88	91.3	6927.65	7.30%		

Please find in the table below the details regarding kidney transplant costs. Kidney transplant costs were also based on the draft NICE CG 2021 but with inclusion of the updated NHS reference costs.

Table 29 Kidney transplant cost

Cost in the dossier	Source value [NICE CG 2021]				Adjustments for the CE model
	Cost item	Source value	Assumptions on the costs	Value considered	Adjustment per model cycle (4 months)
Transplant, post-acute: £2,777	3 months of immunosuppressive	£2,083	-	£2,083	£2,777
Transplant, acute: £16,457	Cost for deceased donor transplant	£12,838	Update from NHS-costs 2019/2020	£14,049	£13,680 +£2,777
	Cost of living donor transplant	£12,292	Update from NHS-costs 2019/2020	£12,775	
	% from live donors among all transplants	29%	-	-	

Section C: Textual clarification and additional points

C1. Please provide a RIS file of the reference library.

Bayer have provided this file with our response.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

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

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**Association of British Clinical Diabetologists and UK Kidney Association Joint Committee**

3. Job title or position	
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ specialists in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	The joint ABCD-UKKA committee seeks to improve the care of people with diabetic kidney disease (DKD) by creation and regular updating of treatment guidelines, promotion of the guidelines to use by the clinical community, supporting medical and non-medical trainees in Renal medicine and Diabetes/Endocrinology, organising a joint ABCD-UKKA conference every two years in the UK, providing expert input into consultations on DKD, providing expert comment on service delivery and development for people with DKD, providing expert advice on priorities for research and audit in DKD. Each organisation is funded by membership fees and industry sponsorship.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the	**No**

appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To reduce progression of CKD in type 2 diabetes (T2D) To reduce the risk of cardiovascular disease (CVD), its associated co-morbidities and mortality in T2D
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	In a randomised controlled trial of 5734 RAS blockade treated diabetes patients with eGFR 25 to 60 ml/min/1.73m^2, albuminuria, ACR 3 to 30 mg/mmol and retinopathy OR eGFR 25 to 75 ml/min/1.73m^2 and ACR 300 to 5000 mg/g Finerenone relative to placebo reduced the relative risk of DKD progression by 18% and composite CVD and CV mortality by 14% with mild increase in hyperkalaemia (defined as a K of >5.5mmol/L), 2.3% vs.0.9%.

x cm, or a reduction in disease activity by a certain amount.)	29 patients needed to be treated over 2.6 years to prevent one primary kidney related event. 42 patients needed to be treated to prevent one cardiovascular event.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. DKD affects 40% people of T2D and is the commonest cause of end stage kidney disease (ESKD) accounting for 30% of patients starting dialysis treatment in the UK (UK Renal Registry Report, August 2021) who suffer from high risk of CVD. Although the current standard of care including the use of RAS blockade (ACE inhibitors and ARBs), is effective in reducing both progression and CVD, the number of patients needing dialysis treatment is rising year on year. Therefore, there is a significant unmet need to reduce progression of DKD further. The new interventions, SGLT2 inhibitors and Finerenone which work differently from RAS blocking agents, provide an opportunity to reduce the human and societal impact of DKD in the UK.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Weight reduction, salt reduction, smoking cessation and exercise are mainstay in addition, to meticulous glycaemic and BP control, and the use RAS blocking drugs (ACEi and ARB). The use of SGLT2 inhibitor therapy is expected to increase.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	ABCD RA (UKKA) guidelines on the management of DKD https://ukkidney.org/sites/renal.org/files/Management-of-hypertension-and-RAAS-blockade-in-adults-with-DKD.pdf https://ukkidney.org/sites/renal.org/files/ABCD%E2%80%93RA_Managing-glycaemia-guideline_2018Publication.pdf (being updated) NICE guideline on the management of CKD (NG 203, August 2021) https://www.nice.org.uk/guidance/ng203

	KDIGO Diebetes Guideline 2020 https://kdigo.org/wp-content/uploads/2020/10/KDIGO-2020-Diabetes-in-CKD-GL.pdf
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Generally well defined although there are some variations across the country that we are trying to address through the Joint ABCD UKKA Committee guidelines.
• What impact would the technology have on the current pathway of care?	This will be an addition to the current pathway. The FIDELIO-DKD trial demonstrated the benefit in terms of 18% RR of DKD progression and 14% RR of CVD and mortality when Finerenone was added to standard of care including RAS blockade
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Finerenone is not currently used in the NHS
• How does healthcare resource use differ between the technology and current care?	There will be the need for more frequent testing of potassium than currently is the case
• In what clinical setting should the technology be	Secondary care and specialist clinics initially, to be rolled out to primary care gradually

used? (For example, primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Facilities for monitoring and point of care testing in the long term and the pathway for monitoring in view of the small risk of hyperkalaemia which may be negated if used as an add on to SGLT2i, or in those who cannot tolerate. Education and training of staff
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, definitely by reducing the kidney and cardiac outcomes including starting dialysis and MI, stroke and heart failure and the resulting reduction in hospitalisations.
• Do you expect the technology to increase length of life more than current care?	Yes, as per the FIDELIO-DKD and FIGARO-DKD studies showing reduction in the risk of CV mortality, non-fatal CV events and hospitalisation
• Do you expect the technology to increase health-related quality of life more than current care?	Yes, by slowing progression of DKD and reducing CV events both of which are associated with reduced quality of life.

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	It may benefit patients with DKD who have albuminuria more than those without, based on FIDELIO-DKD inclusion criteria.
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Patients will require more frequent testing for serum potassium and as the addition of Finerenone to RAS blocking drugs may raise serum potassium level, as seen in 22% of patients on Finerenone treated patients in the trial (potassium>5.5 mmol/L). Finerenone should be considered after maximisation of ACEi/ARB therapy
14. Will any rules (informal or	As above. If serum potassium rises above 6 mmol/l, Finereone should be stopped temporarily with close

formal) be used to start or stop treatment with the technology? Do these include any additional testing?	monitoring of serum potassium with a view to restarting if where possible
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Yes, fewer hospital admissions, cardiovascular events and reduced need for long term dialysis treatment
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	As already mentioned despite optimum treatment with RAS blocking drugs, many patients with DKD progress to ESKD needing dialysis and kidney transplantation. Furthermore, these patients are at a very high risk of CVD, hospitalisation and mortality. Finerenone is likely to mitigate both progression to ESKD and CVD events.

• Is the technology a 'step-change' in the management of the condition?	yes
• Does the use of the technology address any particular unmet need of the patient population?	Yes, need to reduce progression of DKD further and reduce CV risk
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	2.3% of 2833 patients in Finerenone arm discontinued treatment for hyperkalaemia. Therefore, serum potassium will need to be monitored more closely.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	The standard of care treatment in the trial reflects the UK practice. Finerenone was an adjunct in FIDELIO-DKD trial which will also be the case when Finerenone is approved for treatment of DKD in the UK. What is currently unknown is whether the benefits of Finerenone will be seen on top of the use of SGLT2-inhibitors. This class of drugs was not routinely used in the FIDELIO-DKD and FIGARO-DKD but two drugs in class are now licenced for the treatment of DKD (one for CKD in people without diabetes) and so SGLT2-inhibitors may be widely used in CKD patients by the time Finerenone is approved for this indication.

• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Renal Progression based on change in eGFR; ESKD, CV events (Stroke, MI, heart Failure hospitalisations) and death from any cause
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. How do data on real-world experience compare with the	No real-world data of the use of Finerenone is available at the present time.

trial data?	
Equality	
21a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
21b. Consider whether these issues are different from issues with current care and why.	
Key messages	

22. In up to 5 bullet points, please summarise the key messages of your submission.

- CKD affects 40% patients with type 2 diabetes (DKD) and they are at a very high risk of CVD and mortality
- DKD is the commonest cause of ESKD (30%) requiring dialysis and kidney transplantation in the UK
- The current standard of care reduces the risk but there is a significant residual risk of above remain despite optimum treatment.
- Finerenone has been shown to reduce the risk of DKD progression by 18% and that of CVD and mortality by 14% when added to the current standard of care.
- Introduction of Finerenone is likely to reduce the huge human, societal and economic impact of DKD in the UK

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

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

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Kidney Care UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Kidney Care UK is the UK's leading kidney patient support charity providing advice, support and financial assistance to thousands every year. It is not a membership organisation, but it is in touch with thousands of kidney patients through its direct patient services (eg advocacy, counselling, facebook support group, patient grants), social media channels, telephone helpline and website.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	No

If so, please state the name of manufacturer, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	The information and views represented in this submission has been gathered through a range of sources: Kidney Care UK advocacy services and Facebook support group, the views of Kidney Care Staff who are kidney patients, our Patient Advisory Group. We have also run regular surveys to explore the current challenges kidney patients are facing as well as the annual Patient Reported Experience Measures survey which reports on how kidney patients feel about their experience of care.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Many cases of CKD are mild or moderate and risks can be managed by patients and their GPs without ever visiting a hospital. However, for people with CKD that progresses and requires specialist input from the renal team it can be extremely serious and require life changing treatment. A diagnosis of CKD has huge implications for a person's quality of life. Challenges include the stress of coming to terms with a diagnosis of an incurable, progressive condition, as well as difficult decisions about treatment options and the strain of adjusting to new treatments. Many patients must also adhere to strict medication regimes and dietary restrictions. Symptoms include debilitating fatigue, significant pain,

	itching, swelling, restless leg syndrome, muscle cramps and sleep problems. People's capacity to stay in work, maintain relationships and quality of life can be severely compromised. There are almost 30,000 people receiving dialysis in the UK,[i] many of whom spend five hours a day, three days a week, every week, at hospital. Fiona Loud, our policy director and a kidney patient, explains "dialysis meant drinking just 500 ml of fluid a day, an almost impossible diet where chocolate, coffee, bananas, cheese, and so many others things are banned or restricted. And you must spend 5 or 6 hours in a hospital 3 days a week, with 2 big needles plunged into your arm, connected to a machine. And all this gives you just 10% of your normal kidney function, and you probably feel even sicker after treatment than you did before, your blood pressure has dropped way down and you may be bleeding from where those great big needles were for a long time. You may be too weak to walk and you are likely to be depressed and out of work. You have a day off, and then it all starts again…and again….and again." Kidney transplant, while not a cure, is the best form of treatment for kidney disease. However, there are more people waiting for a transplant than there are available organs and people from Black and Minority Ethnic communities have to wait considerably longer than people from White British backgrounds. Kidney transplants from deceased donors last on average 15-20 years and 20-25 years from a living donor, although some longer and some less. Kidney patients may therefore face returning to dialysis if their kidney fails. Unsurprisingly, CKD can take a huge toll on the mental health and emotional wellbeing of patients. Nearly half of in-centre haemodialysis patients experience some form of distress[ii] and up to 1 in 3 kidney patients will experience depression at some point. This in turn exacerbates physical ill health and a person's ability to manage their condition. Symptoms of depression in people with early stage kidney disease increases their risk of progressing to end-stage renal disease (requiring dialysis or a transplant) and death.[iii,iv] In transplant patients, depressive symptoms have been shown to increase the risk of death by 65%.[v] A carer's role will depend partly on the individual's stage of kidney disease, their symptoms (eg fatigue), comorbidities and the treatment they receive. Roles can include helping with activities of daily living and mobility, transportation, personal care, and support with treatment, for example adhering to the medication regime and also with dialysis (for example if the person has dialysis at home). As well as the physical demands of caring, it can be emotionally challenging as the carer and the person with kidney disease

	come to terms with the change in role and the impact of a life changing diagnosis. Caregiving demands in managing dialysis has proved to be taxing on the physical, social and emotional health of informal caregivers.[vi,vii]
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	The most recent Patient Reported Experience Measures found that overall patients rate the overall experience of the service provided by their renal unit highly.[viii] People who progress to kidney failure often find the burden of treatment is very significant. As described above, many patients can find living with five hour dialysis sessions, three times a week every week, as well as the stringent fluid and dietary restrictions, very challenging. Receiving a kidney transplant, although not a cure, can make a huge different to the health and quality of life of a person with kidney disease. People fortunate enough to receive a kidney transplant will also need to follow certain restrictions on their diet and lifestyle, as well as being on medication for the rest of their lives. In the case of deceased donations, transplant comes with the emotional burden of knowing the donor has lost their life. Decisions regarding accepting a living donation can also be challenging.
8. Is there an unmet need for patients with this condition?	There is no cure for chronic kidney disease and limited options for medications that can slow or prevent decline in kidney function, although lifestyle, diet and treatments for problems linked with kidney disease such as high blood pressure are important. Progress in developing new pharmaceutical treatments has been extremely slow.

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Type 2 diabetes is the leading cause of chronic kidney disease worldwide and the numbers of cases is growing. Therefore, the development of a new treatment option for kidney disease in people with type 2 diabetes, that shows benefits, is of significant interest to patients. The benefits identified in the clinical trials of this technology, of lowering risk of CKD progression and cardiovascular events would clearly be significant advantages for kidney patients in the context of a progressive and currently incurable condition such as CKD. Progress in the development of new treatments for kidney disease is perceived by patients to be very slow. Positive findings for this technology as well as the SGLT2 inhibitors, thereby offering different treatment options in addition to ACEi and ARBs, offers real hope to patients. This is particularly the case for those patients for whom SLGT2 inhibitors are not suitable. The existence of treatment options for people with diabetes and chronic kidney disease should also encourage the early identification of kidney damage, which clinical audits show is hampered by a failure to carry out NICE recommended annual checks. As well as pharmaceutical options such as Finerone, early identification should also enable patients to take action on diet and lifestyle to reduce their risk of further kidney damage Kidney patients are at very high risk of death from cardiovascular causes and therefore the evidence that Finerone lowers the risk of death from cardiovascular causes is an important advantage.

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Although few patients discontinued Finerone in the clinical trials due to hyperkalemia, other outcomes related to hyperkalemia were increased in the treatment group compared to placebo. This is a potential area of concern to patients.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Not to our understanding.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Age and ethnicity: "Some ethnic groups, particularly Bangladeshi, appear to be more sensitive to the combined effects of proteinuria and hypertension than other ethnic groups. Also, clinicians need to be aware that younger people with diabetes (<55 years) with CKD are at twice the risk of rapid progression of CKD compared with those >65 years and thus need closer monitoring, management of risk factors and early specialist review to delay progression." (Mathur R, Dreyer G, Yaqoob MM, et al Ethnic differences in the progression of chronic kidney disease and risk of death in a UK diabetic population: an observational

	cohort study BMJOpen 2018;8:e020145. doi: 10.1136/bmjopen-2017-020145)
Other issues	
13. Are there any other issues that you would like the committee to consider?	Kidney Care UK believes it's vital that people are provided with lifestyle and diet advice so they can take action to reduce their risk of further kidney damage, and it is important that any NICE guidance resulting from this review recommends the provision of suitable advice
Key messages	

14. In up to 5 bullet points, please summarise the key messages of your submission:

- A diagnosis of CKD has huge implications for a person's quality of life.
- Treatments for people with renal failure are extremely onerous and therefore any treatments that can delay progress to this stage of the disease have the potential to bring huge benefits to patients.
- Type 2 diabetes is the leading cause of chronic kidney disease worldwide so the development of new treatment options for kidney disease in people with type 2 diabetes is of significant interest to patients, and having alternative treatments to offer if the first option is not suitable would be very welcome.
- Treatment options may encourage early identification of CKD amongst those with diabetes.
- It is important that any NICE guidance resulting from this review recommends the provision of suitable lifestyle and diet advice to help people take action to reduce their risk of further kidney damage.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

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

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**Primary Care Diabetes Society**

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**The PCDS supports every primary care health professional to deliver high-quality, clinically effective care in order to improve the lives of people with diabetes.** **The aim of the Society is to support primary care professionals to deliver high quality clinically effective care, in order to improve the lives of people living with diabetes.** **The PCDS are a charity and they rely on hands off grants from companies as well as donations from individuals to fund their group and educational actives they work on.**
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	**No**

If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	reduce the risk of sustained estimated glomerular filtration rate decline, kidney failure, cardiovascular death, non-fatal myocardial infarction and hospitalization for heart failure.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	Reduction in the rate of decline in eGFR in patients who lose renal function faster than the average age-related decline in GFR. Progressive renal decline is eGFR loss of ⩾3.3% per year. Therefore reversing this will be clinically significant.

x cm, or a reduction in disease activity by a certain amount.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, there is still a residual burden of chronic kidney disease progression in people with diabetes, despite the use of RAAS-I and SGLT2-Is
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Using RAAS-I
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Chronic kidney disease: assessment and management NICE guideline [NG203]Published: 25 August 2021
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please	The pathway is clearly defined

state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes
• How does healthcare resource use differ between the technology and current care?	Health care resource will remain the same
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Primary care
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Training in primary care

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes
• Do you expect the technology to increase length of life more than current care?	Yes
• Do you expect the technology to increase health-related quality of life more than current care?	Yes
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Black patients have been found to have increased rates of kidney failure in comparison to white patients But it is uncertain if this drug is more efficacious in black people or white people
The use of the technology	

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	No
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Monitoring of serum potassium levels
15. Do you consider that the use of the technology will result in any substantial health-	Yes

related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes, Chronic kidney disease associated with type 2 diabetes can have such a debilitating impact on patients' lives. Unfortunately, this disease is far reaching, as up to 40% of all patients with type 2 diabetes develop chronic kidney disease.
• Is the technology a 'step-change' in the management of the condition?	Not really
• Does the use of the technology address any particular unmet need of the patient population?	Yes

17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Increased monitoring of serum potassium levels can potentially increase workload in primary care. Measurement of serum potassium and eGFR in all patients before initiation of treatment with fineronome and dose accordingly. Cannot be initiated if serum potassium is > 5.0 mEq/L
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	n.a
• What, in your view, are the most important outcomes, and were they measured in the trials?	3 FIDELIO-DKD trial demonstrated positive kidney and cardiovascular outcomes in patients with CKD associated with T2D. These are the most important outcomes.
• If surrogate outcome measures were used, do	Yes.

they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. How do data on real-world experience compare with the trial data?	Not available yet
Equality	
21a. Are there any potential equality issues that should be taken into account when considering this treatment?	Unknown

21b. Consider whether these issues are different from issues with current care and why.	

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.

- Currently, many patients with CKD associated with T2D are at risk for CKD progression and the occurrence of cardiovascular events

  Despite the use of RAAS-I
- In people with chronic kidney disease associated with type 2 diabetes, Fineronone will provide kidney protection.
- Serum potassium monitoring can increase the workload in primary care
-
-
-
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

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

A Single Technology Appraisal

Produced by	Peninsula Technology Assessment Group (PenTAG) University of Exeter Medical School South Cloisters St Luke's Campus Heavitree Road Exeter EX1 2LU
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Declared competing interests of the authors

None

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Rider on responsibility for document

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Author Contributions:

Louise Crathorne	Led the delivery of the ERG report. Critical appraisal of the company submission. Summarised and critiqued the decision problem, and clinical effectiveness data within the company submission. Contributed to the writing and editing of the report
Ash Bullement	Acted as health economic project lead, critiqued the company's economic evaluation and contributed towards writing the report. Implemented the ERG's preferred settings and exploratory analyses within the company's economic model.
Naomi Shaw	Critical appraisal of the literature search strategies and contribution to the writing and editing of the report
Jess Mann	Acted as health economist, critiqued the company's economic evaluation and contributed to the writing of the report
Hollie Wheat	Acted as health economist, critiqued the company's economic evaluation and contributed to the writing of the report

Author Contributions:

Fraizer Kiff	Critical appraisal of the underlying health problem, current service provision and clinical effectiveness evidence. Contributed to the writing and editing of the report
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

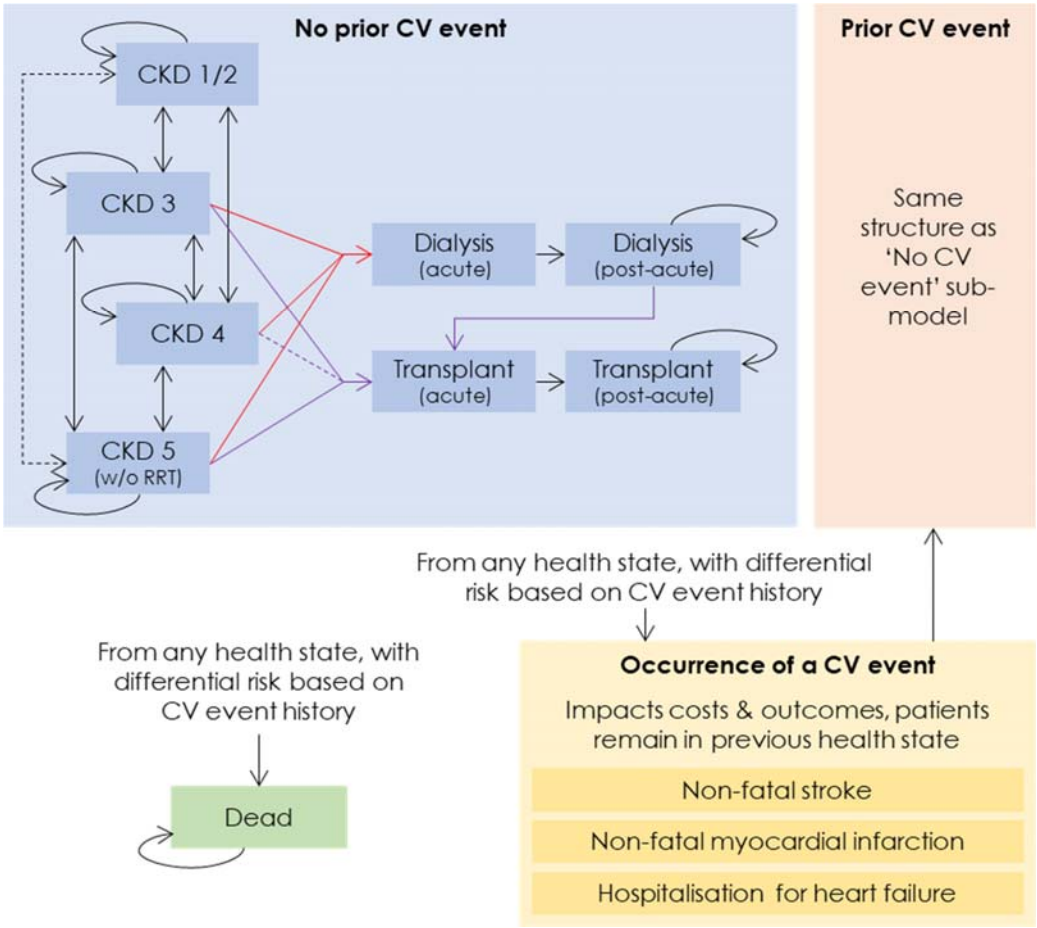
Attribute	Reference case	ERG comment on company's submission
	valued using the prices relevant to the NHS and PSS	
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	✓ No comment

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.

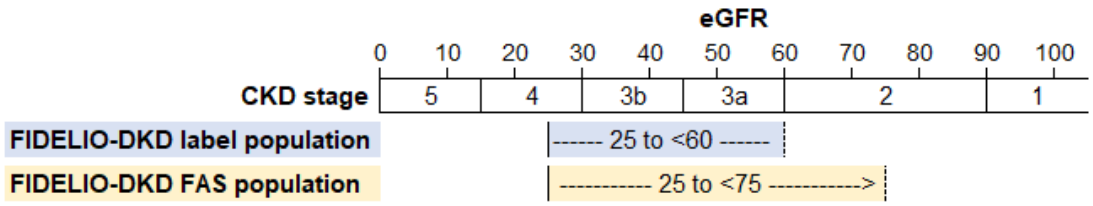
4.2.3. Population

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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National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

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

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Monday 15 November** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Note that table/figure and page numbers in the ERG response column, link to the updated (clean) version of the ERG report in response to FAC.

Issue 1 Uncertainty of ERG in the appropriate population

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Text on page 15 of the ERG report: *"Overall, the evidence presented in the CS focuses on a narrower population than that defined in the NICE scope but is **to some extent** aligned with the proposed European/UK indication (pending January 2022)."* AND *"However, it is unclear as to whether it is narrower again with the addition of the threshold of eGFR ≥25 ml/min/1.73 m^2, which is in the middle of eGFR criteria for Stage 4 CKD. This is important because the evidence presented is for patients with CKD (Stage 3 and 4 with albuminuria), rather than for patients defined with respect to an eGFR range*."	The text should be changed as follows: Overall, the evidence presented in the CS focuses on a narrower population than that defined in the NICE scope but is ~~to some extent~~ aligned with the proposed European/UK indication (pending January 2022) **and associated caution regarding initiation with respect to eGFR levels**. ~~However, it is unclear as to whether it is narrower again with the addition of the threshold of eGFR ≥25 ml/min/1.73 m2, which is in the middle of eGFR criteria for Stage 4 CKD. This is important because the evidence presented is for patients with CKD (Stage 3 and 4 with albuminuria), rather than for patients defined with respect to an eGFR range.~~	The statement is factually incorrect and Bayer apologise if the population was not clearly defined in the submission or in response to ERG questions. The data presented in the submission was specifically requested from the statistical team at Bayer to align with the proposed indication and further, the eGFR threshold for initiation of finerenone. This data has been carefully and consistently presented in the clinical and economic sections and in the economic model. Along with the full analysis set (FAS), Bayer have presented data for the following population for which we seek marketing authorization and appraisal by NICE: **Adults with chronic kidney disease (stage 3 and 4 with**	The ERG has corrected where necessary. 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 (Stage 3

		albuminuria*) and type 2 diabetes. ***eGFR≥ 25ml/min/1.73m^2** Please see pages 10, 36 and 133 of Document B. Bayer apologizes if this was not clear. However, with this further clarity and reassurance that the data presented in the submission and economic model is the appropriate population for decision making we hope that the ERG and NICE agree that this is no longer a key issue.	and Stage 4* with albuminuria [*≥25 ml/min/1.73 m^2]) 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. 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 for discussion. Refer to Key Issue 1, pp 15-16

Issue 2 Model design/ structure

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG report, page 13, Table 1. ERG report, page 17, Key Issue 4 ERG report, page 78, Table 24 ERG report, page 86, 130, The ERG on several occasions suggests concerns regarding the model *structure*, however, the only comment about the structure relates to its diagram. The other comments from the ERG are related to the *model inputs* and in particular time-invariant probabilities of CKD progression and CV events (which are dependent on age only).	We suggest replacing in the ERG report: 'concerns regarding model structure' by 'concerns regarding time-invariant probabilities used in the model'.	Whilst the ERG makes reference to perceived weaknesses in the submitted model structure, the ERG critique does not refer to characteristics of the model design/structure. The ERG does not challenge the model structure, which is consistent with existing literature and has been broadly consulted with health economic and clinical experts. In particular, the model structure is consistent with model described in Schlackow et al., (2017) mentioned by the ERG as an example in the summary of key issue 4. The wording used in expressing the ERG assessment suggests to the reader that the model structure is not appropriate. We understand that the ERG would prefer another approach to the estimation of transition probabilities applied in the model. Indeed, the use of risk equations was considered and discussed with experts in the early stages of model development (i.e. including time variant probabilities), although	The ERG accepts its criticism was focused mostly on the transition probabilities, rather than the specification of specific health states or a cohort-level structure, and so the suggestion for amendment is reasonable in principle. However, the ERG still considers that its critique related to this point to extend beyond *time-varying* transitions only. For example, the ERG questioned in Section 4.2.2. of its report, why risk equations (potentially incorporating characteristics that vary over time) were not considered. The ERG has edited the sections as highlighted by the company but preserving its comment that fundamentally the ERG's concern is with how transitions are modelled. Refer to p13 (Table 1), p18 (Key Issue 4), p78 (Table 24), and p130. The ERG did not identify any text on page 86 of its report

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
		rejected. There is a limited number of major events observed in the FIDELIO-DKD study and this limits the ability of these data being used to adequately estimate the risk equations. Furthermore, there is an established relationship between CKD stage and CV events (fatal or otherwise). As such, the model submitted focuses on the link between CKD stage and these events rather than extending this to an explicit consideration of other risk factors. Bayer note we could have described this in Document B more clearly.	that warranted editing related to this amendment.

Issue 3 Utility values

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG report, page 18, Key Issue 5 It is stated that: *"These include utility values that increase as disease progresses, CV risks that reduce and disease progresses, and risks that seem*	We suggest amending this sentence with the following one: "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	It is factually inaccurate to say that in the model utility values increase as diseases progresses and CV risks reduce. Indeed, the CV risk for CKD 3 is lower than for CKD1/2 and utility higher but parameters for more advanced CKD stages behave according to expectations.	Text has been amended as per the company's proposed amendment. Refer to Key Issue 5, p18

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
to bias against finerenone with no clear rationale."	probabilities that seem to bias against finerenone with no clear rationale."	Taking into account that there are no patients in CKD 1/2 at baseline in the base case it is entirely accurate to say that CV risk increases (and utility values decrease) with disease progression.	

Issue 4 Description of inequalities

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Text on page 23 of ERG report: *"In addition, those from Black and ethnic minority backgrounds are **more** likely to receive a kidney transplant*."	The text should be changed to: "In addition, those from Black and ethnic minority backgrounds are **less** likely to receive a kidney transplant."	This is a factual inaccuracy. Please see Document B page 32.	Text has been corrected as per the proposed amendment. Refer to Section 2.2, p24

Issue 5 *Minor point* - description of ACEI/ ARB use

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Text on page 24 of ERG report: *"ACE-is and ARBs are recommended to manage blood pressure in order to prevent progression of CKD"*	The text should be changed to: "ACE-is and ARBs are recommended to manage blood pressure in order to prevent	This is a minor factual inaccuracy but relevant to the description of management.	Text has been amended for clarity as proposed by the company. Refer to Section 2.3, p25

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
	progression of CKD, **as well as managing proteinuria**"	https://ukkidney.org/health-professionals/information-resources/uk-eckd-guide/hypertension https://www.diabetes.org.uk/guide-to-diabetes/complications/kidneys_nephropathy https://www.medicines.org.uk/emc/product/2758	

Issue 6 Population

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Text on page 31 of the ERG report: *"The company noted in the CS, however, that it anticipates that caution will be advised for the use of finerenone in patients with an [redacted] ml/min/1.73m^2 due to limited clinical data. Given this, the company presented data from the FIDELIO-DKD study in the CS as follows:* *• adults with CKD and T2D which reflected more severe Stage 2 CKD to "fitter" Stage 4 CKD (i.e.*	The text should be amended as follows: The company noted in the CS, however, that it anticipates that caution will be advised for the use of finerenone in patients with an eGFR [redacted] ml/min/1.73m^2 due to limited clinical data. Given this, the company presented data from the FIDELIO-DKD study in the CS as follows: • ~~adults with CKD and T2D which reflected more severe Stage 2 CKD to "fitter" Stage 4 CKD (i.e. eGFR <75 to ≥25 ml/min/1.73m2) as the Company anticipated that caution would be advised in patients with an eGFR <25 ml/min/1.73m2 due to limited clinical data,~~	Factual inaccuracy. Bayer presented the Full Analysis Set (FAS) which included all randomized patients except those excluded for GCP violations (see definition in Table 11, Document B). As such, this included a small number of patients with an eGFR at baseline <25ml/min/1.73m^2.	The ERG has corrected where necessary and clarified its intended meaning which was aligned with the company's justification for amendment. Refer to Section 2.4.1, pp32-33

eGFR <75 to ≥25 ml/min/1.73m^2) as the Company anticipated that caution would be advised in patients with an [redacted] ml/min/1.73m^2 due to limited clinical data, and the trial inclusion criteria determined only "fitter" Stage 2 patients could be included, and…"	~~and the trial inclusion criteria determined only "fitter" Stage 2 patients could be included~~, **the full analysis set (FAS) which included all randomized patients except those excluded for GCP** and…		

Issue 7 Population

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Text on page 31 of the ERG report: *Given this, the company presented data from the FIDELIO-DKD study in the CS as follows:* • *……., and* • *adults with CKD ([redacted]), where the **Company determined** [redacted] was [redacted] mL/min/1.73m^2.*	The text should be amended as follows: Given this, the company presented data from the FIDELIO-DKD study in the CS as follows: • ……., and • adults with CKD (Stage 3 to Stage 4 with albuminuria*). * eGFR <60 to ≥25 mL/min/1.73m^2.	Factual inaccuracy. Bayer did not **determine** stage 3 to stage 4 to be eGFR <60 to ≥25 ml/min/1.73m^2. Rather, the minimum eGFR in the trial inclusion criteria was 25ml/min/1.73m^2 which falls within the stage 4 category and there is limited data and therefore caution in those with stage 4 <25ml/min/1.73m^2 (final SPC wording to be determined).	The ERG has corrected where necessary and clarified its intended meaning which was aligned with the company's justification for amendment. Refer to Section 2.4.1, pp32-33

Issue 8 Population

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Text on page 31 of the ERG report: *"The latter constituted the population which was to some extent aligned with the proposed indication under review by the European Medicines Agency (EMA) (pending January 2022):"*	The text should be amended as follows: "The latter constituted the population which was ~~to some extent~~ aligned with the proposed indication under review by the European Medicines Agency (EMA) (pending January 2022) **and associated caution regarding initiation with respect to eGFR levels**:"	Factual inaccuracy. This population *fully* aligns with the proposed indication and proposed caution.	The ERG has corrected where necessary and clarified its intended meaning which was aligned with the company's justification for amendment. Refer to Section 2.4.1, pp32-33

Issue 9 Population

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Text on page 32 of the ERG report: *"The derivation of this population to align with the proposed label mainly involved removal of one of the FIDELIO-DKD study's capped populations i.e. patients with eGFR [redacted] mL/min/1.73m^2 and very high albuminuria. This was approximately [redacted]% of the total study population.* ***This was referred to in the CS as the "label population"*** *(the ERG has retained this terminology throughout its report)."*	The text should be amended as follows: "The derivation of this population to align with the proposed label mainly involved removal of one of the FIDELIO-DKD study's capped populations i.e. patients with eGFR ≥60 to 75 mL/min/1.73m^2 and very high albuminuria. This was approximately [redacted]% of the total study population. **Bayer further removed for the submitted population those patients who at baseline had an eGFR <25ml/min/1.73m^2.** This was referred to in the CS as the "label population" (the ERG has retained this terminology throughout its report)."	Factual inaccuracy. The label population was defined in the submission as: *FIDELIO-DKD patients with eGFR ≥ 25 to <60ml/min/1.73 m^2 and albuminuria at baseline* (page 36, Document B). As such, the proposed label population wasn't derived ***solely*** from the removal of the capped populations as described by the ERG (but correctly described as mainly). The proposed label population in this submission took account of the proposed indication ***and also*** the proposed caution regarding initiation in patients with an eGFR <	The ERG has corrected where necessary and clarified its intended meaning which was aligned with the company's justification for amendment. Refer to Section 2.4.1, pp32-33

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
		25ml/min/1.73m^2 (in line with the study inclusion criteria).	

Issue 10 Population – for clarity

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Text on page 32 of the ERG report: *"The ERG noted, however, that the proposed label population covered CKD Stage 3 and Stage 4 whereas in reality the eGFR cut-offs applied reflected Stage 3a (eGFR ≥45 to <60), Stage 3b (eGFR ≥30 to <45) and "fitter" Stage 4 patients (eGFR ≥25 to <30); i.e. patients with eGFR ≥15 to <25 were excluded)."* *AND* *"The ERG recognised the data from the FIDELIO-DKD study are aligned with the proposed label population but caution that there is currently no clear indication as to whether the more severe Stage 4 patients (i.e. eGFR ≥15 to <25) will be excluded from the*	The text should be deleted as follows: ~~*"The ERG noted, however, that the proposed label population covered CKD Stage 3 and Stage 4 whereas in reality the eGFR cut-offs applied reflected Stage 3a (eGFR ≥45 to <60), Stage 3b (eGFR ≥30 to <45) and "fitter" Stage 4 patients (eGFR ≥25 to <30); i.e. patients with eGFR ≥15 to <25 were excluded). The ERG recognised the data from the FIDELIO-DKD study are aligned with the proposed label population but caution that there is currently no clear indication as to whether the more severe Stage 4 patients (i.e. eGFR ≥15 to <25) will be excluded from the licence. Therefore, generalisability of the FIDELIO-DKD data presented in the CS is unclear and this constitutes a key issue."*~~	Factual inaccuracy/ for clarity. The trial population included stage 3a and stage 3b patients across the full range of eGFR. It also included some patients in stage 2 and a proportion of stage 4 patients. As noted, the population with eGFR ≥60 to <75 mL/min/1.73 m^2 and very high albuminuria was capped at approximately 10% of the total population with very high albuminuria at screening. It should also be noted that the trial inclusion criteria for eGFR levels were not completely aligned with the eGFR staging according to the "KDIGO grid". As such, it was specified that the lowest eGFR in the trial should be 25 mL/min/1.73 m^2 i.e. "excluding" those patients with an eGFR < 25 mL/min/1.73 m^2. There were however some patients who had an eGFR at baseline of <25ml/min/1.73m^2. These patients are included in the FAS of the trial	The ERG has corrected where necessary and clarified its intended meaning which was aligned with the company's justification for amendment. Refer to Section 2.4.1, pp32-33

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
licence. Therefore, generalisability of the FIDELIO-DKD data presented in the CS is unclear and this constitutes a key issue."		but are proposed as a group of caution in the draft SPC. For clarity, along with the full analysis set (FAS), Bayer have presented data for the following population for which we seek marketing authorization and appraisal by NICE: **Adults with chronic kidney disease (stage 3 and 4 with albuminuria*) and type 2 diabetes.** ***eGFR≥ 25ml/min/1.73m^2 (reflecting the proposed caution).** Bayer has referred to "proposed" throughout, as the final wording will be determined when the marketing authorization is issued. Bayer have stated that they *anticipate* that those patients with an eGFR <25ml/min/1.73m^2 will fall under the "caution" section of the SPC due to limited data (66 patients [2.3%] in the finerenone arm of FIDELIO-DKD) and not being part of the trial inclusion criteria.	

Issue 11 Indicative NHS list price

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Text on page 32 of the ERG report: *"The anticipated list price is £ [redacted] per [redacted] supply. The company's health economic analysis was based on the list price for finerenone."*	The text should be amended as follows: "The ~~anticipated~~ **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."	The price was presented as an indicative NHS list price in the submission.	Text has been amended as proposed by the company. Refer to Section 2.4.2, p33

Issue 12 Incorrect illustration of FIDELIO-DKD FAS population

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 7 on page 33 of the ERG report Figure 2 on page 83 of the ERG report	Depending on what the ERG is trying to illustrate, Table 7 and Figure 2 need to be changed to reflect the fact that there were patients included in FIDELIO DKD FAS that had an eGFR less than 25 ml/ min/ 1.73m^2, as well as a maximum individual eGFR at baseline of [redacted] ml/ min/ 1.73m^2. It may be that the ERG were reflecting the trial inclusion criteria for the "FIDELIO DKD FAS" population in Table 7 rather than the baseline characteristics and if so, we suggest that this is specified for clarity. We are not clear where the ERG have sourced the information for the note below figure 2, but	Both diagrams over-simplify the FIDELIO-DKD FAS population and do not include all patients in that population. Table 10 in Document B sets out the eGFR and UACR values at baseline. For example, this sets out that in the overall study population (FAS), there were a small number of patients with an eGFR < 25 ml/ min/ 1.73m^2.	In Table 7, the ERG was reflecting the trial inclusion criteria. The ERG accept the company's issue that this is misleading as there were participants with baseline eGFR in the FAS of less than 25 mL/min/1.73m^2. Corrections have been made to the diagram to clarify. However, the ERG highlights that the comment raised in relation to the individual with a maximum eGFR of [redacted] ml/ min/ 1.73m^2 raises a concern with the ITT

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
	to the best of our knowledge this is incorrect and should be deleted. ~~Note(s): *FAS population presented here refers to the group of patients that were re-evaluated for eligibility after randomisation ahead of initiation of treatment. Patients with a missing eGFR value or an eGFR < 25 were not treated.~~		population setting within the company's model, [redacted]. The ERG expects this apparent contradiction is because the FAS population included within the model excludes any patients with [redacted] but is noted here for completeness. Figure 2 of the ERG's report was intended to provide a simple overview of the differences in the label and ITT settings included in the company's model. This diagram has been edited for clarity. Refer to Table 7, p34, and Figure 2, p84

Issue 13 *Minor point* Incorrect value

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Text on page 34 of the ERG report, section 2.4.3.1 *"In the FIDELIO-DKD trial, 1,972 participants received ACE-I"*	The text should be amended as follows: "In the FIDELIO-DKD trial, 1,942 participants received ACE-I"	The reported number is incorrect (please see Document B, Table 10).	Text has been corrected as per the proposed amendment. Refer to Section 2.4.3.1, p35

Issue 14 Disease progression in the model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG report, page 37 It is stated that: *"The company's health economic model included data relating to disease progression* ***as determined by a sustained decrease of at least 40% in the eGFR****; 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."*	We suggest amending this sentence with the following one: "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."	The disease progression in the model was not determined by a sustained decrease of at least 40% in the eGFR. Disease progression was modelled based on transition probabilities obtained from patient level data of the FIDELIO-DKD trial.	Text has been corrected as per the proposed amendment. Refer to Section 2.4.4, p38

Issue 15 *Minor point* Inclusion criteria

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Text in Table 10, page 42 of the ERG report • *Men or women ≥18 years of age with:* *- T2DM as defined by the American Diabetes Association in*	The text should be amended as follows:	For accuracy.	Text has been corrected as per the proposed amendment. Refer to Table 11, p43

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
the 2010 Standards of Medical Care in Diabetes, and *- Diagnosis of CKD with at least one of the following criteria at run-in and screening visits – persistent (≥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*	• 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 ~~at least one of~~ 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.		

Issue 16 *Minor points* in Table 13

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
(1) Primary endpoint: composite of kidney failure; a **sustained** eGFR ≥40% from baseline over at least 4 weeks; or, renal death (2) Composite of kidney failure or sustained decrease in eGFR ≥57% from baseline **over 4 weeks** or renal death (3) **Sustained** eGFR ≥40% from baseline over at least 4 weeks (4) Sustained decrease in eGFR ≥57% from baseline **over 4 weeks** (5) Kidney Disease Quality of Life (KDQOL-**35**)	(1) Should say a sustained ***decrease of*** eGFR (2) For this composite – it should also say "over ***at least*** 4 weeks" (3) Should say a sustained ***decrease of*** eGFR (4) Should also say "over ***at least*** 4 weeks" (5) Should say Kidney Disease Quality of Life (KDQOL-**36**)	For accuracy.	Text has been amended to clarify as per the company's proposed amendments. Refer to Table 14, p48

Issue 17 Population

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Text on page 52 of the ERG report *"However, as noted in Section 2.4.1, the proposed label population covers CKD Stage 3 and Stage 4 whereas in reality the eGFR cut-offs applied reflected Stage 3a (eGFR ≥45 to <60), Stage 3b (eGFR ≥30 to <45) and "fitter" Stage 4 patients (eGFR ≥25 to <30); i.e. patients with eGFR ≥15 to <25 were excluded). The ERG recognised the data from the FIDELIO-DKD study were aligned with the proposed label population but caution that there is currently no clear indication as to whether the more severe Stage 4 patients (i.e. eGFR ≥15 to <25) will be excluded from the licence. Therefore, generalisability of the FIDELIO-DKD data presented in the CS to the scoped population is unclear."*	The text should be deleted as follows: ~~"However, as noted in Section 2.4.1, the proposed label population covers CKD Stage 3 and Stage 4 whereas in reality the eGFR cut-offs applied reflected Stage 3a (eGFR ≥45 to <60), Stage 3b (eGFR ≥30 to <45) and "fitter" Stage 4 patients (eGFR ≥25 to <30); i.e. patients with eGFR ≥15 to <25 were excluded). The ERG recognised the data from the FIDELIO-DKD study were aligned with the proposed label population but caution that there is currently no clear indication as to whether the more severe Stage 4 patients (i.e. eGFR ≥15 to <25) will be excluded from the licence. Therefore, generalisability of the FIDELIO-DKD data presented in the CS to the scoped population is unclear."~~	Factual inaccuracy/ for clarity. The trial population included stage 3a and stage 3b patients across the full range of eGFR. It also included some patients in stage 2 and a proportion of stage 4 patients. As noted, the population with eGFR ≥60 to <75 mL/min/1.73 m^2 and very high albuminuria was capped at approximately 10% of the total population with very high albuminuria at screening. It should also be noted that the trial inclusion criteria for eGFR levels were not completely aligned with the eGFR staging according to the "KDIGO grid". As such, it was specified that the lowest eGFR in the trial should be 25 mL/min/1.73 m^2 i.e. "excluding" those patients with an eGFR < 25 mL/min/1.73 m^2. There were however some patients who had an eGFR at baseline of <25ml/min/1.73m^2. These patients are included in the FAS of the trial but are proposed as a group of caution in the draft SPC. For clarity, along with the full analysis set (FAS), Bayer have presented data for the following	The ERG has removed the text following clarification that the label population is aligned with the proposed indication (i.e. eGFR ≥25 to <60 with eGFR <25 anticipated to be a cautionary group in the SmPC given limited data and trial inclusion criteria). Refer to Section 3.2.2.2, p53

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
		population for which we seek marketing authorization and appraisal by NICE: **Adults with chronic kidney disease (stage 3 and 4 with albuminuria*) and type 2 diabetes.** ***eGFR≥ 25ml/min/1.73m^2 (reflecting the proposed caution).** Bayer has referred to "proposed" throughout, as the final wording will be determined when the marketing authorization is issued. Bayer have stated that they anticipate that those patients with an eGFR <25ml/min/1.73m^2 will fall under the "caution" section of the SPC due to limited data (66 patients [2.3%] in the finerenone arm of FIDELIO-DKD) and not being part of the trial inclusion criteria.	

Issue 18 *Minor point* re: description of eGFR bounds

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Text on page 53 of ERG report: *"Given that such a change in eGFR could occur from any current level of eGFR up to 60 ml/min/1.73m^2 and…."*	Text should be amended to: "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**	For accuracy.	Text has been amended to clarify as per the company's proposed amendments. Although has changed "trial inclusion criteria" to "FAS":

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
	75ml/min/1.73m^2 in the trial inclusion criteria and…."		"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 75ml/min/1.73m^2 in the FAS and…." Refer to Section 3.2.3.1, p54

Issue 19 Population

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Text on page 54 of ERG report: *"(given that removing patients with CKD stage 1/2 led to…"*	Text should be amended to: "(given that removing patients with CKD stage 1/2 **and those patients with eGFR < 25 ml/min/1.73m^2** led to…"	For accuracy.	Text has been amended as per the company's proposed amendments. Refer to Section 3.2.3.1, p55

Issue 20 *Minor points* in Table 20

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
(1) FIDELIO-DKD, column 1, n is missing (2) FIDELIO-DKD, column 2, there are 3 errors (3) FIDELIO-DKD, column 6, < symbol missing	(1) Please add n = 5,674 (2) (i) Should say (in both instances), "eGFR **≥**25"; (ii) Should say "(A3 **≥33.9**–≤565 mg/mmol"; (iii) should say "diabetic **retinopathy"** (not nephropathy)	For accuracy	Text has been checked and amended as per the company's proposed amendments. Refer to Table 21, pp69-70

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
(4) FIDELIO-DKD, column 6, outcome missing (5) FIDELIO-DKD label population, column 1, n is missing (6) FIDELIO-DKD label population, column 2, there are 2 errors	(3) Should say "kidney failure (end stage kidney disease or eGFR **<**15 ml/min/1.73 m2) (4) Add "new diagnosis of atrial fibrillation or flutter" (5) Please add n= 4,860 (6) (i) should say "**≥** eGFR 25-<60 ml/min per 1.73 m^{2}"; (2) should say 'ACR **≥ to 3.4 to ≤ to** 565 mg/mmol"		

Issue 21 *Minor points* description of SLR

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 76 and 77 of ERG report Incorrect description of Appendices	Page 76 – please make the following amendment: Appendix H of the CS details systematic searches of the literature used to identify ~~cost effectiveness~~ **health related quality of life** evidence Page 77 – please make the following amendment: Appendix I of the CS details systematic searches of the literature used to identify ~~cost effectiveness~~ **cost and healthcare resource measurement and valuation** evidence	For accuracy.	Text has been corrected. Refer to Section 4.1.1, pp77-78

Issue 22 Population

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 79 of the ERG report describes the population in the model. Bayer would like to provide further clarity.	Please make the following amendment: 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 SPC)**.	For clarity around the modelled population.	Text has been amended to clarify the modelled population. Refer to Section 4.2.2, p80

Issue 23 Diagram discrepancies

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 79 of the ERG report, section 2.2 states: *"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."*	We suggest following wording: "However, the ERG noticed that not all potential transitions were reflected in the company's model structure diagram and therefore opted to produce an alternative diagram […]"	Bayer acknowledge that the diagram proposed by the ERG more thoroughly reflects the transitions considered in the base case scenario. Bayer agree that it is an informative and useful way of presenting the model structure, even if not all of the transitions that are theoretically possible in the model are presented.	Not a factual inaccuracy. The ERG appreciates that the company later provided clarity regarding the model structure, but this statement within the ERG report accurately describes the discrepancies noted in the company's diagrams, and hence why the ERG opted to produce its own diagram. The use of 'discrepancy' to describe incompatibilities between the

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
		In Document B the model structure was presented in a more simplified way in order to show its consistency with the progressive nature of the disease and existing literature. Whilst we accept that we could have made the structure clearer in Document B, in the response to clarification questions (question B4) it was clarified that not all possible transitions were presented in the model diagram. Hence, we believe that suggesting that there were *discrepancies* between the diagram and the economic model by the ERG is misleading.	diagram and the model itself is appropriate in this context.

Issue 24 Model diagram

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 80 of the ERG report, Figure 1. An arrow should be removed as it does not represent a possible transition in the model.	The arrow between CKD 5 w/o RRT to CKD 1/2 should be removed.	The transition probability for CKD 5 w/o RRT to CKD 1/2 is 0 for both arms and, therefore, is not in line with the model structure presented by the ERG. If the ERG diagram included all possible transitions where the probability is zero, the diagram should include many more arrows which would make it unreadable.	Not a factual inaccuracy. This value is zero, but it is technically possible to have it influence transitions within the model as this is part of the transition matrix. In other words, within the company's model, this could be set to a non-zero value, changing the model results.

			The company may wish to clarify that this is both (a) at a value of zero, and (b) impossible in the context of the disease, but this was not stipulated by the company within its submission. The ERG nevertheless expects that transitions from CKD 5 without RRT to CKD 1/2 are not possible, but referring to the issue of parameter uncertainty, the ERG was not able to verify if the company intended for this transition to ever be truly possible.

Issue 25 *Minor point* correction of UACR range and units

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 82 of the ERG report incorrectly reports UACR range definitions.	Please make the following amendment: 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]).	For accuracy.	Checked and amended as per the company's proposed amendment. Refer to Section 4.2.3, p84

Issue 26 *Minor point* regarding reported information

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 83 of the ERG report states: 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). The ERG highlights that these percentages are not possible to directly verify with the **reported information** available from the FIDELIO-DKD trial publication as the cut-offs for CKD stage differ to the groupings presented in the study materials.	Please make the following amendment: 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). ~~The ERG highlights that these percentages are not possible to directly verify with the **reported information** available from the FIDELIO-DKD trial publication as the cut-offs for CKD stage differ to the groupings presented in the study materials.~~	For accuracy and balance. Bayer provided this information in the submission as AIC data. It is not in the trial publication as the trial publication reports the whole trial population, whereas in the submission, we present the whole trial population as well as the proposed label population. For this we have used patient level data.	Checked and amended as per the company's proposed amendment. Refer to Section 4.2.3, p84

Issue 27 *Minor point* description of eGFR ranges

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 83 of the ERG report describes eGFR categories incorrectly.	Please make the following amendment: "…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…."	For accuracy.	Text has been amended for clarity as per the company's proposed amendment. Refer to Section 4.2.3, p84

Issue 28 *Minor point* dose distribution

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 84 of the ERG report incorrectly describes the dose distribution.	Depending on the point the ERG want to make, the dose distribution reported by the ERG ([redacted]% 10mg/day and [redacted]% 20mg/day) does not relate to the starting dose distribution at screening visit. Instead, the values presented is the average distribution of doses over the duration of the FIDELIO-DKD trial.	For accuracy.	Text has been amended for clarity broadly per the company's proposed amendment. Refer to Section 4.2.4, p85

Issue 29 *Minor point* description of eGFR ranges

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 84 of the ERG report describes eGFR categories incorrectly	Please make the following amendments: (1) eGFR **≥**25 - **<**60: 10mg / day (2) 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….	For accuracy.	Text has been amended for clarity as per the company's proposed amendment. Refer to Section 4.2.4, p85

Issue 30 Incorrect reporting of values

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 87 of the ERG report incorrectly reports values and interpretation of these values	Please make the following amendment • Patients with CKD1/2 are ~~more~~ **less** likely to progress to CKD4 if treated with finerenone	For accuracy.	Checked versus Table 43 and Table 44 of the CS (Document B). Text has been corrected as

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
	versus BT ([redacted]% versus [redacted] %), yet are ~~less~~ **more** likely to progress to CKD3 ([redacted]% versus [redacted]%) or CKD 5 without RRT ([redacted]% versus [redacted]%)		per the company's proposed amendment. Refer to Section 4.2.6.1, p88

Issue 31 Relevant transitions

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 87 of the ERG report does not report all of the "impossible" transitions in the model based on the FIDELIO data and incorrectly reports one of these.	Please make the following amendment □ ~~The relevant transitions are~~ some of these include: o [redacted] to [redacted] for [redacted] o [redacted] to [redacted] for [redacted] o [redacted] to [redacted] for ~~finerenone~~ [redacted]	For accuracy. This is not a complete list of the "impossible" transitions based on the FIDELIO data. For example, there is also no possibility to transition from [redacted] to [redacted].	Text has been amended for clarity as per the company's proposed amendment. Refer to Section 4.2.6.1, p88

Issue 32 Error in description of clarification question

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 90 of the ERG report incorrectly refers to clarification question B10 being in relation to CV events	Depending on the point being made by the ERG – should CV event be replaced by CV death in this section?	For accuracy. Clarification question B10 related to CV and renal deaths.	Text has been amended for clarity as per the company's proposed amendment, with additional text to refer the reader to section of mortality.

			Refer to Section 4.2.3.2, p91

Issue 33 Reduction in CV events

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 90 of the ERG report, it is stated that: *"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."*	We suggest deleting this sentence.	The reduction in CV events estimated in the model has been compared to the results of the FIDELIO-DKD trial within the model validation exercise. It has been shown that model predictions are consistent with trial results, hence the comment from the ERG is not accurate.	Not a factual inaccuracy. The ERG considers this comment to be appropriate, especially in light of the fact that the model projects lifetime costs and effects based on the FIDELIO-DKD study which does not have complete follow up.

Issue 34 Error in description of hyperkalaemia

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 92 -3 of the ERG report incorrectly refers to statistical significance: *"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 a statistically significant increase in risk associated with finerenone*	Please make the following amendment. "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 a ~~statistically~~ significant increase in risk associated with finerenone observed in the FIDELIO-DKD study"	For accuracy. The words "statistically significant" are based on assertion by the ERG, not the data presented. There were no statistical tests presented for safety. We believe the ERG have misrepresented the text in Table 40, Document B.	Checked and amended to remove reference to statistical significance. The text now states "an increase in risk" rather than "a statistically significant increase in risk". Refer to Section 4.2.6.2, p93-94

observed in the FIDELIO-DKD study"			

Issue 35 *Minor point* error in description of AE

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 93 of the ERG report incorrectly refers to hypokalaemia instead of hyperkalaemia	Please make the following amendment. From this, the ERG inferred that over the lifetime horizon of the model, an average of 0.93 ~~hypokalaemia~~ **hyperkalaemia** events occur for finerenone patients, versus 0.60 for the BT arm.	For accuracy.	Corrected to hyperkalemia. Refer to Section 4.2.6.2, p94

Issue 36 Inclusion of clinically relevant events in the model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 94 of the ERG report, Sustained decrease in eGFR ≥ 40% from baseline (over at least 4 weeks). It is stated that: *"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 and costs, that this event is one component of the primary composite endpoint of the FIDELIO-DKD study, and that a statistically significant reduction*	Please make the following amendment: "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 ~~and costs~~, 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."	It was clear in Document B that the event *Sustained decrease in eGFR ≥ 40% from baseline (over at least 4 weeks)* was related only with an impact on HRQoL, not costs. This point is clarified later in the ERG report but retaining the expected cost impact in this paragraph can be misleading for the reader.	Text has been corrected to remove reference to an impact on costs aligned with the company's proposed amendment. Refer to Section 4.2.6.2, p96

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
in risk associated with finerenone observed in the FIDELIO-DKD study."			

Issue 37 Disutility in relation to CV events

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 105 of the ERG report. It is stated that: *"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 first 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*	This statement should be changed to reflect that in the model the post-acute disutility related to CV events is also applied in the acute phase and not the other way around as it is stated by the ERG.	The results of the multivariate model represent the post-acute phase after CV events. Indeed, all EQ-5D assessments of patients with any CV events within the FIDELIO-DKD trial have been considered in obtaining this disutility.	Text has been amended for clarity as per the company's proposed amendment. Refer to Section 4.2.7, pp106-107

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
decreasing as patients recover from their CV event).”			

Issue 38 EQ-5D assessments

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 106 of the ERG report, it is stated that: *“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).* ***The ERG assumes that this was still used to classify prior CV events when acute and post-acute were combined in the analysis****. It is therefore unclear to the ERG whether all CV events were captured in the analysis, as it is 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 is*	All of these ERG considerations should be removed together with the corresponding scenario analysis proposed by the ERG.	These considerations as well as the corresponding scenario analysis proposed by the ERG result from an incorrect assumption (highlighted in bold). In the multivariate analysis all EQ-5D assessments were taken into account for patients after any CV event within the study, not only those experienced within the last 4 months before a given visit.	The ERG acknowledges the company’s explanation that the definitions of acute and post-acute were essentially not used in the multivariate analysis, and instead all CV events that occurred within the trial were captured. Therefore, the ERG has edited the text on page 106 of its report accordingly. However, the ERG has maintained its original interpretation as it relates to the content of the company’s submission, while also clarifying this has now been resolved. Some latter aspects of the ERG’s report were also edited in light of this, though some are still appropriate in light of the limitations of the CV event analysis (i.e., that a single disutility is modelled), and so these aspects (including

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
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 does not align with the methodology used in the multivariate analysis. *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 data were excluded, but prior CV events were determined based on the prior 4 months; the ERG,*			scenario analyses) are left unchanged in the ERG's report. Refer to Section 4.2.7, p109

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
therefore, note that some patients entering the trial will have perhaps experienced a CV event within 4 months of the trial start (or perhaps before this time period), and therefore should be reflected in the analysis as 'post-acute CV event' rather than 'no CV event'."			

Issue 39 Disutility for CV events

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 107 of the ERG report incorrectly describes the approach taken by Bayer. The report states: *"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 first CV events were MI's, strokes, and hospitalisations due to HF, rather*	Please amend the text as follows: "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 ~~first~~ **all** CV events were MI's, strokes, and hospitalisations due to HF, ~~rather than being based on the distribution of subsequent CV events. However, the ERG recognizes that these data are likely not available, so in the absence of alternative data this approach is left unchanged."~~	For accuracy. Please clarify if the ERG still considers this to be a limitation. This is factually incorrect. The utility decrement is weighted based on what proportion of all CV events were MI's, strokes, and hospitalisations due to HF.	Text has been partially amended for clarity as per the first part of the company's proposed amendment. However, this is still a limitation of the model, and so the remainder of the text has been left largely unchanged. Refer to Section 4.2.7.3, p108

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
than being based on the distribution of subsequent CV events. However, the ERG recognizes that these data are likely not available, so in the absence of alternative data this approach is left unchanged."			

Issue 40 Incorrect referral to NICE clinical guideline

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 112 of the ERG report refers to the published NICE NG203 as a source for Bayer.	Please make the following amendment. The costs for each CKD health state were taken from two sources: NICE TA35849 (tolvaptan for treating autosomal dominant polycystic kidney disease), and **the draft of** NICE NG203[4] ~~(which was published on 25 August 2021).~~	For accuracy. We did not use the published NG203 as a source as it was only published in August 2021. Instead, we used the draft document which was published as part of the consultation.	Text has been amended to clarify: "and NICE NG2034 ***(draft guideline for consultation)*** ~~(which was published on 25 August 2021)~~." Refer to Section 4.2.8.3, p113-114

Issue 41 Incorrect referral to NICE clinical guideline

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 113 of the ERG report refers NICE	Please make the following amendment.	For accuracy. We did not ultimately use CG182 as a source. Instead we used the draft	Text has been amended to clarify NG203 "The company stated that they had used the

CG182 as a source for Bayer.	The company stated that they had used the draft CKD clinical guideline published in March 2021 ~~(CG182)~~ to inform the costs used in its model	document which was published as part of the consultation for the development of NG203. https://www.nice.org.uk/guidance/ng203/history This is reference 116 in Document B. As this was available on the NICE website we did not provide the document in the reference pack. The ERG should be able to verify the costs from this source as well as the 15% figure referred to in the following paragraph in the ERG report. CG182 was one of the NICE guidelines replaced and updated by the publication of NG203.	draft CKD clinical guideline published in March 2021 (~~CG182~~***NG203 [draft for consultation]***) to inform the costs used in its model." Also, later in this paragraph, the ERG has edited the text to clarify that the draft guideline was later updated. Refer to Section 4.2.8.3, p113-114

Issue 42 Incorrect referral to cost of a CV event

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 113 of the ERG report refers to the length of the post-acute period for a CV event.	Please make the following amendment. 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 **or other transitions**).	For accuracy.	Not a factual error. It is the ERG's understanding that costs for CV events in the post-acute period are applied within the company's model until death, and that there is no other transition that would lead to these costs no longer being applied. Therefore, in absence of a clear rationale for a

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
			different transition which causes these costs to no longer apply, the ERG has left this wording unchanged.

Issue 43 Interrelated parameters

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 117 of the ERG report, paragraph 5.1.2. It is stated that: *"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)."*	A different example of interrelated parameters excluded from being varied simultaneously than the utility estimates should be given, if any exists in the opinion of ERG.	The utility value estimates are varied simultaneously in the most correlated part i.e. utilities assigned to health states reflecting CKD progression.	Not a factual error. The individual utility values are varied independently within the model, even if they are sampled using the same random number. This means that the relative difference between the values is maintained in probabilistic draws, which is methodologically inappropriate, warranting this comment in the ERG's report.

Issue 44 Bounds of uncertainty

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 117, ERG report, paragraph 5.1.2. It is stated that:	This comment should be deleted.	This comment is inaccurate as the referred bounds most likely do not	Not a factual error.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
"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."		represent the uncertainty at the individual level. For example, the bounds of uncertainty for the cost of an acute IS stroke were based on 95% CI from Alva 2015.	Without the context provided in the company's submission, the ERG considered it appropriate to offer a possible explanation for why the bounds of uncertainty were seemingly wide for some model parameters. Based on the justification provided by the company, the ERG is still unclear why the bounds are wide for other parameters (more notably, utility values).

Issue 45 *Minor point* Incorrect reporting of utility bound

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 117 of the ERG report refers to an incorrect value.	Please make the following amendment. For example, the utility for CKD3 is varied between bounds of [redacted] and [redacted], centred at [redacted].	For accuracy.	Text has been checked vs company submission (Document B) and corrected as per company's proposed amendment. Refer to Section 5.1.2, p119

Issue 46 Adjustments vs errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 123 of the ERG report, it is stated that:	We suggest amending this sentence (and the title of section 6.1) to:	There were no errors identified by the ERG in the model, hence the	The ERG considers the adjustment of the treatment

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
"Section 6.1 details the impact of errors identified in the ERG's validation of the executable model."	"Section 6.1 details the impact of **adjustments** made by the ERG in the company base case model"	ERG report should describe the adjustments rather than corrections. Referring to errors and corrections can be misleading to the reader.	discontinuation rate to constitute a correction, and so the text has been edited accordingly. Refer to Section 6, p125

Issue 47 Incorrect reporting of CKD health state

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 126-127 of the ERG report incorrectly refers to CKD3.	Please make the following amendment. • 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 ~~CKD3~~ CKD 1/2).	For accuracy.	Text has been amended for clarity as per the company's proposed amendment. Refer to Section 6.2.2, p129

Issue 48 Description of sub-model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 127 of the ERG report incorrectly refers to a 'prior CV event' sub-model (in two places on this page).	We suggest keeping wording consistent with Document B i.e. 'post-CV event' sub model.	Using the description 'prior CV event' may suggest that this sub model concerns patients with CV history, whereas this is not the case. As described in Document B, the sub model reflects the first modelled CV event and states after the first CV event.	Text has been amended for clarity as per the company's proposed amendment. Refer to Section 6.2.3, p129

Location of incorrect marking	Description of incorrect marking	Amended marking	ERG response
ERG report page 32, paragraph 1	*"eGFR [redacted] mL/min/1.73m^2."* This does not need to be marked as confidential as per Document B.	"eGFR ≥60 to 75 mL/min/1.73m^2."	Marking has been updated in the ERG report aligned with company's indicated amendment.
ERG report page 34, section 2.4.3.1	AIC marking missing *"received ACE-i (1,633 participants in the label population) and 3,725 participants received ARB (3,222 participants in the label population)."*	"received ACE-i ([redacted] participants in the label population) and 3,725 participants received ARB ([redacted] participants in the label population)."	Marking has been updated in the ERG report aligned with company's indicated amendment.
ERG report page 44, Table 11	The values for potassium supplements should be marked as AIC in this table (Bayer omitted this marking in error in Document B)	[redacted]%; [redacted]%	Marking has been updated in the ERG report aligned with company's indicated amendment.
ERG report, page 49, section 3.2.2.2	AIC marking missing *Mean eGFR was slightly lower at 41.8 mL/min/1.73 m^2*	Mean eGFR was slightly lower at [redacted] mL/min/1.73 m^2	Marking has been updated in the ERG report aligned with company's indicated amendment.
ERG report, page 54	AIC marking missing. *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 and none of the disaggregated outcomes for finerenone plus BT*	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]	Marking has been updated in the ERG report aligned with company's indicated amendment.

Location of incorrect marking	Description of incorrect marking	Amended marking	ERG response
	versus placebo plus BT reached statistical significance		
ERG report, page 54	AIC marking missing. *The incidence of CV deaths and fatal non-CV or non-renal events was lower with finerenone plus BT than with placebo plus BT but results were not statistically significant*	The incidence of CV deaths and [redacted]was lower with finerenone plus BT than with placebo plus BT [redacted]	Marking has been updated in the ERG report aligned with company's indicated amendment.
ERG report, page 54	AIC marking missing. *The incidence of CV deaths and fatal non-CV or non-renal events were [redacted]with finerenone plus BT than with placebo plus BT but results were not statistically significant*	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]	Marking has been updated in the ERG report aligned with company's indicated amendment.
ERG report, page 54 and page 97	AIC marking not necessary. the risk of CV death [i.e., the HR increased from [redacted]to [redacted], meaning the risk reduction fell from [redacted]% 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]%])	Marking has been updated in the ERG report aligned with company's indicated amendment.
ERG report, page 55	AIC marking missing. None of CV hospitalisation, hospitalisation for HF, or other hospitalisation for finerenone plus BT versus placebo plus BT reached statistical significance	[redacted]	Marking has been updated in the ERG report aligned with company's indicated amendment.
ERG report, page 55	AIC marking missing.	(hazard ratio, 0.76; 95% CI, 0.65 to 0.90; p=[redacted]) (Table 15). [redacted](Table 16). As for the	Marking has been updated in the ERG report aligned with

Location of incorrect marking	Description of incorrect marking	Amended marking	ERG response
	(hazard ratio, 0.76; 95% CI, 0.65 to 0.90; p=0.001) (Table 15). Results in the label population were similar to those reported for the FAS (Table 16). As for the primary composite kidney outcome, 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]	primary composite kidney outcome, the [redacted] observed on the composite outcome for finerenone plus BT vs. placebo plus BT [redacted]	company's indicated amendment.
ERG report, page 63	AIC marking missing. In those subgroups where secondary outcomes are reported within Appendix E, the results were broadly similar to those in the overall population.	In those subgroups where secondary outcomes are reported within Appendix E, [redacted].	Marking has been updated in the ERG report aligned with company's indicated amendment.
ERG report, page 63	AIC marking not necessary. All of the values in this table are marked as AIC.	None of the values in the table need to be marked as AIC.	Marking has been updated in the ERG report aligned with company's indicated amendment.
ERG report, page 73	AIC marking not necessary. While the company focuses on a subgroup of the trial population, the subgroup makes up [redacted]% of the trial population	While the company focuses on a subgroup of the trial population, the subgroup makes up 85% of the trial population	Marking has been updated in the ERG report aligned with company's indicated amendment.
ERG report, page 74	AIC marking missing. In the label population, finerenone showed numerical benefits on the primary outcome (composite of onset of kidney failure, a	In the label population, finerenone showed [redacted] benefits on the primary outcome (composite of onset of kidney failure, a sustained	Marking has been updated in the ERG report aligned with company's indicated amendment.

Location of incorrect marking	Description of incorrect marking	Amended marking	ERG response
	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), but this effect was only significant for the first outcome. It is important to note that when the primary outcome was disaggregated, the statistically significant improvement observed on the composite outcome for finerenone vs. placebo was also only reproduced for one of the disaggregated outcomes, sustained decrease ≥ 40% in eGFR from baseline.	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.	
ERG report, page 85	AIC marking is missing. The model calculates costs and outcomes over a 'lifetime' horizon, set to 34.2 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 34.2 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 34.2	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	Marking has been updated in the ERG report aligned with company's indicated amendment.

Location of incorrect marking	Description of incorrect marking	Amended marking	ERG response
	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). As 65.8 is marked as AIC, by implication 34.2 needs to be marked as AIC	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).	
ERG report, page 128	AIC marking not necessary. …reflecting a utility higher than CKD3 [redacted].	…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 Table 58).	Marking has been updated in the ERG report aligned with company's indicated amendment.

Additional table caption and cross-referencing issue identified by ERG:

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG report, p36: "…in which a reduction in the primary outcome was observed, although the sample size is small (Table 2."	ERG report, p36: "…in which a reduction in the primary outcome was observed, although the sample size is small (Table ~~2~~***8***)." And ERG report p 37	Manual table caption and manual table cross reference was incorrect. Table caption inserted and cross reference updated	NA

And ERG report p 37 Table 2. Primary composite renal outcome according to prespecified subgroup SGLT-2i at baseline	Table ~~2~~***8***. Primary composite renal outcome according to prespecified subgroup SGLT-2i at baseline		

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Technical engagement response form

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

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

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We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **Monday 14 March 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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About you

Table 1 About you

Your name	Lesley Gilmour
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Bayer plc
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Current Situation** • Bayer does not have direct or indirect links with, or funding from, manufacturers, distributors or sellers of smoking products but Bayer provides pesticides for crops, which would therefore include tobacco crops. • Bayer is a member of the Cooperation Centre for Scientific Research Relative to Tobacco (CORESTA) (http://www.coresta.org/) within the scope of recommendations of pesticides used for protection of tobacco plants. • It is also a member of country and EU business federations such as the Confederation of British Industry (CBI) and 'Business Europe', which include tobacco companies. **Past Situation** In 2006, Bayer and its subsidiary Icon Genetics piloted a new process for producing biotech drugs in tobacco plants. Icon Genetics was acquired by Nomad Bioscience GmbH from Bayer in 2012.

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Key Issue 1: Uncertainty in the appropriate population	**Yes**/No	Bayer do not consider there to be uncertainty in the population. Bayer acknowledged in the factual accuracy check of the ERG report that we may have caused confusion in how the population was described in the original submission documentation. In response to the factual accuracy check we provided further clarity on the populations presented in the submission and that for which we were seeking a NICE recommendation. For clarity for the appraisal committee meeting, we describe the population presented in the submission below. The EU and GB license for finerenone is for a narrower population than that studied in FIDELIO-DKD (approximately 89% of the study population): *"Finerenone is indicated for the treatment of chronic kidney disease (stage 3 and 4 with albuminuria) associated with type 2 diabetes in adults."*

		The study included some individuals with higher eGFR i.e. patients in the G2 category of CKD, but their entry to the study was capped. Stage 4 CKD includes those with an eGFR between 15 and 29 ml/min/1.73m^2. The inclusion criteria for FIDELIO-DKD had a lower limit of eGFR at screening of 25ml/min/1.73m^2. Despite this, there were 2.4% of patients who had a lower eGFR (<25 ml/min/1.73 m^2) at baseline. This number represents patients who had an eGFR level qualifying for participation at the screening phase, but later deteriorated, reaching a level of <25 ml/min/1.73 m^2 at the baseline. As a result of the trial inclusion criteria and limited clinical data, the SPC states that finerenone should not be initiated in patients with an eGFR < 25ml/min/1.73m^2. As such, Bayer presented data for the following population, in line with the marketing authorisation, and this is the population for which we seek appraisal by NICE: **Adults with chronic kidney disease (stage 3 and 4 with albuminuria*) and type 2 diabetes.** ***eGFR≥ 25ml/min/1.73m^2** For completeness, Bayer also presented in the submission clinical data and cost effectiveness results based on the full analysis set (FAS), which included all randomised patients except those excluded for GCP violations (see definition in Table 11, Document B). We do have the data for the small number of patients who did receive finerenone in the study, in violation of the study inclusion criteria i.e. patients with an eGFR at baseline <25ml/min/1.73m^2 (n=66; 2.3%). Indeed, these patients are included in the FAS analysis. For clarity these are not included in the base case population, which is the population addressed by the marketing authorisation. According to the figure in Appendix E to the submission, there was no evidence of interaction in the primary outcome of FIDELIO-DKD when analysis was conducted by baseline eGFR, including the category “eGFR <25ml/min/1.73m^2”.

To address the concerns of the ERG, Bayer have performed analyses to check the influence of inclusion of patients with eGFR < 25ml/min/1.73m^2 in the model. The full data set required in the model for the "label" population with inclusion of patients with eGFR < 25ml/min/1.73m^2 was obtained from statistical analyses of patient level data from the FIDELIO-DKD study. Analogous data were obtained to those considered in the original submission but for this slightly broader population. The results from the requested population i.e., CKD 3 and CKD 4 patients (i.e., eGFR ≥15 to < 60ml/min/1.73m^2 at baseline) with albuminuria and type 2 diabetes are presented in the table below (Table 1). There was minimal difference compared to the base case results.

Table 1. Deterministic results for subpopulation of patients with CKD 3 and CKD 4 (i.e., eGFR ≥15 to < 60ml/min/1.73m^2 at baseline) with albuminuria and type 2 diabetes based on FIDELIO-DKD data.

Population	Incremental costs, undiscounted	Incremental costs, discounted	Incremental QALYs, undiscounted	Incremental QALYs, discounted	ICER, undiscounted	ICER, discounted
Base case: CKD 3 and CKD 4 patients with albuminuria (i.e., eGFR ≥ 25 to <60ml/min/1.73m^2 at baseline) and type 2 diabetes	£2,041	£1,779	0.15	0.10	£13,893	£17,552
Scenario: CKD 3 and CKD 4 patients with albuminuria (i.e., eGFR ≥15 to <60ml/min/1.73m^2 at baseline) and type 2 diabetes	£2,477	£2,102	0.17	0.12	£14,252	£17,340

		Bayer maintain that the population presented and for which we seek recommendation from NICE is completely aligned with the GB marketing authorisation.
Key Issue 2: Missing comparison with SGLT-2i	Yes/**No**	The premise of finerenone treatment in chronic kidney disease is that it targets a new treatment pathway to delay CKD progression (1-3). There remains a residual risk of progression to more advanced CKD stages with existing therapies for CKD in T2D (4-7) and by utilising a new treatment pathway, the addition of finerenone to existing therapy provides further opportunity to expand the current therapeutic approach. The clinical study upon which finerenone's licence is based was designed with this in mind (8). In the phase III FIDELIO-DKD study, finerenone was added into optimised (maximum labelled dose) background therapy, consisting of an ACEI or ARB - the mainstay treatment for retarding the progression toward end-stage renal disease for decades - alongside glucose-lowering therapies including insulin, metformin, DPP-4 inhibitors, GLP-1 receptor agonists and SGLT2 inhibitors and other concomitant medications (e.g., beta blockers, diuretics, anti-platelets and statins). This flexible approach, has enabled finerenone to be studied in a setting as close to 'clinical practice' as possible, taking account of the polypharmacy needs of a diabetic population with cardiovascular and renal risks. As a novel, selective, non-steroidal mineralocorticoid receptor (MR) antagonist, finerenone does not replace the therapeutic actions of existing therapies in CKD in T2D and its introduction would not alter any current recommendations and choices associated with background therapy or displace any current treatment. The MR is expressed extensively in the heart, kidneys and blood vessels (1, 2, 9). In CKD, the MR is overactivated, contributing to organ damage, through mediation of pro-inflammatory and pro-fibrotic effects, as well as via increased sodium and water retention and endothelial dysfunction (2, 10-12). With the implications of MR activation in CKD, the addition of finerenone – a nonsteroidal, selective, MR antagonist (MRA) – to current standard of care, provides an additional process in addressing CKD progression. The modest effect on systolic blood pressure suggests a largely non-haemodynamic mechanism of action for finerenone, which also had no clinically meaningful effect on HbA1c (8), suggesting little overlap of key medications already taken by T2D patients with CKD. Finerenone is the only therapy targeting the MR to be

		approved for use in patients with CKD and T2D, thus providing an independent treatment alongside other therapies used to treat CKD in T2D. When considering relevant comparators for finerenone, Bayer considered that central to any therapeutic approach in CKD in T2D is ACEI/ARB treatment and that other interventions, be it the *type* of glucose-lowering medication or any concomitant medication or lifestyle adjustments, would vary. This corresponds with established clinical practice and is reflected in the comparator arm in the FIDELIO-DKD phase III study and cost-effectiveness model within Bayer's submission. Despite the recent licence amendments and addition into guideline recommendations for CKD in T2D (13, 14), SGLT2is are not considered as relevant comparators within the finerenone appraisal for the following reasons: **(a)** Currently in the UK, very few patients are receiving SGLT2Is in line with these guidelines. NICE recommendations with regards to SGLT2i in T2D and CKD were only introduced in November 2021 and are yet to translate into routine clinical practice. While usage is anticipated to increase, Bayer contend that SGLT2is are not currently embedded within clinical practice in the UK for the management of CKD, a pre-requisite according to the NICE methods guide (see d below). **(b)** Even with a hypothetical 'full' adherence to NICE guidelines, not all patients would be receiving SGLT2Is according to patient need, preference and suitability (15-19), however all patients would still be treated according to the core therapeutic approach of ACEI/ARB treatment. As with the choice of glucose-lowering therapies, concomitant medications and lifestyle adjustments, SGLT2Is thus remain a variable rather than a constant, with regard to background therapy. **(c)** Consultee feedback (both patient and professional group) on the draft scope also confirmed that SGLT2Is should not be considered a comparator as they are not yet part of standard care. **(d)** Bayer have already set out in detail our reasons for considering that SGLT2is do not meet the definition of a comparator according to the NICE methods guide (20). This can be found in response to the draft scope, during decision problem discussions and in prior related submission documents. In Section 6.2.2 / 6.2.3 of the NICE methods guide it is stated that when selecting the most appropriate comparators, the committee

		must consider five factors, which won't be considered equally; rather, the committee will normally be guided by established practice in the NHS. A summary of the factors Bayer considers are still not met is discussed below: **(d1)** Established NHS practice in the UK - Most importantly, sales data estimate the market share (by volume) of SGLT2 inhibitors at approximately [redacted]% of drugs for T2D (Bayer, data on file). It is also not known what proportion of this low volume is for patients with both type 2 diabetes and CKD. This does not suggest SGLT2is are sufficiently prescribed to represent part of routine care for patients with diabetes and CKD. For additional context, the market share by volume for biguanides is approximately [redacted]% of drugs for T2D (Bayer, data on file). **(d2)** Existing NICE guidance – It is only during the submission process for finerenone in CKD in T2D, that NICE have updated their Chronic Kidney disease [November 2021; NG203 (14)] and Type 2 diabetes [February 2022; NG28 (13)] guidelines to state that SGLT2Is can now be: - Offered to 'adults with CKD and T2D, who are taking an ARB or an ACE inhibitor (titrated to the highest licensed dose that they can tolerate), in addition to an ARB or an ACE inhibitor if ACR is > 30 mg/mmol, and they meet the criteria in the marketing authorisation (including relevant eGFR thresholds). - Considered for 'adults with CKD and T2D, who are taking an ARB or an ACE inhibitor (titrated to the highest licensed dose that they can tolerate), in addition to an ARB or an ACE inhibitor if ACR is between 3 and over 30 mg/mmol, and they meet the criteria in the marketing authorisation (including relevant eGFR thresholds). **(d3)** The licensing status of the comparator – amendments to two of the SGLT2 inhibitor's licenced indications regarding renal outcomes were recently made. The other SGLT2 inhibitors, empagliflozin and ertugliflozin have no indication specifically related to CKD. Bayer maintain that the recentness of any changes to NICE guidelines and marketing authorisations, coupled with the sales estimates for SGLT2is show that it cannot reasonably be stated, whilst licensed or unlicensed, that SGLT2 inhibitors represent an established part of clinical practice for the treatment of CKD patients with diabetes. **(e)** The mode of action of the two classes of drugs are different which would limit the suitability and quality of a comparison. Metabolic and haemodynamic consequences of SGLT-2i use, including glycosuria and lowering of intraglomerular pressure via activation of tubuloglomerular feedback, are the main mechanisms

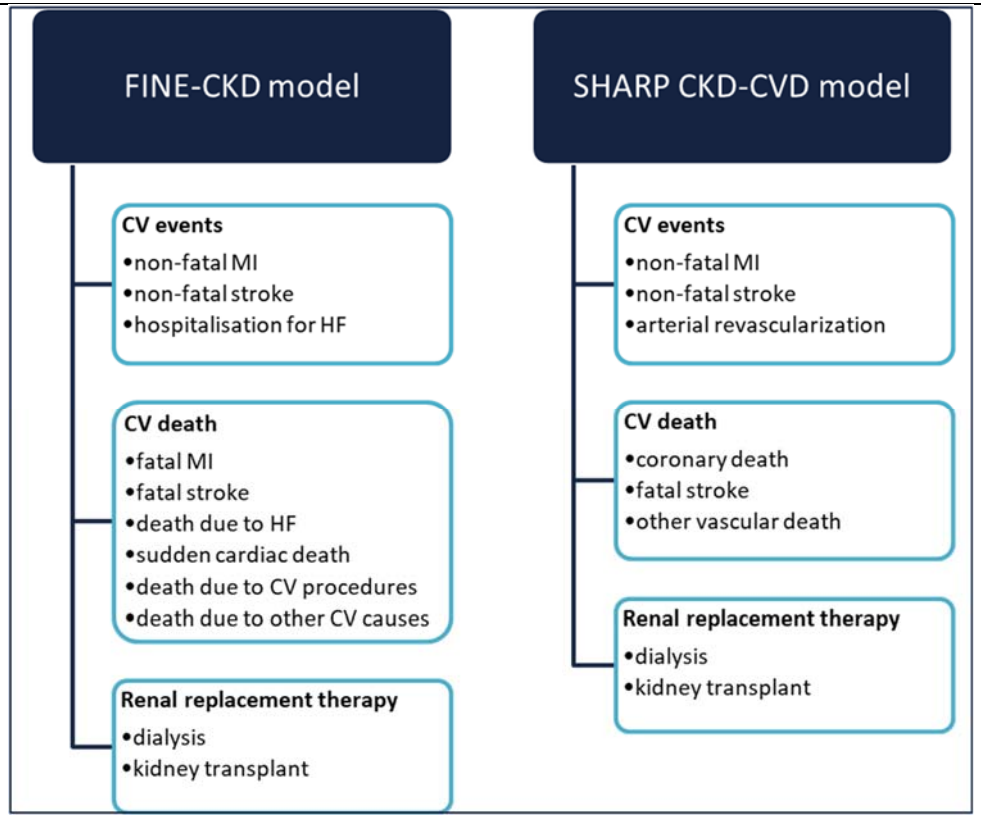
		believed to contribute to improved kidney and CV outcomes in patients treated with SGLT-2is (21-23). In contrast, as discussed earlier in this section, the mechanism of kidney and CV protection with finerenone involves inhibition of mineralocorticoid receptor overactivation, leading to anti-inflammatory and anti-fibrotic effects, as demonstrated in the heart and kidneys in preclinical models (2, 10, 11, 24-26). Feedback from clinicians has indicated that the availability of finerenone gives them another treatment modality to add to their "tool box" where for decades, they have been solely reliant on ACE inhibitors and ARBs. **(f)** A comparison between SGLT2 inhibitors and finerenone would be limited by fundamental differences in the trial populations and methodology implemented in the FIDELIO-DKD trial vs recent SGLT2i studies. **In conclusion, Bayer considers that the presented analysis comparing finerenone in addition to standard of care with standard of care alone is the relevant comparison for decision making.**
Key Issue 3: Uncertainty in the clinical relevance of trial outcomes	**Yes**/No	The ERG has expressed uncertainty in the trial outcomes as the statistically significant improvement on the composite primary outcome of the FIDELIO-DKD study was only reproduced for one of the disaggregated outcomes, namely, sustained decrease ≥40% in eGFR from baseline. Firstly, it should be noted that the study was powered to show significance on the composite endpoint, not the components. Whilst the ERG are correct in their observation, for all of the following components of the primary composite endpoint (kidney failure, end stage renal disease, sustained decrease in eGFR <15ml /min/ 1.73m^2, and sustained decrease of ≥40% in the eGFR from baseline), the HR was <1.0 for the finerenone arm. For the component renal death, there were <0.1% cases in each study arm, demonstrating that this is a rare event in the chosen trial population over the studied period(8). Indeed, progression of CKD is usually slow, so there is general acceptance that surrogate measures are valid for the development and approval of new drugs in this therapy area; kidney failure or a doubling of serum creatinine requires prolonged follow-up with very large sample size.

		According to the EPAR (yet to be published), the primary endpoint was *"considered appropriate and in line with scientific advice from CHMP" as well as "considered clinically relevant."* Decreasing eGFR and increasing albuminuria (UACR) are robust independent and additive predictors of increasing risk of CV events, mortality and accelerated progression of kidney disease(27). Changes in either measure have biological plausibility as an endpoint in clinical trials. Indeed, both are considered to fulfil the criteria for surrogacy as end points in phase 3 clinical trials for chronic kidney disease progression by The National Kidney Foundation (NKF) in collaboration with the EMA and FDA(28). Decline in glomerular filtration rate is an intermediate step on the pathway to end-stage renal disease (ESRD). The endpoint 'a sustained decrease of eGFR ≥40% from baseline over at least 4 weeks' is an established surrogate that predicts progression to kidney failure. A strong association between a decline in eGFR and risk of end-stage kidney disease (ESKD) has been found in observational studies. Patients with an eGFR below 60 ml/min/1.73 m^2 who have a decline in the eGFR of ≥40% from baseline have a ten-fold higher risk of kidney failure over two years than those with a stable eGFR(29). To assess heterogeneity of the individual components of the primary composite efficacy endpoint in FIDELIO-DKD, a new Cox model was calculated including the time to event information for each component of the endpoint individually. The same Cox model (including stratification) as for the composite endpoint was used, only adding a factor for the respective component and for the interaction between treatment and component. A significant interaction between treatment and component would have been interpreted as a sign of heterogeneity between the components of the composite endpoint. As the p-value was found to be [redacted], no sign of heterogeneity was identified (Bayer, data on file). In addition, post hoc analyses exploring whether the risk of kidney failure increases after previous occurrence of sustained eGFR reduction of 40% or more from baseline value over at least 4 weeks were performed based on data from FIDELIO-DKD. In order to examine the relationship between these 2 endpoints, the occurrence of kidney failure was compared before and after the occurrence of sustained eGFR reduction of 40% or more from baseline value over at least 4 weeks. This was assessed by Cox proportional hazard model stratified by the stratification factor used for randomization, and with the time-

		dependent covariate "*sustained eGFR reduction of 40% or more from baseline value over at least 4 weeks*". The HR for kidney failure was [redacted] (95% confidence interval: [redacted]) comparing after and before the occurrence of 40% eGFR reduction. This result suggests that the risk of developing kidney failure after the onset of sustained eGFR reduction of 40% is [redacted] than that before the onset of sustained eGFR reduction of 40%. This finding confirms that in FIDELIO-DKD, the surrogate endpoint "*sustained eGFR reduction of at least 40% from baseline lasting at least 4 weeks*" was strongly associated with the hard endpoint "*onset of kidney failure*". Consequently, reducing the occurrence of the 40% eGFR decline endpoint as demonstrated in FIDELIO-DKD translates into a reduction of the risk of kidney failure (i.e. chronic dialysis or kidney transplant)(30). The secondary renal composite endpoint in FIDELIO-DKD included 'a sustained decrease in eGFR of ≥57% from baseline over at least 4 weeks'. This relates to a doubling of serum creatinine from the baseline and is considered a late event in CKD(31). A doubling of creatinine has also been found to be a particularly strong predictor of end-stage kidney disease. A 57% eGFR decline over 2 years is associated with a 32-times increased risk for kidney failure in those with an eGFR <60 ml/min per 1.73 m^2 (29). In FIDELIO-DKD, a sustained decrease in eGFR ≥57% from baseline over at least 4 weeks occurred in 167 patients (5.9%) in the finerenone arm and 245 patients (8.6%) in the placebo arm(8) (HR 0.68, 95% CI 0.55- 0.82, log-rank test [redacted]). Although this analysis was exploratory, due to hierarchical statistical testing, the treatment effect of finerenone in delaying progression of CKD is clearly demonstrable within this outcome. To address this issue, the ERG recommends seeking clinical expert opinion to determine the clinical relevance of the results. Bayer note that in the papers shared as part of technical engagement, professional organisations refer to decline in eGFR as being an important outcome in these patients. In summary, the results of the primary endpoint confirm the clinical relevance of finerenone in delaying progression of CKD. The positive effect on kidney protection is supported by the consistency observed among the single renal components, the strong correlation between a 40% eGFR decline and kidney failure and the even stronger effect of a 23.7% lower relative risk on the secondary renal composite

		endpoint containing the component 57% eGFR decline (equivalent to a doubling of serum creatinine). The data further strengthens the validity of the 40% eGFR component as an early marker of irreversible damage(30). **In conclusion, Bayer considers the use of sustained decrease of eGFR ≥40% from baseline over at least 4 weeks as part of the primary composite endpoint, to be clinically relevant, as supported by regulators and by evidence of its strong association with the risk of end-stage kidney disease.**
Key Issue 4: Model transitions subject to substantial limitations	**Yes**/No	Upon completion of their review of the Bayer cost-effectiveness model ('FINE-CKD'), the ERG highlights a potential key issue relating to perceived structural limitations (Key issue 4). The ERG proposed that an alternative modelling structure, incorporating time-varying risks would be preferred, referencing specifically the paper of Schlackow et al 2017(32). We understand that the ERG would prefer another approach to the estimation of transition probabilities applied in the model. Indeed, the use of risk equations was considered and discussed with experts in the early stages of model development (i.e. including time variant probabilities), although rejected. There is a limited number of major events observed in the FIDELIO-DKD study and this limits the ability of these data being used to adequately estimate the risk equations. Furthermore, there is an established relationship between CKD stage and CV events (fatal or otherwise). As such, the model submitted focuses on the link between CKD stage and these events rather than extending this to an explicit consideration of other risk factors. Whilst Bayer disagree with the extent to which this identified 'key issue' represents a driver of uncertainty in the results of this appraisal, a further model validation exercise has been achieved, comparing the results of FINE-CKD with a model with a different approach for handling transitions/risks. The objective of this cross-validation was to understand if the FINE-CKD model is similar in terms of the provided outcomes. Additionally, Bayer has asked an external and independent UK health economic expert (Professor B A. van Hout, PhD) for his opinion on the validation performed and the FINE-CKD model itself. Results of this external assessment are presented within the responses to key issues 4,5 and 6.

		Methods The SHARP (Study of Heart and Renal Protection) CKD-CVD model, a Markov model described in Schlackow 2017(32) is the model, that Bayer referred to in its submission, and the ERG highlighted in their report, that we use for this exercise. For cross-validation purposes, however, the online version of the SHARP CKD-CVD model was used. This was appropriate because the publication did not present results for T2D patients, the population for which finerenone is indicated. The following clinical outcomes were chosen for this comparison: • CV events or CV death, • CV death, • initiation of RRT (dialysis and transplantation). These are the main clinical outcomes analysed in both models, which were defined in a similar way between models as presented below.



For cross-validation purposes, the patient baseline characteristics from FIDELIO were entered into the SHARP CKD-CVD model. Where there were no data available from FIDELIO, the default values from the SHARP CKD-CVD model were used.

The full lists of inputs are presented in the table below. It was not possible to source all of the parameters needed for the SHARP CKD-CVD model from the data available from FIDELIO-DKD. Therefore, for the validation, we report results as the base case value with ranges corresponding to minimum and maximum

values of each outcome possible to be obtained in the SHARP CKD-CVD model after checking all possible values for the model parameters.

Table 2. Baseline patient characteristics for validation with the SHARP CKD-CVD model

Parameter	Values used for validation	FIDELIO - label
Age	66	[redacted]
Sex	Male	[redacted]
Ethnicity	White	[redacted]
Highest education attainment	Any post-secondary education	NA
Adult dependants	No	NA
Smoking status	Never smoked	NA
Alcohol drinker	No	NA
Body mass index	≥30kg/m2	[redacted]
Clinical factors		
Diastolic blood pressure	75-84 mmHg	NA
Systolic blood pressure	130-149 mmHg	[redacted]
HDL cholesterol	0.9-1.1 mmol/L	NA
Albumin	3.9-4.1 g/dL	NA
Haemoglobin	11.6-12.9 g/dL	NA
Phosphate	1.2-1.4 mmol/L	NA
Urinary albumin: creatinine ratio	≥300 mg/g	[redacted]

		Disease history
		Latest CV event | None | NA
		Diabetes | Yes | 100% patients
		CKD stage | CKD 3B | [redacted]
		CKD duration | 17 | 16.6
		Renal diagnosis | Diabetic nephropathy | [redacted]

For the purposes of this validation, the results of the FINE-CKD model were presented as cumulative event probabilities (of major CV event or CV death, initiation of RRT, and CV death) per 1,000 participants at the end of year 5 and year 10 and were calculated using the Kaplan-Meier product.

The results of two models with different inputs were compared taking into account the ranges of estimates possible to be obtained in the SHARP CKD-CVD model and confidence intervals from the probabilistic sensitivity analysis run in FINE-DKD model.

Results

Results of the comparison with the SHARP CKD-CVD model are presented in **Table 3** for those patients who used standard of care alone (BT arm in the FINE-CKD model).

In addition to the validation of the base case inputs, as CKD progression and CV events were assessed in the SHARP CKD-CVD model by risk equations and vary in each cycle, the following parameters were also tested to generate ranges for the estimates:

- Smoking status (current smoker, ex-smoker)
- BMI (25-29 kg/m2),
- Albumin (<3.9, ≥ 4.2 d/dL),
- Haemoglobin (<11.6, ≥13 g/dL),

- Phosphate (<1.2, ≥1.5 mmol/L),
- UACR (<30, 30-300 mg/g),
- Renal diagnosis (other known or unknown cause).

The results of these tests are presented in the table below.

Table 3 Results of validation – SHARP CKD-CVD model vs. FINE-CKD model, ranges

	At 5 years			At 10 years		
	Major CV event or CV death	**Initiation of RRT**	**CV death**	**Major CV event or CV death**	**Initiation of RRT**	**CV death**
Cumulative probabilities per 1,000 participants						
SHARP CKD-CVD	236	276	92	431	670	244
FINE-CKD model (95% CI)	273 (247; 297)	106 (103; 107)	87 (73; 104)	541 (491; 587)	249 (241; 255)	181 (147; 214)
SHARP CKD-CVD (ranges)	155 - 316	41 - 413	55 - 135	283 - 549	156 - 820	137 - 349

Note that, although they are similar in structure, differences exist between the SHARP CKD-CVD model and the FINE-CKD model. The SHARP CKD-CVD model restricts health states to CKD stage 3b onwards, whereas the FINE-CKD model also includes health states for those with mild CKD in stages 1/2 and 3a (within CKD 3 stage). Consideration of more severe patients in the SHARP CKD-CVD model partially explains the higher incidence of renal events in this model, as shown in the results of the analyses undertaken which considered ranges from the SHARP CKD-CVD model. For example, analysing patients with lower UACR level (i.e., 30-300 mg/g) in the SHARP CKD-CVD model reduces the cumulative probability of RRT initiation to 94 per 1,000 participants at 5 years and 327 at 10 years. These estimates are very close to the FINE-CKD model outcomes. Other examples of parameters having impact on estimates of SHARP CKD-CVD which were not possible to be fully adjusted to the FIDELIO-DKD trial population are presented in the exploratory analysis in the table below. Please note however that the parameters “sex” and “ethnicity” have not been varied in the ranges presented in the table above.

Table 4 Results of SHARP CKD-CVD model – scenario analysis

	At 5 years			At 10 years		
Parameter	**Major CV event or CV death**	**Initiation of RRT**	**CV death**	**Major CV event or CV death**	**Initiation of RRT**	**CV death**
Cumulative probabilities per 1,000 participants						
Sex: Female	178	227	68	335	592	179
Ethnicity: Asian, lives outside China	182	252	101	349	635	263
UACR: 30-300 mg/g	**196**	**94**	**60**	**358**	**327**	**158**
Renal diagnosis: other known or unknown cause	175	234	66	333	619	178

The results of the FINE-CKD model are within the ranges that can be obtained from the SHARP CKD-CVD model, as seen in the table above.

Overall, the clinical progression modelled in the FINE-CKD model appears aligned with the results of the SHARP CKD-CVD model.

Discussion

The FINE-CKD model was developed based on the findings of a systematic literature review (SLR) and is consistent with other models in this area. Following good practice renders the model transparent and reduces the uncertainty related to unnecessary complexity. The application of a Markov framework appropriately allows for evaluation of the cost-effectiveness of finerenone in patients with CKD and T2D.

		Indeed, in the SLR among the included cost-utility analysis and cost-effectiveness analysis (n=66), there were mainly Markov or semi-Markov models (n=41) followed by decision trees together with Markov models (n=7). The model development was overseen and guided by a steering committee consisting of clinical and health economic experts. These experts confirmed and validated the model methodology as well as all the inputs and assumptions. The reliability of the model was verified by comparing the predicted outcomes of the model against those of the trial data upon which the model was based (i.e., the FIDELIO-DKD analysis) and now through a cross-validation with the SHARP CKD-CVD model. Cross-validation with other published models was challenging due to differences in both model structure and underlying assumptions, as well as due to insufficient information reported in the associated publications to enable alignment with the models' base case or to adequately compare results. Nonetheless, the FINE-CKD model was compared with the SHARP CKD-CVD model due to its availability online, which specifically considered a subgroup of patients with T2D. Despite the high flexibility of the SHARP CKD-CVD model, there were differences that rendered it difficult to obtain the same results as in FINE-CKD for some outcomes. The SHARP CKD-CVD model, for example, predicted a higher incidence of renal events. This difference positions the FINE-CKD model estimates as more conservative from a cost-effectiveness perspective because a higher baseline risk of such events, in conjunction with an advantageous clinical benefit relative to standard of care, would translate to a greater scope to offer value through treatment. Overall, however, the clinical progression modelled by the FINE-CKD model appears well-aligned with the results of the SHARP CKD-CVD model. The alignment was more precise for CV outcomes, though the number of patients starting RRT estimated by FINE-CKD model was within the possible ranges of scenario analyses using the SHARP CKD-CVD model. Despite the positive results of the cross-validation, some uncertainty remains, as evident in the wide ranges obtained from the SHARP CKD-CVD model and in being the only identified model sufficient for cross-validation. Nevertheless, the results of the FINE-CKD model are at the lower end of the reference range in terms of initiation of RRT. Estimates of the FINE-CKD model can, therefore, be considered conservative in the context of the model being used for cost-effectiveness assessment.

		Conclusions Following ISPOR recommendations, a model should be declared 'valid' only in the context of its future applications. In this context, the most important requirements of the model are transparency and an ability to adequately reflect the available clinical data. Together, these provide a basis for reliable extrapolation relative to the existing predictive tools. This study demonstrates that the FINE-CKD model meets these requirements, while also being potentially conservative in its approach. Bayer consider that this validation exercise demonstrates that the chosen method for managing transitions and risks, while simplified, generates similar results to a model which uses multivariate multinomial logistic regression as well as risk equations. **A Validation of the validation by an external expert** *The ERG report has triggered an external validation of the model comparing the FINE-CKD model with the SHARP-CKD/CVD model. One might argue that the latter model is the more useful model when addressing different types of patients and to analyse the cost effectiveness of a treatment for sub-groups defined by their base-line characteristics. The explanation regarding the higher incidence of the need for renal replacement therapy seems – as argued – related to the severity of the patients. When choosing healthier patients, by imputing lower UACR levels, one obtains estimates which are very much in line with the FINE-CKD model, and the FINE-CKD population. Naturally, this concordance between results may not come as a surprise as both models aim to do the same and both models are subtle enough to capture the long term expectations in terms of survival and events. Of course, differences may be expected, simply because the results of the FINE-CKD model are based on averages from the whole trial population while the SHARP CKD-CVD study presents the expectation of a single patient. As such the SHARP CKD-CVD model might be more representative for the median than for the mean, and, given that one may expect a skewed distribution, differences are a logical consequence.* **Additional validation by an external expert** ***Introduction***

The analysis of the costs effectiveness of finerenone for treating chronic kidney disease in people with type 2 diabetes is mainly based on one large randomised clinical trial; the FIDELIO-DKD trial. The general picture from the trial as summarised in the NEJM is that in patients with CKD and type 2 diabetes, treatment with finerenone resulted in lower risks of CKD progression and cardiovascular events than placebo. Outcomes that are addressed in the submission and its subsequent review concern: renal disease progression, cardiovascular outcomes, health related quality of life, mortality and adverse events; and of course costs.

A critical review of the submission

The analysis underlying the submission is – with respect to efficacy and quality of life - completely driven by the results from the FIDELIO-DKD trial. As indicated in the ERG review this doesn't always make sense. Whereas the ERG report mentions some of the estimates concerning utilities one might also point at some of the results with respect to the transition-probabilities. Below table presents the probability of worsening (or going further in the treatment cascade), staying in a health state or improving. Opportunistically one would assume that the probability to worsen is always higher for the control group than for the active group but this is not the case. The research group has kept themselves to the data from the trial and have taken the point estimates as they were without fitting some logic into the analysis which would have undoubtedly benefitted the cost effectiveness. This should be acknowledged.

	CONTROL			ACTIVE		
	worsen	**stay**	**better**	**worsen**	**stay**	**better**
CKD1/2	43.09%	56.91%	0.00%	45.16%	54.85%	0.00%
CKD3	10.42%	87.08%	2.50%	10.81%	87.57%	1.62%
CKD4	5.88%	79.45%	14.67%	4.88%	78.92%	16.21%
CKD5 without dialysis	19.93%	70.86%	9.21%	20.34%	68.85%	10.82%
Dialysis (acute)	100.00%			100.00%		
Dialysis	2.49%	97.51%		2.49%	97.51%	
Kidney Transplant (acute)	100.00%			100.00%		
Kidney Transplant (post-acute)	0.73%	99.27%		0.73%	99.27%	
DEATH		100.00%			100.00%	

		Similarly, within the estimates of utilities they have stayed as close to the data as possible. One may have the view that this has kept the cost effectiveness ratio artificially high. When using the matrices of transition-probabilities to run the Markov chain one may find that the average utility after entering end stage renal disease program is about 0.747 while the average utility among the CKD stages is 0.751. This is decrement of only 0.005, partly because of the higher utility after transplant. This small difference may come as unexpected and one may have doubts about the admittedly very elegant analysis of the quality of life data. The reason for this doubt – which may be personal - lies in the estimate of the effect of age. It is estimated that with each year ones utility decreases with 0.001. That is a funny result, as this implies that – ceteris paribus - one would have to wait for 100 years to obtain a decrement of 0.1. As indicated in the report one may find much higher decrements in the literature, as high as 0.35, suggesting that the estimate as used here is rather conservative. *It is possible to build far simpler models than the company's model or any other model with even more subtleties. But there are decreasing marginal benefits of adding subtleties. As mentioned earlier, the company's model has been driven by data and consequently there may be some logic has been missing not in line with the progressive nature of the disease. It is however difficult to imagine, that if such logic would have been brought into the model, that the benefits, as they are estimated now would have been estimated lower.* **In conclusion, Bayer consider that the chosen model structure and transitions, which has been extensively validated, is appropriate for decision making.**
Key Issue 5: Several influential model inputs lack clinical plausibility affecting overall face validity of model results	**Yes**/No	The ERG expressed concerns, from a clinical perspective, regarding the face validity of several model inputs. Bayer would like to underline that all questioned model inputs were obtained directly from the FIDELIO-DKD study. **External expert opinion** *The company has made the choice to stay as close to the data as possible and have – as far as I can see – made no compromises to seek alternative estimates, with potentially more favourable results. Had it done so, then it is easy to imagine that such model, using parametric function which follow the logic concerning*

		increasing risk to deteriorate, decreasing utility values with increasing severity etc, would have given lower cost effectiveness ratio's. It seems to me that the company should be praised for choosing this approach. Generalisability with respect to modelled transition probabilities has been discussed in the response to key issue 4. The remaining inputs are discussed below. **CV events** The ERG was concerned that the risk of a CV event for CKD stage 3 is lower than for CKD stage 1/2. Apart of these two CKD stages, the risk of CV events increases in the model until the start of RRT and then decreases after transplantation. Taking into account that there are no patients in CKD 1/2 at baseline in the base case it can be said that CV risk increases with disease progression. Nevertheless, Bayer acknowledges the concerns of the ERG. Especially that the ERG is worried that the combination of the company's approach to estimate transition probabilities by arm and the approach to include the effect of finerenone on CV events carries the risk of double counting the potential "cardioprotective effects of finerenone". Bayer explored the possibility of such double counting at the stage of model development and found it to be negligible when applying FIDELIO-DKD study results. However, Bayer would like to reduce the uncertainty resulting from the approach to CV risks in the model by applying the same CV risk throughout all CKD stages. This is the same approach taken by the ERG in its preferred base case; the only difference is that Bayer is applying the total risk from the BT arm of FIDELIO-DKD study. **CV death** The ERG has expressed similar concerns regarding CV death. Bayer would like to address ERG comments in the same way as for CV events, i.e. by applying the same risk of CV death throughout all CKD stages. This is the same approach taken by the ERG in its preferred base case; the only difference is that Bayer is applying the total risk from the BT arm of FIDELIO-DKD study. **Finerenone effect after start of RRT**

		A further concern of the ERG was related to lack of data available to robustly estimate the potential "cardioprotective effect" of finerenone in patients that are on dialysis or have had a transplant. Bayer understands this concern and indeed the final SmPC for finerenone states that "*Due to limited clinical data, finerenone treatment should be discontinued in patients who have progressed to end-stage renal disease (eGFR < 15 mL/min/1.73 m^2)*." As such, a functionality has been implemented in the model allowing the user to stop treatment with finerenone after starting RRT. In order to address the doubts of the ERG, Bayer proposes using this functionality in the new base case. Bayer understands that using this option increases drug discontinuation in the model and would like to address this issue and it is discussed below. **Discontinuation of finerenone** The ERG considers that the treatment discontinuation has been overestimated in the model. The argument is made that this is due to possible double counting of discontinuation due to death in the company's model. This double counting is argued to have arisen as a result of the reasons for discontinuation not having been 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. Bayer agrees with this approach and has re-performed this re-calibration of the discontinuation rate. The calibration has been performed after implementing other changes that have an impact on the duration of treatment e.g., stopping the use of finerenone after start of RRT. **Mortality** In the model, patients can die from three causes: • Cardiovascular (CV) death • Renal death • Other-cause death. The revised approach to CV death has been discussed above. This change has been applied to address the doubts raised by the ERG.

		Moreover, Bayer agrees with the ERG regarding the limitations of renal deaths included in the model. These limitations are mostly driven by a very strict definition of renal death in the FIDELIO-DKD trial (i.e., one of the criteria required that RRT had not been started although clinically indicated) which resulted in a very low number of deaths which could have been classified as having a renal cause. The definition of renal deaths in other sources is different (e.g. in the ONS statistics(33) report, deaths from renal failure are all cases of death within the ICD-10 codes N17-N19), and therefore renal deaths may have been underestimated in the model as suggested by the ERG. Bayer would like to remove this source of uncertainty from the model by not differentiating renal deaths. In the proposed new base case, Bayer set the risk of renal death to 0 in both arms of the model and do not reduce the general mortality with the proportion of deaths from renal causes. Another concern of the ERG is that the increased risk for death from other causes has been linked to CKD progression, based on the studies for *all-cause* mortality, not *other-cause* mortality (adjusted to remove the impact of CV and renal deaths). Bayer agrees with the ERG that it is unclear how much the risk of death for other causes increases while CKD progresses. This issue was discussed with UK clinical experts who suggested that the other-cause mortality is also increased due to CKD and advised us to use the HR obtained from the available sources. Bayer followed this recommendation in our submission because inclusion of increased mortality is a conservative approach. Lack of any increase of mortality due to CKD progression results in finerenone being the dominant treatment over BT. Nevertheless, Bayer still considers the approach to increased mortality due to CKD progression applied in our submission to be the most reliable based on the available data and we do not suggest any changes in this regard. **Health-related quality of life** Bayer 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. Bayer considered that utilities derived directly from the FIDELIO-DKD trial for use within the cost-effectiveness model would be preferred by the ERG and NICE over those reported in the literature or derived from other sources. The ERG agreed that the use of EQ-5D data from the trial is generally preferred versus other non-trial sources, however, was concerned with the face validity of the resultant values. Bayer was aware of the limitations related to the utilities obtained from FIDELIO-DKD study, hence, a scenario was presented in the submission with the use of utility values based on the systematic literature review of utilities performed as part of the submission. Given that the utility data was retrieved from a methodologically rigorous systematic literature review, in conjunction with the extent of evidence reported for the utilities of

		interest, the results of the performed scenario can be considered reliable. Addressing the comments from the ERG, Bayer propose using utilities from the literature in the revised base case analysis. **CV event history** The ERG noted that the company's model reflects CV history with respect to the FIDELIO-DKD study period only. Bayer requested the ERG version of the model during technical engagement to further explore the ERG adjustments in relation to this issue; it was not provided. Bayer agrees with the ERG that a proportion of the FIDELIO-DKD cohort with a recorded CV event history could be included in the model, however these should not enter the 'post CV event' sub-model at baseline. 'Post CV event' states in the model correspond to the incidence of the first event observed within the FIDELIO-DKD study and all the benefits of finerenone in terms of reducing the risk of CV events are modelled from this perspective. Hence, all patients should start the model in 'no CV event' states. Nevertheless, it is true that 45.9% of patients enter the FIDELIO-DKD study with a history of a previous CV event. Bayer believes that from the model perspective these patients could experience post-acute costs and disutilities due to CV events before entering the model. As such, it is inappropriate to account for these post-acute consequences again in the model. Accounting for the acute consequences of CV events should not be amended in the model for this group of patients as it is assumed to be the same irrespective of the history of CV event. To account for the suggestion from the ERG that a history of CV events before entering the model should be considered, Bayer did not apply the post-acute consequences of CV events to 45.9% of patients entering FIDELIO-DKD with a history of CV events in a scenario. **Costs** Bayer applied the ERG suggestion regarding removal of the cost of death from the model. Bayer applied the cost of BT as revised by the ERG. Bayer agrees that the wastage of finerenone could be applied in the model, however, only half a pack should be considered. A whole pack would be wasted in a few cases, whereas no wastage would be seen for the other patients. Considering wastage of half a pack is the most common and reasonable approach, corresponding to the idea of half cycle correction commonly applied in cost-effectiveness models.

Impact on the ICER: ERG preferred assumptions vs Bayer revisions
Based on the above considerations Bayer has implemented several changes to the ERG preferred base case (Table 5).

Table 4. ERG's preferred model assumptions (as reported in the ERG report, table 29, page 134)

Preferred assumption	Cumulative ICER (ERG) £/QALY
Company's original base-case	17,552
# 1: ERG-corrected company's base-case	17,882
#2: Set risk of CV events to be independent of CKD stage	18,309
#3: Amend application of renal deaths	18,357
#4: Set risk of CV death to be independent of CKD stage	17,413
#5: Assume 45.9% of patients enter post-CV event sub-model	22,510
#6: Remove all death costs	22,528
#7: Edit BT cost to ERG's calculations	22,423
#8: Include one additional pack of finerenone to reflect wastage	23,066
#9: Assume utility for CKD1/2 is 0.80	23,587
#10. Assume post-acute disutility is half of acute disutility	23,706

The results of additional analyses performed by Bayer are presented in the table below (Table 6).

Table 5. Bayer revision of the ERG preferred model assumptions

Bayer revision of the ERG preferred model assumptions	Cumulative ICER (Bayer) £/QALY
Company's original base-case	17,552

		Calculating the average risk of CV events for all CKD stages and applying it in all model health states (revision of #2 ERG assumption)	17,835
		Remove renal deaths from the model and add them back to general mortality (revision of #3 ERG assumption)	17,882
		Calculating the average risk of CV death for all CKD stages and applying it in all model health states (revision of #4 ERG assumption)	16,892
		Setting finerenone to be stopped after RRT and calibrating discontinuation (revision of #1 ERG assumption)	15,260
		Assume utilities from the literature (revision of #9 and #10 ERG assumptions)	12,474
		Corrected implementation of 45.9% of patients with history of CV events (revision of #5 ERG assumption)	13,491
		Remove all death costs (revision of #6 ERG assumption)	13,513
		Edit BT cost to ERG's calculations (revision of #7 ERG assumption)	13,431
		Include additional half of the pack of finerenone to reflect wastage (revision of #8 ERG assumption)	13,626
		Conclusion Bayer appreciates the concerns of the ERG regarding face validity of some model inputs. Bayer asked for the ERG version of the model to verify the ERG approach to amendments but, as this was not provided, have attempted to replicate the ERG results in our model. Bayer believes that some of the scenarios explored by the ERG to reduce the uncertainty could be further improved. In particular, we believe the inclusion of patients with history of CV events at baseline by the ERG has been incorrectly implemented in the model. Corrected implementation of this amendment showed significantly lower impact on the model results. Moreover, the limitations of the health state utilities from FIDELIO-DKD study can be overcome by applying values obtained based on a systematic literature review. The literature-based utilities provided should address concerns regarding face validity.	

		The additional analyses presented demonstrate that addressing concerns regarding the face validity of model inputs does not impact the model conclusions regarding the cost-effectiveness of finerenone vs BT. Moreover, the base case presented in the original submission can be considered conservative. Stability of the results despite several suggested changes, increases the plausibility of model estimates, which have been validated with FIDELIO-DKD study outcomes and the results of the model suggested by the ERG(32) as an example of good modelling practice in CKD (see answer to key issue 4).
Key Issue 6: Overall uncertainty in the results of the model is not adequately captured by the company's sensitivity analyses	**Yes**/No	The ERG expressed concerns regarding the company's sensitivity analyses. The following issues were raised: **For both DSA and PSA** • *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.* In terms of the baseline patient distribution, Bayer considers that grouping is suitable as the parameters are interrelated (must sum to 100%);.this was acknowledged by the ERG in its report. In terms of the utilities, they were grouped for the DSA simulations only. In terms of the PSA, the parameters concerning utilities varied independently (please see the *PSA - simulations* worksheet columns EY: FF). Grouping parameters related to utilities is also considered appropriate. Otherwise, more advanced health states would have higher utility than less severe CKD stages. In such a situation, the DSA inputs would lack face validity to a greater extent than in the base case scenario presented in the submission, and questioned by the ERG: *Patients with CKD 3 were estimated to have an increase in utility of 0.001 when compared to CKD 1/2; the ERG highlighted this as clinically implausible at clarification (…) the ERG does not consider the resultant utility values to be suitable to populate the model as a result of this flaw in logic.*

		• *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].* Bayer explained that the FIDELIO-DKD trial was not designed nor powered to make conclusions based on HRQoL. The results of the multivariate regression model fitted to the FIDELIO-DKD data were associated with a high degree of uncertainty. Bayer were aware of the limitations related to the utilities obtained from the FIDELIO-DKD study, hence, a scenario was presented in the submission with the use of utility values based on the systematic literature review of utilities performed as part of the submission. Given that the utility data was retrieved from a methodologically rigorous systematic literature review, in conjunction with the extent of evidence reported for the utilities of interest, the results of the performed scenario can be considered reliable. Addressing the comments from the ERG, Bayer propose using utilities from the literature in the revised base case analysis. For the revised base case analysis, separate DSA and PSA were performed. For utilities based on the literature, the bounds tested in the sensitivity analyses were first based on the mean and SE from the direct source (assuming beta distribution) and if not identified in the source, the 10% variations around the base case were tested. • *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.* For clarity, the ranges for DSA and PSA for IS stroke were calculated based on 95%CI from the source (Alva et al.(34)). It is true that this range of uncertainty is relatively high. As an alternative, Bayer suggest testing the fixed variation (+/-30% from the base case) for all costs based on Alva et al. Nevertheless, it should be noted that the sensitivity analyses results presented in the original submission considered higher uncertainty. If the bounds are more precisely calculated the sensitivity

		analyses results would have been closer to the base case value. Therefore, the results in the original submission can be considered conservative regarding the estimated probability of finerenone being cost-effective in comparison to BT. • *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.* Bayer was aware of the limitations related to the utilities and the high ICER for their lower bound tested in the DSA. Therefore, a scenario was presented in the submission with the use of utility values based on the systematic literature review of utilities performed as part of the submission. Bayer would like to provide the updated DSA results with the following changes: o The utilities based on literature in the base case with the bounds tested in DSA from the direct source and if not identified in the source, with inclusion of the 10% variations o The costs parameters based on Alva et al tested with +/-30% variations from base case **PSA only** **Additionally, the ERG has concerns regarding 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. The Normal distribution for costs were adopted by Bayer as requested by the ERG. • 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. Bayer would like to omit this parameter from DSA and PSA, as there are no credible ranges to be tested. In addition, a scenario analysis was considered which excluded this parameter showing negligible impact on model results.

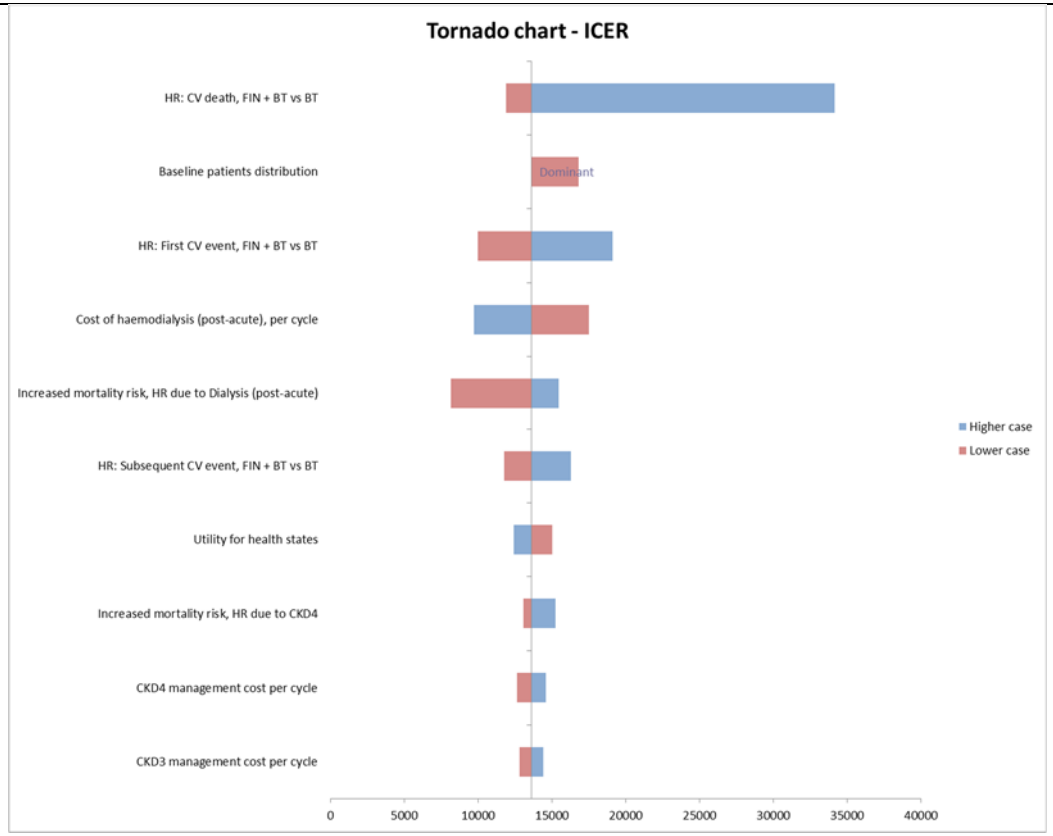
Table 7: Health event eGFR decline from baseline excluded

Scenario	Incremental costs, undiscounted	Incremental costs, discounted	Incremental QALYs, undiscounted	Incremental QALYs, discounted	ICER, undiscounted	ICER, discounted
Base case (Bayer revision of ERG's preferred model assumptions)	£2,011	£1,796	0.19	0.13	£10,629	£13,626
Scenario: Health event eGFR decline ≥ from baseline excluded)	£2,011	£1,796	0.19	0.13	£10,843	£13,928

The results of the DSA and PSA after corrections described in the response to Key Issue 5 are presented below.

DSA results – Figure 1

Figure 1. Updated DSA results – including the response to the Key Issue 5

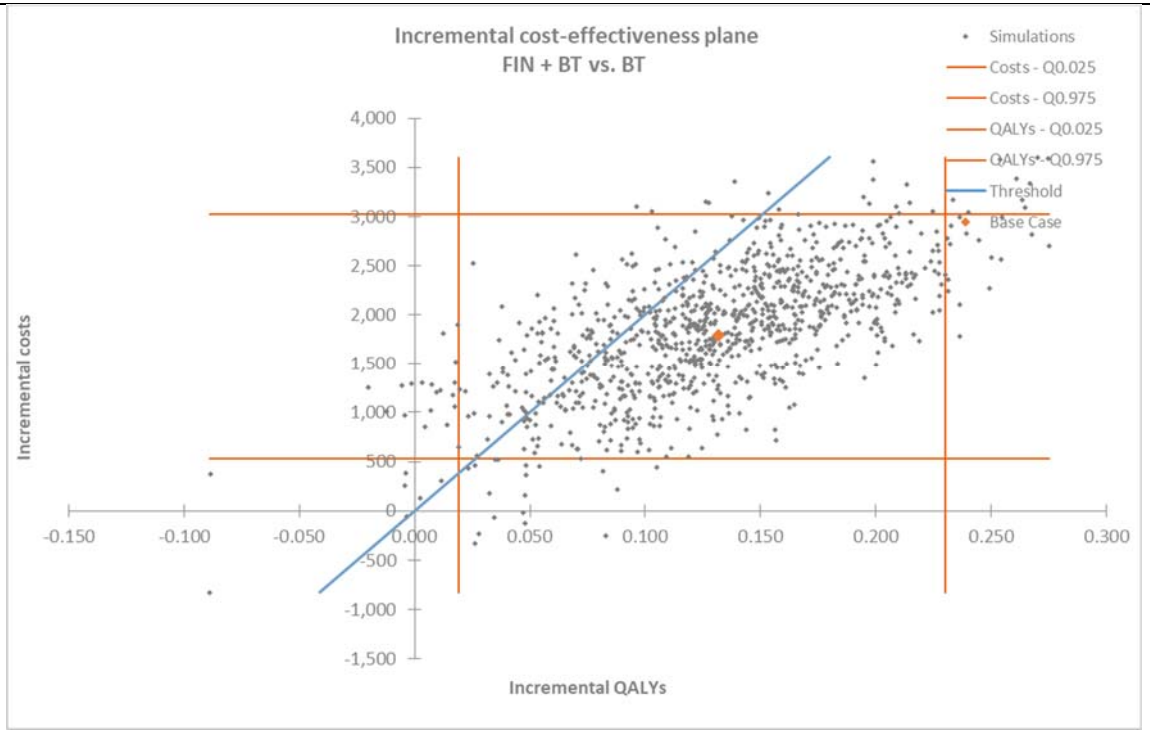

Tornado chart - ICER
HR: CV death, FIN + BT vs BT
Baseline patients distribution
Dominant
HR: First CV event, FIN + BT vs BT
Cost of haemodialysis (post-acute), per cycle
Increased mortality risk, HR due to Dialysis (post-acute)
HR: Subsequent CV event, FIN + BT vs BT
Utility for health states
Increased mortality risk, HR due to CKD4
CKD4 management cost per cycle
CKD3 management cost per cycle
Higher case
Lower case
0
5000
10000
15000
20000
25000
30000
35000
40000

PSA results

Table 8. Updated PSA results – including the response to the Key Issue 5

	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Base Case	1,796	0.132	13,626
Mean	1,841	0.129	14,241
Std Deviation	642	0.054	39,333
Median	1,887	0.129	13,991
Min	-826	-0.089	-1,018,051
Q 0.025	531	0.019	5,749
Q 0.975	3,028	0.230	37,585
Max	3,602	0.275	393,372
Probability of being cost-effective			82.7%
Probability of being dominant			0.6%
Probability of being dominated			0.8%

Figure 2. Updated CE plane - including the response to the Key Issue 5



Addressing the ERG comments concerning sensitivity analyses in the model results in lower variability of the model outcomes in the DSA and PSA. **New base case analysis presented by Bayer following the ERG comments estimates a lower ICER for finerenone vs BT with higher probability of finerenone being a cost-effective treatment.**

Additional issues

All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Table 3 Additional issues from the ERG report

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 2: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Key Issue 5: Several influential model inputs lack clinical plausibility affecting overall face validity of model results	The company's base case were: • Not calibrated finerenone's discontinuation • CV events. CV death and renal death based on FIDELIO-DKD, separate for each CKD stage • No corrections for patients with prior CV event history • Remove renal death from the general mortality • Death costs included	Bayer revised the ERG preferred model assumptions, and present the updated model results with the following assumptions: • Calculating the average risk of CV events for all CKD stages and applying it in all model health states • Remove renal deaths from the model and add them back to general mortality • Calculating the average risk of CV death for all CKD stages and applying it in all model health states	ICER after changes is £13,626 (lower than the company's base case by £3,926)

	• No finerenone wastage included • Utility inputs from FIDELIO-DKD trial	• Setting finerenone to be stopped after RRT and calibrating discontinuation • Assume utilities from the literature • Corrected implementation of 45.9% of patients with history of CV events • Edit BT cost to ERG's calculations • Include additional half of the pack of finerenone to reflect wastage	
Company's base case following technical engagement (or revised base case)	Incremental QALYs: 0.13	• Incremental costs: £1,796	£13,626

Sensitivity analyses around revised base case
Please see the sensitivity analyses corresponding with the response to Key Issue 5.

Figure 1. Updated DSA results – including the response to the Key Issue 5

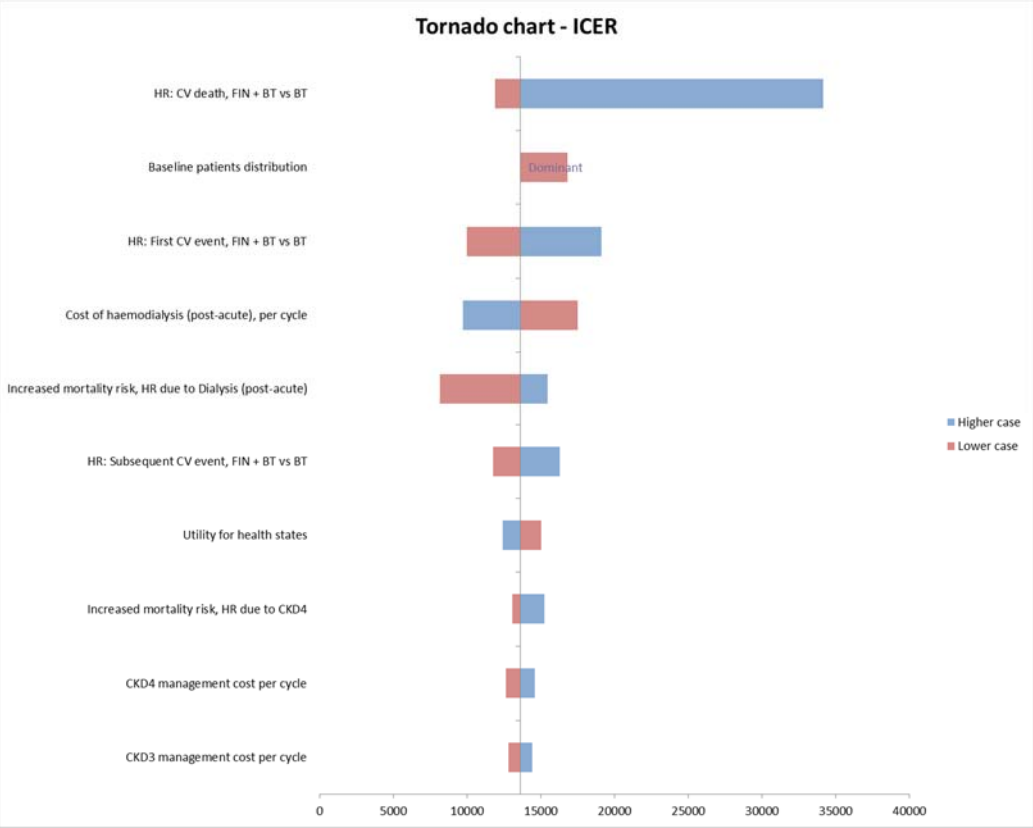


Table 8. Updated PSA results – including the response to the Key Issue 5

Description	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Base Case	1,796	0.132	13,626
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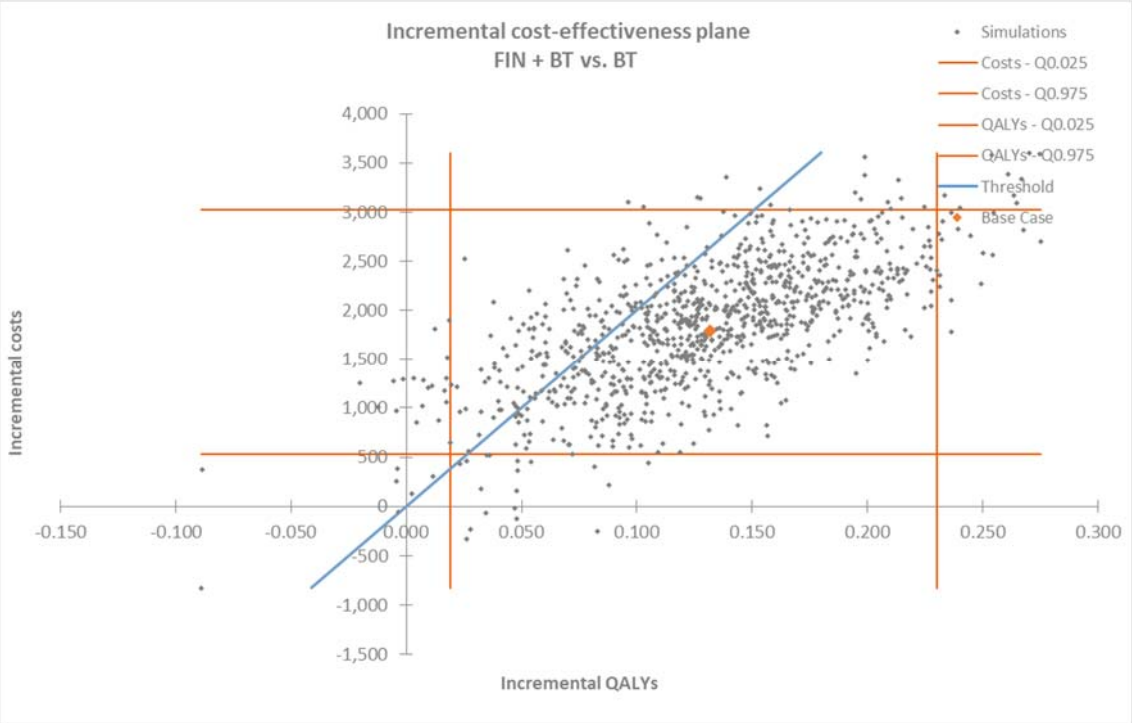
Figure 2. Updated CE plane - including the response to the Key Issue 5



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NICE National Institute for Health and Care Excellence

Technical engagement proposed new evidence form (company only)

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

As the company for this appraisal, you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses will be used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting. As part of your response, you may intend to provide new evidence to address some or all of the key issues identified in the executive summary of the ERG report (that is, evidence that has not already been provided during the appraisal).

We would like to understand the extent of new evidence that you propose to provide in your response to technical engagement. This will help the ERG to plan its critique of your response. You do not have to provide new evidence in response to every issue. However, in general, any new evidence provided should have the purpose of addressing a key issue identified in the executive summary of the ERG report. Decisions about whether NICE will accept new evidence will be made on a case by case basis. Please note that NICE may need to extend timelines and reschedule the appraisal committee meeting to allow new evidence to be considered. Therefore, it is important that you notify NICE about new evidence in advance by completing this form as comprehensively as possible. Please be aware that NICE will not routinely accept new evidence provided after the deadline for technical engagement responses.

Deadline for returning this form: **5pm** on Monday 28 February 2022.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses.
- Please ensure your response clearly identifies which key issue from the executive summary of the ERG report your proposed new evidence is intended to address. Please use the same issue numbers that have been used in the executive summary of the ERG report.
- If you intend to provide new evidence to address issues in the ERG report that have not been identified as key issues, please make this clear.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink.

NICE National Institute for Health and Care Excellence

Summary of proposed new evidence

Please use the table below to provide details of any proposed new evidence that you intend to submit in response to technical engagement.

Please be as comprehensive as possible.

Key issue(s) that the new evidence will address	Summary of the proposed new evidence (short title)	How will the new evidence address the key issue(s)?	Is the new evidence expected to alter the company's base-case ICER?	Additional details about the proposed new evidence (if available)
Key Issue 1: Uncertainty in appropriate population	Testing the sensitivity of the model to inclusion of patients with eGFR < 25ml/min/1.73m^2	Bayer would like to address the ERG comments if possible and perform additional analyses to check the influence of inclusion of patients with eGFR < 25ml/min/1.73m^2 in the model.	Not expected to substantially impact the ICER.	We have requested the full data set for the "label" population including patients with eGFR < 25ml/min/1.73m^2 from our global statistical team. However, we are not guaranteed access within the timeframe due to multiple demands on the statistical team at this time. No challenges are anticipated regarding assessing this new evidence, should it be available, as it will be limited to exploring alternative model inputs with the use of the submitted model.
Key Issue 3: Uncertainty in clinical	Test for heterogeneity of the individual components of	The ERG has expressed concerns about the clinical relevance of the study findings. Bayer have presented the justification for the chosen composite endpoint, and input from professional	No	The results of a new Cox model will be presented. No challenges are anticipated regarding assessing this new evidence as it will be limited to

relevance of trial outcomes	the primary composite endpoint in FIDELIO-DKD	groups shared within the technical engagement papers, provide support for the importance of the component of the primary endpoint i.e. renal progression based on change in eGFR. This new evidence provides further supportive evidence from a statistical viewpoint.		presentation of the results of this analysis.
Key Issue 4: Model transitions subject to substantial limitations	Validation of the model estimates with Schlackow et al., (2017)	The ERG suggests limitations with respect to how the model reflects the patient journey over the model's lifetime horizon giving as an example the model Schlackow et al., (2017) as a possible alternative approach. Bayer agrees that there are several possible approaches to transition probabilities in the model. Many of these approaches were considered at the time of model design and Bayer consulted with clinicians and health economists comprising a scientific committee supervising model development. Using transition probabilities directly from the clinical trial was deemed the most appropriate solution that balanced model accuracy and complexity. Bayer believes that the submitted model (FINE-CKD) provides reliable evidence for assessing the cost-effectiveness of finerenone. In order to provide additional proof of accuracy of model estimates, we propose to compare them with the results of Schlackow et al., (2017) i.e. the model using one of the alternative	No	Schlackow et al., (2017) described the results of the SHARP (Study of Heart and Renal Protection) CKD-CVD model. For validation purposes, the online version of the SHARP CKD-CVD model will be used as the publication does not present results for T2D patients, the population of interest. The following clinical outcomes have been selected for the comparison: • CV events or CV death, • CV death, • initiation of RRT (dialysis and transplantation). The patient baseline characteristics from FIDELIO-DKD will be entered into the SHARP CKD-CVD model. Where there are no data available from FIDELIO-DKD, the default values from the SHARP CKD-CVD model will be used.

		approaches to transition probabilities suggested by the ERG.		As an additional test, CKD progression rates in the background therapy (BT) arm will be replaced in the FINE-DKD model with the transition rates from the SHARP CKD-CVD model. In the next validation step, first modelled CV events' risks will be substituted with four-month rates calculated from major vascular events reported in SHARP for patients aged 65 years and over. The results of two models with different inputs will be compared considering the ranges of estimates possible to be obtained in the SHARP CKD-CVD model and confidence intervals from the probabilistic sensitivity analysis run in the FINE-DKD model. No challenges are anticipated regarding assessing this new evidence as it will be a comparison of the results of two models presented in a Word document.
Key Issue 5: Several influential model inputs lack clinical plausibility	Alternative inputs or assumptions for the model components questioned by the ERG	According to the ERG's suggestion, performing additional (alternative) analyses to populate the model might help with resolving this key issue. Bayer would like to address the ERG comments and perform additional analyses to strengthen the reliability of the model results.	Yes – unknown size of impact	Bayer is currently exploring various analyses, but no details are available at this stage. No challenges are anticipated regarding assessing this new evidence as it will be limited to exploring alternative model inputs and

affecting overall face validity of model results				assumptions with the use of the submitted model.
Key Issue 6: Overall uncertainty in the results of the model is not adequately captured by the company's sensitivity analyses	Revised sensitivity analyses	According to the ERG's suggestion, the company could re-program its sensitivity analyses to incorporate the ERG comments and help resolve this key issue. Bayer is currently exploring the possibility of addressing this ERG suggestion and if this is possible will submit alternative results of PSA/DSA analyses.	Yes – unknown size of impact	Bayer is currently exploring various analyses, but no details are available at this stage. No challenges are anticipated regarding assessing this new evidence as it will be limited to exploring alternative model inputs and assumptions with the use of the submitted model.

Additional evidence in response to technical engagement

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

Bayer plc

14th March 2022

Bayer have responded to the technical engagement stage of the appraisal by completing the "technical engagement response form". Within this, we have presented new evidence to address the Key Issues.

We understand that NICE would like the additional evidence as a stand-alone appendix.

We have left the new evidence in the technical engagement response form as a means of addressing the Key Issues, but we replicate the new evidence here.

Key Issue 1 - Uncertainty in the appropriate population

To address the concerns of the ERG, Bayer have performed analyses to check the influence of inclusion of patients with eGFR < 25ml/min/1.73m^2 in the model. The full data set required in the model for the "label" population with inclusion of patients with eGFR < 25ml/min/1.73m^2 was obtained from statistical analyses of patient level data from the FIDELIO-DKD study. Analogous data were obtained to those considered in the original submission but for this slightly broader population. The results from the requested population i.e., CKD 3 and CKD 4 patients (i.e., eGFR ≥15 to < 60ml/min/1.73m^2 at baseline) with albuminuria and type 2 diabetes are presented in the table below (Table 1). There was minimal difference compared to the base case results.

Table 1. Deterministic results for subpopulation of patients with CKD 3 and CKD 4 (i.e., eGFR ≥15 to < 60ml/min/1.73m^2 at baseline) with albuminuria and type 2 diabetes based on FIDELIO-DKD data.

Population	Incremental costs, undiscounted	Incremental costs, discounted	Incremental QALYs, undiscounted	Incremental QALYs, discounted	ICER, undiscounted	ICER, discounted
Base case: CKD 3 and CKD 4 patients with albuminuria (i.e., eGFR ≥ 25 to <60ml/min/1.73 m^2 at baseline) and type 2 diabetes	£2,041	£1,779	0.15	0.10	£13,893	£17,552
Scenario: CKD 3 and CKD 4 patients with albuminuria (i.e., eGFR ≥15 to <60ml/min/1.73 m^2 at baseline) and type 2 diabetes	£2,477	£2,102	0.17	0.12	£14,252	£17,340

Key Issue 2 - Missing comparison with SGLT-2i

No new evidence is presented.

Key Issue 3 - Uncertainty in the clinical relevance of trial outcomes

To assess heterogeneity of the individual components of the primary composite efficacy endpoint in FIDELIO-DKD, a new Cox model was calculated including the time to event information for each component of the endpoint individually. The same Cox model (including stratification) as for the composite endpoint was used, only adding a factor for the respective component and for the interaction between treatment and component. A significant interaction between treatment and component would have been interpreted as a sign of heterogeneity between the components of the composite endpoint. As the p-value was found to be [redacted], no sign of heterogeneity was identified (Bayer, data on file).

In addition, post hoc analyses exploring whether the risk of kidney failure increases after previous occurrence of sustained eGFR reduction of 40% or more from baseline value over at least 4 weeks were performed based on data from FIDELIO-DKD. In order to examine the relationship between these 2 endpoints, the occurrence of kidney failure was compared before and after the occurrence of sustained eGFR reduction of 40% or more from baseline value over at least 4 weeks. This was assessed by Cox proportional hazard model stratified by the stratification factor used for randomization, and with the time-dependent covariate "*sustained eGFR reduction of 40% or more from baseline value over at least 4 weeks*". The HR for kidney failure was [redacted] (95% confidence interval: [redacted]) comparing after and before the occurrence of 40% eGFR reduction. This result suggests that the risk of developing kidney failure after the onset of sustained eGFR reduction of 40% is [redacted] than that before the onset of sustained eGFR reduction of 40%. This finding confirms that in FIDELIO-DKD, the surrogate endpoint "*sustained eGFR reduction of at least 40% from baseline lasting at least 4 weeks*" was strongly associated with the hard endpoint "*onset of kidney failure*". Consequently, reducing the occurrence of the 40% eGFR decline endpoint as demonstrated in FIDELIO-DKD translates into a reduction of the risk of kidney failure (i.e. chronic dialysis or kidney transplant)(30).

Key Issue 4: Model transitions subject to substantial limitations

Upon completion of their review of the Bayer cost-effectiveness model ('FINE-CKD'), the ERG highlights a potential key issue relating to perceived structural limitations (Key issue 4). The ERG proposed that an alternative modelling structure, incorporating time-varying risks would be preferred, referencing specifically the paper of Schlackow et al 2017(32).

We understand that the ERG would prefer another approach to the estimation of transition probabilities applied in the model. Indeed, the use of risk equations was considered and discussed with experts in the early stages of model development (i.e. including time variant probabilities), although rejected. There is a limited number of major events observed in the FIDELIO-DKD study and this limits the ability of these data being used to adequately estimate the risk equations. Furthermore, there is an established relationship between CKD stage and CV events (fatal or otherwise). As such, the model submitted focuses on the link between CKD stage and these events rather than extending this to an explicit consideration of other risk factors.

Whilst Bayer disagree with the extent to which this identified 'key issue' represents a driver of uncertainty in the results of this appraisal, a further model validation exercise has been achieved, comparing the results of FINE-CKD with a model with a different approach for handling transitions/risks. The objective of this cross-validation was to understand if the FINE-CKD model is similar in terms of the provided outcomes.

Additionally, Bayer has asked an external and independent UK health economic expert (Professor B A. van Hout, PhD) for his opinion on the validation performed and the FINE-CKD model itself. Results of this external assessment are presented within the responses to key issues 4,5 and 6

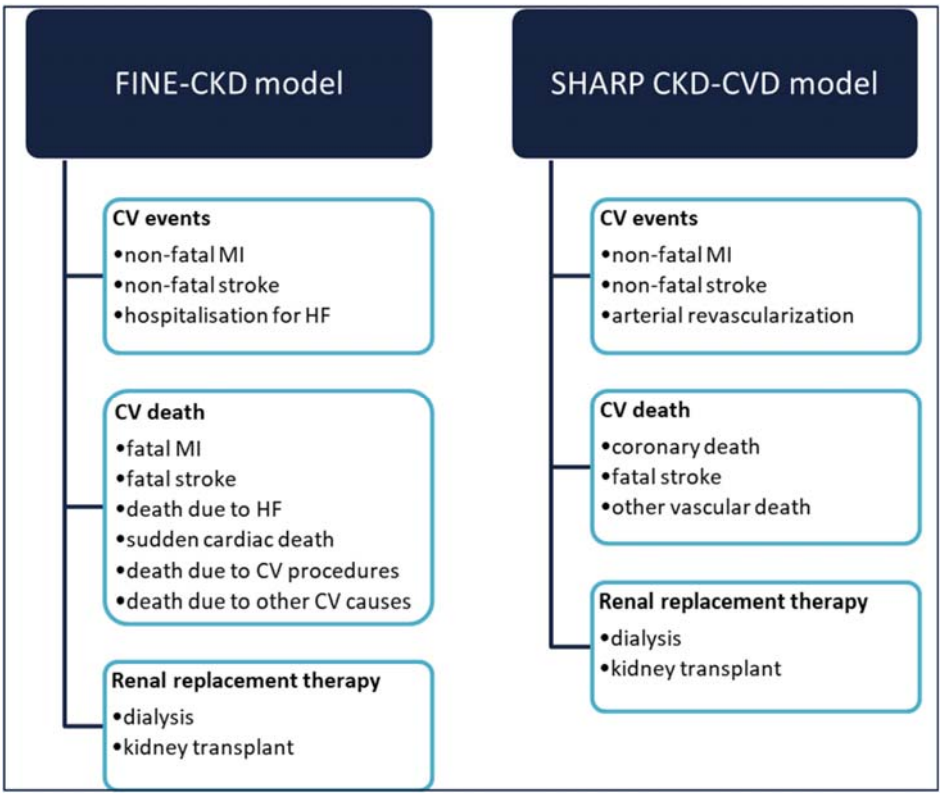
Methods

The SHARP (Study of Heart and Renal Protection) CKD-CVD model, a Markov model described in Schlackow 2017(32) is the model, that Bayer referred to in its submission, and the ERG highlighted in their report, that we use for this exercise. For cross-validation purposes, however, the online version of the SHARP CKD-CVD model was used. This was appropriate because the publication did not present results for T2D patients, the population for which finerenone is indicated.

The following clinical outcomes were chosen for this comparison:

- CV events or CV death,
- CV death,
- initiation of RRT (dialysis and transplantation).

These are the main clinical outcomes analysed in both models, which were defined in a similar way between models as presented below.



For cross-validation purposes, the patient baseline characteristics from FIDELIO were entered into the SHARP CKD-CVD model. Where there were no data available from FIDELIO, the default values from the SHARP CKD-CVD model were used.

The full lists of inputs are presented in the table below. It was not possible to source all of the parameters needed for the SHARP CKD-CVD model from the data available from FIDELIO-DKD. Therefore, for the validation, we report results as the base case value with ranges corresponding to minimum and maximum values of each outcome possible to be obtained in the SHARP CKD-CVD model after checking all possible values for the model parameters.

Table 2. Baseline patient characteristics for validation with the SHARP CKD-CVD model

Parameter	Values used for validation	FIDELIO - label
Age	66	[redacted]
Sex	Male	[redacted]
Ethnicity	White	[redacted]
Highest education attainment	Any post-secondary education	NA
Adult dependants	No	NA
Smoking status	Never smoked	NA
Alcohol drinker	No	NA
Body mass index	≥30kg/m2	[redacted]
Clinical factors		
Diastolic blood pressure	75-84 mmHg	NA
Systolic blood pressure	130-149 mmHg	[redacted]
HDL cholesterol	0.9-1.1 mmol/L	NA
Albumin	3.9-4.1 g/dL	NA
Haemoglobin	11.6-12.9 g/dL	NA
Phosphate	1.2-1.4 mmol/L	NA
Urinary albumin: creatinine ratio	≥300 mg/g	[redacted]
Disease history		
Latest CV event	None	NA
Diabetes	Yes	100% patients
CKD stage	CKD 3B	[redacted]
CKD duration	17	16.6
Renal diagnosis	Diabetic nephropathy	[redacted]

For the purposes of this validation, the results of the FINE-CKD model were presented as cumulative event probabilities (of major CV event or CV death, initiation of RRT, and CV death) per 1,000 participants at the end of year 5 and year 10 and were calculated using the Kaplan-Meier product.

The results of two models with different inputs were compared taking into account the ranges of estimates possible to be obtained in the SHARP CKD-CVD model and confidence intervals from the probabilistic sensitivity analysis run in FINE-DKD model.

Results

Results of the comparison with the SHARP CKD-CVD model are presented in **Table 3** for those patients who used standard of care alone (BT arm in the FINE-CKD model).

In addition to the validation of the base case inputs, as CKD progression and CV events were assessed in the SHARP CKD-CVD model by risk equations and vary in each cycle, the following parameters were also tested to generate ranges for the estimates:

- Smoking status (current smoker, ex-smoker)
- BMI (25-29 kg/m2),
- Albumin (<3.9, ≥ 4.2 d/dL),
- Haemoglobin (<11.6, ≥13 g/dL),
- Phosphate (<1.2, ≥1.5 mmol/L),
- UACR (<30, 30-300 mg/g),
- Renal diagnosis (other known or unknown cause).

The results of these tests are presented in the table below.

Table 3 Results of validation – SHARP CKD-CVD model vs. FINE-CKD model, ranges

	At 5 years			At 10 years		
	Major CV event or CV death	**Initiation of RRT**	**CV death**	**Major CV event or CV death**	**Initiation of RRT**	**CV death**
Cumulative probabilities per 1,000 participants						
SHARP CKD-CVD	236	276	92	431	670	244
FINE-CKD model (95% CI)	273 (247; 297)	106 (103; 107)	87 (73; 104)	541 (491; 587)	249 (241; 255)	181 (147; 214)
SHARP CKD-CVD (ranges)	155 - 316	41 - 413	55 - 135	283 - 549	156 - 820	137 - 349

Note that, although they are similar in structure, differences exist between the SHARP CKD-CVD model and the FINE-CKD model. The SHARP CKD-CVD model restricts health states to CKD stage 3b onwards, whereas the FINE-CKD model also includes health states for those with mild CKD in stages 1/2 and 3a (within CKD 3 stage). Consideration of more severe patients in the SHARP CKD-CVD model partially explains the higher incidence of renal events in this model, as shown in the results of the analyses undertaken which considered ranges from the SHARP CKD-CVD model. For example, analysing patients with lower UACR level (i.e., 30-300 mg/g) in the SHARP CKD-CVD model reduces the cumulative probability of RRT initiation to 94 per 1,000 participants at 5 years and 327 at 10 years. These estimates are very close to the FINE-CKD model outcomes. Other examples of parameters having impact on estimates of SHARP CKD-CVD which were not possible to be fully adjusted to the FIDELIO-DKD trial population are presented in the exploratory analysis in the table below. Please note however that the parameters “sex” and “ethnicity” have not been varied in the ranges presented in the table above.

Table 4 Results of SHARP CKD-CVD model – scenario analysis

	At 5 years			At 10 years		
Parameter	**Major CV event or CV death**	**Initiation of RRT**	**CV death**	**Major CV event or CV death**	**Initiation of RRT**	**CV death**
Cumulative probabilities per 1,000 participants						

Sex: Female	178	227	68	335	592	179
Ethnicity: Asian, lives outside China	182	252	101	349	635	263
UACR: 30-300 mg/g	**196**	**94**	**60**	**358**	**327**	**158**
Renal diagnosis: other known or unknown cause	175	234	66	333	619	178

The results of the FINE-CKD model are within the ranges that can be obtained from the SHARP CKD-CVD model, as seen in the table above.

Overall, the clinical progression modelled in the FINE-CKD model appears aligned with the results of the SHARP CKD-CVD model.

Discussion

The FINE-CKD model was developed based on the findings of a systematic literature review (SLR) and is consistent with other models in this area. Following good practice renders the model transparent and reduces the uncertainty related to unnecessary complexity. The application of a Markov framework appropriately allows for evaluation of the cost-effectiveness of finerenone in patients with CKD and T2D.

Indeed, in the SLR among the included cost-utility analysis and cost-effectiveness analysis (n=66), there were mainly Markov or semi-Markov models (n=41) followed by decision trees together with Markov models (n=7).

The model development was overseen and guided by a steering committee consisting of clinical and health economic experts. These experts confirmed and validated the model methodology as well as all the inputs and assumptions. The reliability of the model was verified by comparing the predicted outcomes of the model against those of the trial data upon which the model was based (i.e., the FIDELIO-DKD analysis) and now through a cross-validation with the SHARP CKD-CVD model.

Cross-validation with other published models was challenging due to differences in both model structure and underlying assumptions, as well as due to insufficient information reported in the associated publications to enable alignment with the models' base case or to adequately compare results.

Nonetheless, the FINE-CKD model was compared with the SHARP CKD-CVD model due to its availability online, which specifically considered a subgroup of patients with T2D. Despite the high flexibility of the SHARP CKD-CVD model, there were differences that rendered it difficult to obtain the same results as in FINE-CKD for some outcomes. The SHARP CKD-CVD model, for example, predicted a higher incidence of renal events. This difference positions the FINE-CKD model estimates as more conservative from a cost-effectiveness perspective because a higher baseline risk of such events, in conjunction with an advantageous clinical benefit relative to standard of care, would translate to a greater scope to offer value through treatment.

Overall, however, the clinical progression modelled by the FINE-CKD model appears well-aligned with the results of the SHARP CKD-CVD model. The alignment was more precise for CV outcomes, though the number of patients starting RRT estimated by FINE-CKD model was within the possible ranges of scenario analyses using the SHARP CKD-CVD model. Despite the positive results of the cross-validation, some uncertainty remains, as evident in the wide ranges obtained from the SHARP CKD-CVD model and in being the only identified model sufficient for cross-validation. Nevertheless, the results of the FINE-CKD model are at the lower end of the reference range in terms of initiation of RRT. Estimates of the FINE-CKD model can, therefore, be considered conservative in the context of the model being used for cost-effectiveness assessment.

Conclusions
Following ISPOR recommendations, a model should be declared 'valid' only in the context of its future applications. In this context, the most important requirements of the model are transparency and an ability to adequately reflect the available clinical data. Together, these provide a basis for reliable extrapolation relative to the existing predictive tools. This study demonstrates that the FINE-CKD model meets these requirements, while also being potentially conservative in its approach. Bayer consider that this validation exercise demonstrates that the chosen method for managing transitions and risks, while simplified, generates similar results to a model which uses multivariate multinomial logistic regression as well as risk equations.

A Validation of the validation by an external expert

The ERG report has triggered an external validation of the model comparing the FINE-CKD model with the SHARP-CKD/CVD model. One might argue that the latter model is the more useful model when addressing different types of patients and to analyse the cost effectiveness of a treatment for sub-groups defined by their base-line characteristics. The explanation regarding the higher incidence of the need for renal replacement therapy seems – as argued – related to the severity of the patients. When choosing healthier patients, by imputing lower UACR levels, one obtains estimates which are very much in line with the FINE-CKD model, and the FINE-CKD population. Naturally, this concordance between results may not come as a surprise as both models aim to do the same and both models are subtle enough to capture the long term expectations in terms of survival and events. Of course, differences may be expected, simply because the results of the FINE-CKD model are based on averages from the whole trial population while the SHARP CKD-CVD study presents the expectation of a single patient. As such the SHARP CKD-CVD model might be more representative for the median than for the mean, and, given that one may expect a skewed distribution, differences are a logical consequence.

Additional validation by an external expert

Introduction

The analysis of the costs effectiveness of finerenone for treating chronic kidney disease in people with type 2 diabetes is mainly based on one large randomised clinical trial; the FIDELIO-DKD trial. The general picture from the trial as summarised in the NEJM is that in patients with CKD and type 2 diabetes, treatment with finerenone resulted in lower risks of CKD progression and cardiovascular events than placebo. Outcomes that are addressed in the submission and its subsequent review concern: renal disease progression, cardiovascular outcomes, health related quality of life, mortality and adverse events; and of course costs.

A critical review of the submission

The analysis underlying the submission is – with respect to efficacy and quality of life - completely driven by the results from the FIDELIO-DKD trial. As indicated in the ERG review this doesn't always make sense. Whereas the ERG report mentions some of the estimates concerning utilities one might also point at some of the results with respect to the transition-probabilities. Below table presents the probability of worsening (or going further in the treatment cascade), staying in a health state or improving. Opportunistically one would assume that the probability to worsen is always higher for the control group than for the active group but this is not the case. The research group has kept themselves to the data from the trial and have taken the point estimates as they were without fitting some logic into the analysis which would have undoubtedly benefitted the cost effectiveness. This should be acknowledged.

	CONTROL			ACTIVE		
	worsen	stay	better	worsen	stay	better
CKD1/2	43.09%	56.91%	0.00%	45.16%	54.85%	0.00%
CKD3	10.42%	87.08%	2.50%	10.81%	87.57%	1.62%
CKD4	5.88%	79.45%	14.67%	4.88%	78.92%	16.21%
CKD5 without dialysis	19.93%	70.86%	9.21%	20.34%	68.85%	10.82%
Dialysis (acute)	100.00%			100.00%		
Dialysis	2.49%	97.51%		2.49%	97.51%	
Kidney Transplant (acute)	100.00%			100.00%		
Kidney Transplant (post-acute)	0.73%	99.27%		0.73%	99.27%	
DEATH		100.00%			100.00%	

Similarly, within the estimates of utilities they have stayed as close to the data as possible. One may have the view that this has kept the cost effectiveness ratio artificially high. When using the matrices of transition-probabilities to run the Markov chain one may find that the average utility after entering end stage renal disease program is about 0.747 while the average utility among the CKD stages is 0.751. This is decrement of only 0.005, partly because of the higher utility after transplant. This small difference may come as unexpected and one may have doubts about the admittedly very elegant analysis of the quality of life data. The reason for this doubt – which may be personal - lies in the estimate of the effect of age. It is estimated that with each year ones utility decreases with 0.001. That is a funny result, as this implies that – ceteris paribus - one would have to wait for 100 years to obtain a decrement of 0.1. As indicated in the report one may find much higher decrements in the literature, as high as 0.35, suggesting that the estimate as used here is rather conservative.

It is possible to build far simpler models than the company's model or any other model with even more subtleties. But there are decreasing marginal benefits of adding subtleties. As mentioned earlier, the company's model has been driven by data and consequently there may be some logic has been missing not in line with the progressive nature of the disease. It is however difficult to imagine, that if such logic would have been brought into the model, that the benefits, as they are estimated now would have been estimated lower.

In conclusion, Bayer consider that the chosen model structure and transitions, which has been extensively validated, is appropriate for decision making.

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

CV events
The ERG was concerned that the risk of a CV event for CKD stage 3 is lower than for CKD stage 1/2. Apart of these two CKD stages, the risk of CV events increases in the model until the start of RRT and then decreases after transplantation.

Taking into account that there are no patients in CKD 1/2 at baseline in the base case it can be said that CV risk increases with disease progression. Nevertheless, Bayer acknowledges the concerns of the ERG. Especially that the ERG is worried that the combination of the company's approach to estimate transition probabilities by arm and the approach to include the effect of finerenone on CV events carries the risk of double counting the potential "cardioprotective effects of finerenone". Bayer explored the possibility of such double counting at the stage of model development and found it to be negligible when applying FIDELIO-DKD study results. However, Bayer would like to reduce the uncertainty resulting from the approach to CV risks in the model by applying the same CV risk throughout all CKD stages. This is the same approach taken by the ERG in its preferred base case; the only difference is that Bayer is applying the total risk from the BT arm of FIDELIO-DKD study.

CV death
The ERG has expressed similar concerns regarding CV death. Bayer would like to address ERG comments in the same way as for CV events, i.e. by applying the same risk of CV death throughout all CKD stages. This is the same approach taken by the ERG in its preferred base case; the only difference is that Bayer is applying the total risk from the BT arm of FIDELIO-DKD study.

Finerenone effect after start of RRT
A further concern of the ERG was related to lack of data available to robustly estimate the potential "cardioprotective effect" of finerenone in patients that are on dialysis or have had a transplant. Bayer understands this concern and indeed the final SmPC for finerenone states that "*Due to limited clinical data, finerenone treatment should be discontinued in patients who have progressed to end-stage renal disease (eGFR < 15 mL/min/1.73 m^2)*." As such, a functionality has been implemented in the model allowing the user to stop treatment with finerenone after starting RRT. In order to address the doubts of the ERG, Bayer proposes using this functionality in the new base case. Bayer understands that using this option increases drug discontinuation in the model and would like to address this issue and it is discussed below.

Discontinuation of finerenone
The ERG considers that the treatment discontinuation has been overestimated in the model. The argument is made that this is due to possible double counting of discontinuation due to death in the company's model. This double counting is argued to have arisen as a result of the reasons for discontinuation not having been 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.

Bayer agrees with this approach and has re-performed this re-calibration of the discontinuation rate. The calibration has been performed after implementing other changes that have an impact on the duration of treatment e.g., stopping the use of finerenone after start of RRT.

Mortality
In the model, patients can die from three causes:

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

The revised approach to CV death has been discussed above. This change has been applied to address the doubts raised by the ERG.

Moreover, Bayer agrees with the ERG regarding the limitations of renal deaths included in the model. These limitations are mostly driven by a very strict definition of renal death in the FIDELIO-DKD trial (i.e., one of the criteria required that RRT had not been started although clinically indicated) which resulted in a very low number of deaths which could have been classified as having a renal cause. The definition of renal deaths in other sources is different (e.g. in the ONS statistics(33) report, deaths from renal failure are all cases of death within the ICD-10 codes N17-N19), and therefore renal deaths may have been underestimated in the model as suggested by the ERG. Bayer would like to remove this source of uncertainty from the model by not differentiating renal deaths. In the proposed new base case, Bayer set the risk of renal death to 0 in both arms of the model and do not reduce the general mortality with the proportion of deaths from renal causes.

Another concern of the ERG is that the increased risk for death from other causes has been linked to CKD progression, based on the studies for *all-cause* mortality, not *other-cause* mortality (adjusted to remove the impact of CV and renal deaths). Bayer agrees with the ERG that it is unclear how much the risk of death for other causes increases while CKD progresses. This issue was discussed with UK clinical experts who suggested that the other-cause mortality is also increased due to CKD and advised us to use the HR obtained from the available sources. Bayer followed this recommendation in our submission because inclusion of increased mortality is a conservative approach. Lack of any increase of mortality due to CKD progression results in finerenone being the dominant treatment over BT. Nevertheless, Bayer still considers the approach to increased mortality due to CKD progression applied in our submission to be the most reliable based on the available data and we do not suggest any changes in this regard.

Health-related quality of life
Bayer 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. Bayer considered that utilities derived directly from the FIDELIO-DKD trial for use within the cost-effectiveness model would be preferred by the ERG and NICE over those reported in the literature or derived from other sources. The ERG agreed that the use of EQ-5D data from the trial is generally preferred versus other non-trial sources, however, was concerned with the face validity of the resultant values. Bayer was aware of the limitations related to the utilities obtained from FIDELIO-DKD study, hence, a scenario was presented in the submission with the use of utility values based on the systematic literature review of utilities performed as part of the submission. Given that the utility data was retrieved from a methodologically rigorous systematic literature review, in conjunction with the extent of evidence reported for the utilities of interest, the results of the performed scenario can be considered reliable. Addressing the comments from the ERG, Bayer propose using utilities from the literature in the revised base case analysis.

CV event history

The ERG noted that the company's model reflects CV history with respect to the FIDELIO-DKD study period only. Bayer requested the ERG version of the model during technical engagement to further explore the ERG adjustments in relation to this issue; it was not provided.

Bayer agrees with the ERG that a proportion of the FIDELIO-DKD cohort with a recorded CV event history could be included in the model, however these should not enter the 'post CV event' sub-model at baseline. 'Post CV event' states in the model correspond to the incidence of the first event observed within the FIDELIO-DKD study and all the benefits of finerenone in terms of reducing the risk of CV events are modelled from this perspective. Hence, all patients should start the model in 'no CV event' states.

Nevertheless, it is true that 45.9% of patients enter the FIDELIO-DKD study with a history of a previous CV event. Bayer believes that from the model perspective these patients could experience post-acute costs and disutilities due to CV events before entering the model. As such, it is inappropriate to account for these post-acute consequences again in the model. Accounting for the acute consequences of CV events should not be amended in the model for this group of patients as it is assumed to be the same irrespective of the history of CV event. To account for the suggestion from the ERG that a history of CV events before entering the model should be considered, Bayer did not apply the post-acute consequences of CV events to 45.9% of patients entering FIDELIO-DKD with a history of CV events in a scenario.

Costs

Bayer applied the ERG suggestion regarding removal of the cost of death from the model.
Bayer applied the cost of BT as revised by the ERG.

Bayer agrees that the wastage of finerenone could be applied in the model, however, only half a pack should be considered. A whole pack would be wasted in a few cases, whereas no wastage would be seen for the other patients. Considering wastage of half a pack is the most common and reasonable approach, corresponding to the idea of half cycle correction commonly applied in cost-effectiveness models.

Impact on the ICER: ERG preferred assumptions vs Bayer revisions

Based on the above considerations Bayer has implemented several changes to the ERG preferred base case (Table 5).

Table 4. ERG's preferred model assumptions (as reported in the ERG report, table 29, page 134)

Preferred assumption	Cumulative ICER (ERG) £/QALY
Company's original base-case	17,552
# 1: ERG-corrected company's base-case	17,882
#2: Set risk of CV events to be independent of CKD stage	18,309
#3: Amend application of renal deaths	18,357
#4: Set risk of CV death to be independent of CKD stage	17,413
#5: Assume 45.9% of patients enter post-CV event sub-model	22,510
#6: Remove all death costs	22,528
#7: Edit BT cost to ERG's calculations	22,423
#8: Include one additional pack of finerenone to reflect wastage	23,066
#9: Assume utility for CKD1/2 is 0.80	23,587
#10. Assume post-acute disutility is half of acute disutility	23,706

The results of additional analyses performed by Bayer are presented in the table below (Table 6).

Table 5. Bayer revision of the ERG preferred model assumptions

Bayer revision of the ERG preferred model assumptions	Cumulative ICER (Bayer) £/QALY
Company's original base-case	17,552
Calculating the average risk of CV events for all CKD stages and applying it in all model health states (revision of #2 ERG assumption)	17,835
Remove renal deaths from the model and add them back to general mortality (revision of #3 ERG assumption)	17,882
Calculating the average risk of CV death for all CKD stages and applying it in all model health states (revision of #4 ERG assumption)	16,892
Setting finerenone to be stopped after RRT and calibrating discontinuation (revision of #1 ERG assumption)	15,260
Assume utilities from the literature (revision of #9 and #10 ERG assumptions)	12,474
Corrected implementation of 45.9% of patients with history of CV events (revision of #5 ERG assumption)	13,491
Remove all death costs (revision of #6 ERG assumption)	13,513
Edit BT cost to ERG's calculations (revision of #7 ERG assumption)	13,431
Include additional half of the pack of finerenone to reflect wastage (revision of #8 ERG assumption)	13,626

Conclusion

Bayer appreciates the concerns of the ERG regarding face validity of some model inputs. Bayer asked for the ERG version of the model to verify the ERG approach to amendments but, as this was not provided, have attempted to replicate the ERG results in our model.

Bayer believes that some of the scenarios explored by the ERG to reduce the uncertainty could be further improved. In particular, we believe the inclusion of patients with history of CV events at baseline by the ERG has been incorrectly implemented in the model. Corrected implementation of this amendment showed significantly lower impact on the model results.

Moreover, the limitations of the health state utilities from FIDELIO-DKD study can be overcome by applying values obtained based on a systematic literature review. The literature-based utilities provided should address concerns regarding face validity.

The additional analyses presented demonstrate that addressing concerns regarding the face validity of model inputs does not impact the model conclusions regarding the cost-effectiveness of finerenone vs BT. Moreover, the base case presented in the original submission can be considered conservative. Stability of the results despite several suggested changes, increases the plausibility of model estimates, which have been validated with FIDELIO-DKD study outcomes and the results of the model suggested by the ERG(32) as an example of good modelling practice in CKD (see answer to key issue 4).

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

The ERG expressed concerns regarding the company's sensitivity analyses. The following issues were raised:

For both DSA and PSA

• *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.*

In terms of the baseline patient distribution, Bayer considers that grouping is suitable as the parameters are interrelated (must sum to 100%);.this was acknowledged by the ERG in its report. In terms of the utilities, they were grouped for the DSA simulations only. In terms of the PSA, the parameters concerning utilities varied independently (please see the PSA - simulations worksheet columns EY: FF).

Grouping parameters related to utilities is also considered appropriate. Otherwise, more advanced health states would have higher utility than less severe CKD stages. In such a situation,

the DSA inputs would lack face validity to a greater extent than in the base case scenario presented in the submission, and questioned by the ERG:

Patients with CKD 3 were estimated to have an increase in utility of 0.001 when compared to CKD 1/2; the ERG highlighted this as clinically implausible at clarification (…) the ERG does not consider the resultant utility values to be suitable to populate the model as a result of this flaw in logic.

• *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].

Bayer explained that the FIDELIO-DKD trial was not designed nor powered to make conclusions based on HRQoL. The results of the multivariate regression model fitted to the FIDELIO-DKD data were associated with a high degree of uncertainty. Bayer were aware of the limitations related to the utilities obtained from the FIDELIO-DKD study, hence, a scenario was presented in the submission with the use of utility values based on the systematic literature review of utilities performed as part of the submission. Given that the utility data was retrieved from a methodologically rigorous systematic literature review, in conjunction with the extent of evidence reported for the utilities of interest, the results of the performed scenario can be considered reliable. Addressing the comments from the ERG, Bayer propose using utilities from the literature in the revised base case analysis.

For the revised base case analysis, separate DSA and PSA were performed. For utilities based on the literature, the bounds tested in the sensitivity analyses were first based on the mean and SE from the direct source (assuming beta distribution) and if not identified in the source, the 10% variations around the base case were tested.

• *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.*

For clarity, the ranges for DSA and PSA for IS stroke were calculated based on 95%CI from the source (Alva et al.(34)). It is true that this range of uncertainty is relatively high. As an alternative, Bayer suggest testing the fixed variation (+/-30% from the base case) for all costs based on Alva et al.

Nevertheless, it should be noted that the sensitivity analyses results presented in the original submission considered higher uncertainty. If the bounds are more precisely calculated the sensitivity analyses results would have been closer to the base case value. Therefore, the results in the original submission can be considered conservative regarding the estimated probability of finerenone being cost-effective in comparison to BT.

• *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.

Bayer was aware of the limitations related to the utilities and the high ICER for their lower bound tested in the DSA. Therefore, a scenario was presented in the submission with the use of utility values based on the systematic literature review of utilities performed as part of the submission. Bayer would like to provide the updated DSA results with the following changes:

- The utilities based on literature in the base case with the bounds tested in DSA from the direct source and if not identified in the source, with inclusion of the 10% variations
- The costs parameters based on Alva et al tested with +/-30% variations from base case

PSA only

Additionally, the ERG has concerns regarding 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.

The Normal distribution for costs were adopted by Bayer as requested by the ERG.

- 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.

  Bayer would like to omit this parameter from DSA and PSA, as there are no credible ranges to be tested. In addition, a scenario analysis was considered which excluded this parameter showing negligible impact on model results.

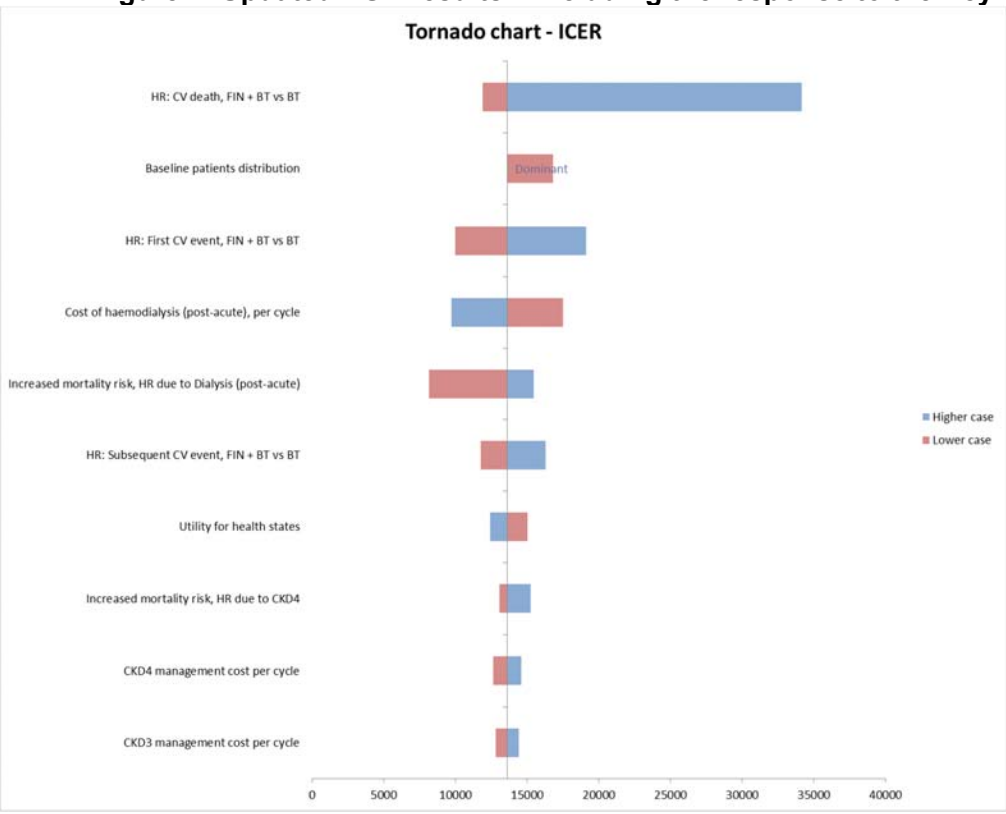
  Table 7: Health event eGFR decline from baseline excluded

Scenario	Incremental costs, undiscounted	Incremental costs, discounted	Incremental QALYs, undiscounted	Incremental QALYs, discounted	ICER, undiscounted	ICER, discounted
Base case (Bayer revision of ERG's preferred model assumptions)	£2,011	£1,796	0.19	0.13	£10,629	£13,626
Scenario: Health event eGFR decline ≥ from baseline excluded)	£2,011	£1,796	0.19	0.13	£10,843	£13,928

The results of the DSA and PSA after corrections described in the response to Key Issue 5 are presented below.

DSA results – Figure 1

Figure 1. Updated DSA results – including the response to the Key Issue 5

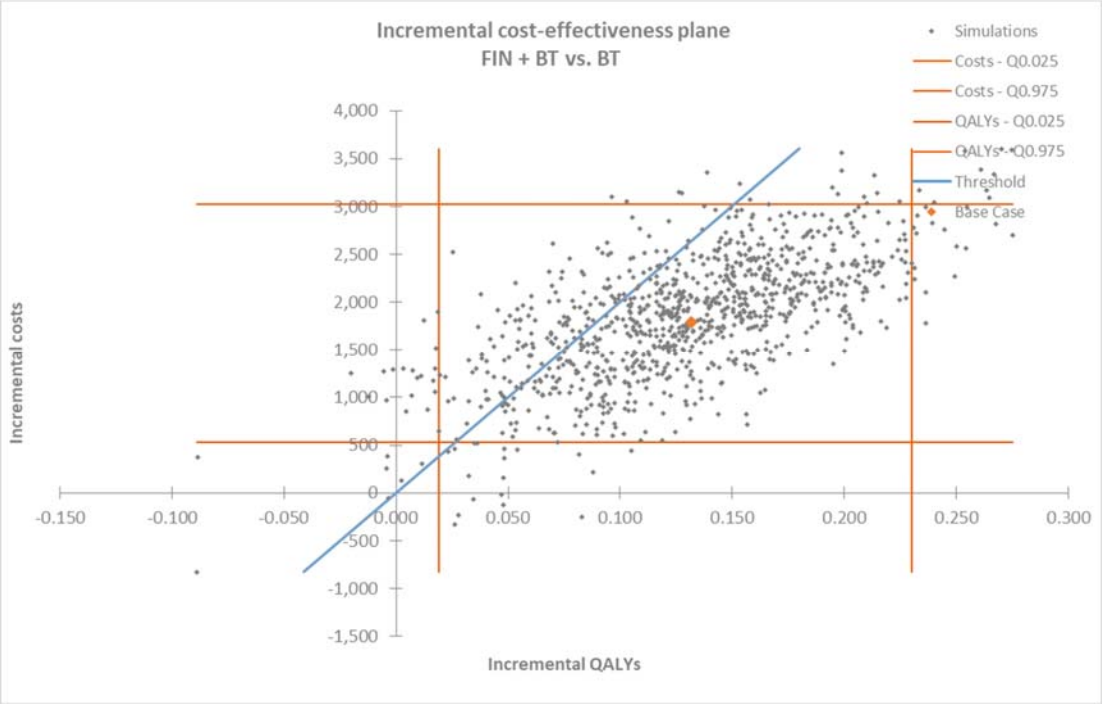


PSA results

Table 8. Updated PSA results – including the response to the Key Issue 5

	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Base Case	1,796	0.132	13,626
Mean	1,841	0.129	14,241
Std Deviation	642	0.054	39,333
Median	1,887	0.129	13,991
Min	-826	-0.089	-1,018,051
Q 0.025	531	0.019	5,749
Q 0.975	3,028	0.230	37,585
Max	3,602	0.275	393,372
Probability of being cost-effective			82.7%
Probability of being dominant			0.6%
Probability of being dominated			0.8%

Figure 2. Updated CE plane - including the response to the Key Issue 5



Addressing the ERG comments concerning sensitivity analyses in the model results in lower variability of the model outcomes in the DSA and PSA. **New base case analysis presented by Bayer following the ERG comments estimates a lower ICER for finerenone vs BT with higher probability of finerenone being a cost-effective treatment.**

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Clinical expert statement and technical engagement response form

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

Thank you for agreeing to comment on the evidence review group (ERG) report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report (sections 1.1, 1.3–1.5). You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

Clinical expert statement

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Deadline for comments by **5pm** on **14 March 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

Clinical expert statement

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Part 1: Treating chronic kidney disease and type 2 diabetes and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	[redacted]
2. Name of organisation	Association of British Clinical Diabetologists (ABCD)
3. Job title or position	[redacted]
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with chronic kidney disease and type 2 diabetes? ☒ A specialist in the clinical evidence base for chronic kidney disease and type 2 diabetes or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

8. What is the main aim of treatment for chronic kidney disease and type 2 diabetes? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	There are a number of aims when treating people with type 2 diabetes who have chronic kidney disease (CKD). First is to reduce the frequency of co-morbidities such as cardiovascular disease, which includes heart attack, heart failure and stroke. Second is to slow the progression of loss of kidney function and thus prevent the development of end-stage kidney failure, with the requirement for dialysis and/or kidney transplantation. Diabetes is currently the most common cause of end-stage kidney failure.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	I believe that the primary composite outcome used in the FIGARO-DKD trial (a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalisation for heart failure) and the FIDELIO-DKD trial (kidney failure, a sustained decrease of at least 40% in the eGFR from baseline, or death from renal causes) are clinically significant. They are also becoming standard for diabetes trials in these clinical domains.
10. In your view, is there an unmet need for patients and healthcare professionals in chronic kidney disease and type 2 diabetes?	Yes, there is definitely an unmet clinical need for both patients and the healthcare professionals involved in their care. People with type 2 diabetes and CKD have a significant additional risk of cardiovascular disease and diabetes is the most common cause of end-stage kidney failure.
11. How is chronic kidney disease and type 2 diabetes currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE has issued guidelines for the assessment and management of CKD in adults (CG182, updated 2015) and for the management of type 2 diabetes (CG28, currently being updated). For many years, the pharmacological management of CKD in type 2 diabetes has been optimal control of blood pressure, with the initial treatment seeking to block the renin-angiotensin system. This involved the use of

• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	ACE-inhibitors or angiotensin receptor blockers and then other anti-hypertensive agents to achieve blood pressure targets. Over the last couple of years, evidence has shown that the use of sodium-glucose co-transporter 2 (SGLT2) inhibitors provide an additional reduction in cardiorenal endpoints. SGLT2 inhibitors are now included in most modern guidelines for the management of CKD in type 2 diabetes and will figure prominently for this indication in an on-going review of NICE CG28. There is no disagreement between healthcare professionals in the NHS regarding the treatment pathways, however, the very recent inclusion of SGLT2 inhibitors means that there will still be much variation across United Kingdom, with many patients not receiving a SGLT2 inhibitor. Finerenone represents another significant advance in the management of CKD in type 2 diabetes. Its positioning with regards to the SGLT2 inhibitor class is uncertain since the FIGARO-DKD and FIDELIO-DKD studies were designed and initiated before SGLT2 inhibitors were recommended for this indication (indeed, only two – canagliflozin and dapagliflozin – currently have a licence for treatment of CKD in type 2 diabetes).
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic)	Finerenone (Kerendia) only received authorisation from the Medicines & Healthcare products Regulatory Agency (MHRA) to treat CKD associated with type diabetes on 14-March 2022. So, it has not been used in the NHS for the indication that is currently being appraised. I believe that the majority of patients that were included in the seminal trials (urine albumin:creatinine [UACR] 30-5000 mg/g & estimated glomerular filtration rate [eGFR] ≥25 mL/min) will be cared for by specialist nephrology services and so finereone initiation and monitoring would take place in that setting.

• What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	There would be no need for additional facilities, equipment or training since patient monitoring would be the same as currently takes place.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	I anticipate that finerenone will prolong life and provide health-related quality of life in comparison to the former standard of care (optimal renin-angiotensin blockade with ACE inhibitors or angiotensin receptor blockers). It is less certain whether patients who are also being treated with an SGLT2 inhibitor will receive equivalent benefits although the different modes of action of these agents suggest that this is likely. A subgroup analysis of FIDELIO-DKD did show a 25% reduction in UACR for patients who received the combination but the cohort was small (4.6% of the trial population). Additional clinical trials and real-world evidence are awaited. Patients who cannot tolerate an SGLT2 inhibitor will certainly benefit.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	A pre-specified meta-analysis of FIDELIO-DKD and FIGARO-DKD (N=13,171 subjects) suggest benefits of finerenone across a spectrum of CKD severity in type 2 diabetes. Other sub-group analyses are awaited.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient	I do not anticipate any additional difficulties associated with the use of finerenone in the target population. These patients will already be having regular checks of renal function, which will include serum potassium.

acceptability or ease of use or additional tests or monitoring needed)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Starting rules would simply be the point at which a patient satisfies the inclusion criteria used in the FIDELIO-DKD and FIGARO-DKD trials. Stopping rules would relate to the occurrence of clinically significant hyperkalaemia.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	I am not aware of any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Although the results from the recent trials of SGLT2 inhibitors in CKD (CREDENCE, DAPA CKD & EMPA-KIDNEY) are very encouraging, people with the combination of CKD and type 2 diabetes remain at very high risk of morbidity and premature mortality. This unmet need is being partially addressed by finerenone, which I would regard as a 'step-change' in management.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Hyperkalaemia is seen more frequently with finerenone than with placebo and serum potassium levels will need to be monitored. In a small number of cases

	(1.4-2.3% in the trials) finerenone will need to be discontinued due to hyperkalaemia.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	When the seminal clinical trials (FIGARO-DKD and FIDELIO-DKD) were designed and initiated, finereone was being compared to placebo on the background of standard of care, namely maximum tolerated blockade of the renin-angiotensin system. The recent licence changes for canagliflozin (2020) and dapagliflozin (2021) mean that modern standard of care for people with type 2 diabetes and CKD would include one of these agents, although widespread adoption is likely to be slow. There will also be patients for whom these drugs are not appropriate. As stated above, I believe the primary composite outcome in FIGARO-DKD (a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalisation for heart failure) and FIDELIO-DKD (kidney failure, a sustained decrease of at least 40% in the eGFR from baseline, or death from renal causes) are important and likely to be seen in a UK population. No new, unexpected adverse events came to light during these large studies.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	I am aware of a network meta-analysis of SGLT2 inhibitors versus finerenone (Zhao et al), which is currently undergoing peer review.

22. How do data on real-world experience compare with the trial data?	I am not aware of any real-world evidence at this point (due to finerenone having only recently been licenced for clinical use).
23. NICE considers whether there are any equalities issues at each stage of an appraisal. Are there any potential equality issues that should be taken into account when considering chronic kidney disease and type 2 diabetes and finerenone? Please explain if you think any groups of people with chronic kidney disease and type 2 diabetes are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this appraisal could • exclude any people for which finerenone is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people.	I do not think that there are any equalities issues for this appraisal.

Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. **Find more general information about the Equality Act and equalities issues here.**	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Key Issue 1: Uncertainty in the appropriate population	I am unclear as to why there is an uncertainty about the 'appropriate population' for treatment with fineronone. There is a clear definition of the population in the FIDELIO-DKD trial and these people have significant risk of progression to end-stage kidney disease and cardiovascular events, with increased hospitalisations and mortality. Even with the current best standard of care, there remains a significant residual risk of progression. The ERG suggests that generalisability to people with eGFR<25 mL/min73m2 is an issue since only those with eGFR 25 to <60 mL/min were recruited to the FIDELIO-DKD trial. The FIDELITY analysis (a combined analysis of FEDELIO-DKD and FIGARO-DKD data, published in the European Heart Journal [43, 474–484; 2022]) has reported on the small numbers of patients (81 in each arm) with eGFR<25 mL/min. The hazard ratio 0.48 (95%CI, 0.22–1.03) consistent with a benefit of finerenone at a lower limit of eGFR.

Clinical expert statement

Key Issue 2: Missing comparison with SGLT-2i	To date, there have been no head-to-head trials comparing finerenone with a SGLT2 inhibitor. However, patients receiving optimal doses of an ACE inhibitor or ARB in combination with a SGLT2 inhibitor have substantial cardiorenal residual risk. The FIDELITY analysis showed that addition of finerenone in patients on a SGLT2 inhibitor at baseline reduced the risk of a composite of cardiovascular endpoints by 37% (HR 0.63 [95%CI 0.40 - <1.0]) compared with placebo (438 and 439 patients in each arm). In addition, there will be patients for whom treatment with a SGLT2 inhibitor will not be tolerated.
Key Issue 3: Uncertainty in the clinical relevance of trial outcomes	Most clinicians would regard a composite of 'kidney failure, a sustained decrease of at least 40% in eGFR from baseline or death from renal causes' is a relatively hard endpoint. A sustained decrease in eGFR ≥40% from baseline is now a recognised endpoint in clinical trials and accepted by the Food & Drugs Administration (FDa) and European Medicines Agency (EMA) ('GFR decline as an end point for clinical trials in CKD: a scientific workshop sponsored by the National Kidney Foundation and the US Food and Drug Administration'. Am J Kidney Dis. 2014; 64: 821-835).
Key Issue 4: Model transitions subject to substantial limitations	Cardiovascular risk increases exponentially with the stage of CKD (Go et al, N Engl J Med 2004; 351:1296-1305; DOI: 10.1056/NEJMoa041031) so the use of CKD stage seems appropriate, albeit not the preferred base-case for the ERG.
Key Issue 5: Several influential model	I am uncertain as to the issues here.

Clinical expert statement

inputs lack clinical plausibility affecting overall face validity of model results	
Key Issue 6: Overall uncertainty in the results of the model is not adequately captured by the company's sensitivity analyses	I am uncertain as to the issues here.
Of the comparator background therapies listed in Table 26 of the ERG report, what proportion of each therapy is likely to be used in a primary care setting compared with secondary care?	Some of the doses quoted are low (e.g. losartan 50mg OD and atorvastatin 10mg OD). Acarbose is rarely used in the UK. Insulin and liraglutide would typically be secondary (specialist) care prescriptions, whereas the rest would be primary care (although this will vary in different parts of the UK). I'm not sure how '30x5mg' gets into the canagliflozin row (I note the subsequent comment in the text).
Are there any important issues that have been missed in ERG report?	I do not think so.

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

People with type 2 diabetes and CKD have substantial cardiorenal morbidity and premature mortality.

Treatment of cardiorenal morbidity is extremely expensive

Optimal medical management still leaves patients with cardiorenal residual risk

Finerenone provides cardiorenal protection in large well-conducted randomised controlled clinical trails

Finerenone represents an important therapy advance for people with type 2 diabetes and CKD

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☒ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Clinical expert statement and technical engagement response form

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

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Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Deadline for comments by **5pm** on **14 March 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

Clinical expert statement

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

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NICE National Institute for Health and Care Excellence

Part 1: Treating chronic kidney disease and type 2 diabetes and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	[redacted]
2. Name of organisation	Barts Health
3. Job title or position	[redacted]
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with chronic kidney disease and type 2 diabetes? ☐ A specialist in the clinical evidence base for chronic kidney disease and type 2 diabetes or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nil

8. What is the main aim of treatment for chronic kidney disease and type 2 diabetes? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	To prevent progression of diabetic kidney disease (DKD)
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Reduction in proteinuria from baseline despite optimal therapy of 20% or greater, any statistically significant difference in GFR decline, or combined renal end points (GFR decline of >40%, progression to CKD5, starting RRT, death, or MACE)
10. In your view, is there an unmet need for patients and healthcare professionals in chronic kidney disease and type 2 diabetes?	Yes
11. How is chronic kidney disease and type 2 diabetes currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	There is a recent update by NICE on the management of diabetic kidney disease. There is variations in practice, driven in part by the rapid growth in evidence for novel therapies to alter renal progression from GLP-1 RA, SGLT2i and now novel mineraolcorticiod receptor antagonists such that there my be some disparity across the county on getting patient son evidenced based therapies.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care?	I would expect this technology to be used as an add on to standard care in those patients who remain at increased risk of renal progression with evidence of proteinuria despite optimised care. This therapy is likely to start being used in secondary care, but I see no reason why in time, this agent would not be used in primary care. There are no additional facilities/training etc required for this therapy

• In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes, large trials have demonstrated a benefit in terms of a composite for hard renal end points including development of end stage renal failure which is very strong driver of reduced quality of life for patients
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	I would use this agent only in the same population that was studied in the trials, in line with the inclusion/exclusion criteria. The current evidence is strong for those with diabetes and proteinuria, however trials are ongoing looking at other cohorts of patients with CKD not due to diabetes which, if shown to be beneficial in these groups may extend the role of this therapy.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	This therapy will be an additional tablet for people with diabetic kidney disease, so there may be an issue on pill burden, it may require an additional blood test to check the serum potassium both otherwise will have little untoward impact on patients.

16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	As with other therapies which can cause hyperkalaemia such as ACEi or ARB or older MRA, patient may develop hyperkalaemia with this medication. There are well established pathway for managing hyperkalaemia which may require additional testing.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	For those patients who are prevented from developing progressive CKD and ending up on dialysis the health benefits are huge, I am unable to provide direct health economic benefits in terms of QALY, but I would imagine a specialist group has been set up to look at this?
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	I believe this is innovative, in the sense that it is a novel therapy which has been shown in outcome trials to prevent heard renal end points in large scale trials in people with diabetic kidney disease. Until recently since the advent of SGLT2i trials we have not had proven new therapies for almost 2 decades in this area.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	If patients develop hyperkalaemia (as with other standard of care therapies), then this may require stopping the medicine, and additional safety blood tests
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting?	Yes: the UK recruited many patients into these trials Important outcomes: MACE, renal death, starting dialysis Drug not being used routinely in UK practice so no new safety signals

• What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How do data on real-world experience compare with the trial data?	Drug not licenced in the UK, so no routine care data
23. NICE considers whether there are any equalities issues at each stage of an appraisal. Are there any potential equality issues that should be taken into account when considering chronic kidney disease and type 2 diabetes and finerenone? Please explain if you think any groups of people with chronic kidney disease and type 2 diabetes are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this appraisal could	Patients with diabetic kidney disease (DKD) are a vulnerable patient group, with increased prevalence of DKD in higher social deprivation areas and increased prevalence in ethnic minority populations. Patients with significant CKD have frequently been excluded from large scale CVOT in the past. I feel strongly that this comorbid group of patient needs proven therapies to prevent the devastating complication of progressive CKD and ESRD. I can see finerenone being used to reduce the health inequalities experienced by patients with DKD, as fewer people with develop progressive CKD/ESRD. From the trial data, the effect of finerenone was not impacted buy age, sex or ethnicity.

• exclude any people for which finerenone is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. **Find more general information about the Equality Act and equalities issues here.**	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Key Issue 1: Uncertainty in the appropriate population	I am not sure I understand this issue? I would imagine this therapy would be used according to the inc/ex criteria of the published trials so people with diabetes, who have a GFR 25-75ml/min, who are on optimised therapy and have albuminuria of 30-5000mg/g.
Key Issue 2: Missing comparison with SGLT-2i	I agree there is a gap in the evidence here, however their mechanisms of action are different and so would not appear to complete with each other. There were a small number of patient on SGLT2i in the study, when analysed albeit in a post hoc analysis, there was no difference in the beneficial effects of finerenone whether or not patient were on an SGLT2i at baseline. This has led the international renal guidelines to recommend finerenone in patient with DKDs who are on optimised therapy (RASi/SGLT2i) and remain proteinuric (https://kdigo.org/wp-content/uploads/2022/03/KDIGO-2022-Diabetes-Management-GL_Public-Review-draft_1Mar2022.pdf)

Clinical expert statement

Key Issue 3: Uncertainty in the clinical relevance of trial outcomes	The outcomes are similar to those studied in other CVOT trials in this population in SGLT2i
Key Issue 4: Model transitions subject to substantial limitations	Not in a position to comment due lack of specialist expertise in modelling
Key Issue 5: Several influential model inputs lack clinical plausibility affecting overall face validity of model results	Not in a position to comment due lack of specialist expertise in modelling
Key Issue 6: Overall uncertainty in the results of the model is not adequately captured by the company's sensitivity analyses	Not in a position to comment due lack of specialist expertise in modelling
Of the comparator background therapies listed in Table 26 of the ERG report, what proportion of each therapy is likely to be used in a primary care setting	If I understand the question correctly it is about whether the patients seen in the study in secondary care were similar to those seen in primary care in terms of medication use? I would say that the concomitant medication of the trial groups are very similar to those seen in both primary and secondary care in terms of classes of agents used both for their diabetes and CKD.

Clinical expert statement

compared with secondary care?	
Are there any important issues that have been missed in ERG report?	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Advanced renal care and dialysis confers a huge burden to patients and their families and is associated with significantly reduced left expectancy

Renal replacement therapy is a hugely costly therapy for healthcare

There is a large treatment gap for patients with DKD to prevent cardio renal outcomes

Finerenone appears to be well tolerated and provide patients with improved cardio renal outcomes

Click or tap here to enter text.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Technical engagement response form

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

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

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We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

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About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	**United Kingdom Kidney Association (UKKA)** **Association of British Clinical Diabetologists (ABCD)** - **Joint Response**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Key Issue 1: Uncertainty in the appropriate population	Yes	We do not understand as to why there is an uncertainty about the appropriate population who may be considered for treatment with Fineronone. There is a clear definition of this population within the FIDELIO DKD study which includes people with diabetes and evidence of CKD. The CKD is defined by the presence of a GFR of less than 60 ml/min/1.73m2 or the presence of albuminuria greater than an ACR of 3 mg/mmol. This population has a significant risk of progression to end-stage kidney disease (ESKD) and cardiovascular events with increased hospitalisations and mortality (CVD). This is a group where there are a number of treatments that have demonstrated benefit. However even with the current best standard of care, there remains significant residual risk of progression to ESKD and CV events for people with diabetes, CKD and albuminuria. The ERG suggests that generalisability in people with eGFR<25 ml/min/1.73m2 is an 'issue' because the 'label population' included are those with eGFR 25 to <60 ml/min/1.73m2 from the FIDELIO DKD trial. Furthermore, the company could have conducted an analysis including those

		with eGFR<25. We would like to bring to the attention of the ERG that the suggested analysis has already been done as part of the FIDELITY study (combined analysis of FEDELIO DKD and FIGARO DKD data, European Heart Journal (2022) 43, 474–484; https://doi.org/10.1093/eurheartj/ehab777). There were 81 patients in each of finerenone and placebo arm and the HR was 0.48 (95%CI 0.22 – 1.03, suppl file). This suggests finerenone may also be effective in reducing cardio-renal endpoints in those with eGFR<25.
Key Issue 2: Missing comparison with SGLT-2i	Yes	The publication of recent studies, demonstrating the benefits of dapagliflozin and canagliflozin in preventing progression of CKD in the DAPA CKD and CREDENCE studies has had a significant impact on the definition of standard of care for people with diabetes and CKD. It is important however to note that even with the use of SGLT2I on top of the use of inhibitors of the renin angiotensin system (RAASi) there remains a significant residual risk for both progression of CKD and CVD. There is a real clinical need to further reduce the residual risk in this group of patients. Although there is no head-to-head comparison between finerenone and an SGLT2i, a recent exploratory post hoc analyses of FIDELIO-DKD compared FIDELIO results with the reported CREDENCE study results, simulating the CREDENCE study design. The relative risk reduction of cardio-renal endpoints was 26% [HR 0.74 (95% CI 0.63–0.87)] with finerenone compared to a 30% risk reduction observed with canagliflozin [HR 0.70 (95% CI 0.59–0.82)]. (Nephrol Dial Transplant (2022) 0: 1–9;https://doi.org/10.1093/ndt/gfab336)

		As for the complimentary benefits of finerenone and SGLT2i, a prespecified exploratory analysis of FIDELIO DKD has shown that finerenone reduced urinary albumin:creatinine ratio (UACR) by 25% in patients who were already receiving a SGLT-2i (Kidney Int Rep (2022) 7, 36–45; https://doi.org/10.1016/j.ekir.2021.10.008). As the CREDENCE study has shown, UACR reduction is independently associated with reduction in cardio-renal endpoints. The FIDELITY analysis, mentioned above, shows that finerenone used in patients who had been on a SGLT2i at baseline reduced the risk of composite CV endpoints by 37% compared with placebo (438 and 439 patients in each arm respectively) – HR 0.63 (95%CI 0.40 - <1.0) These recent data support our opinion that finerenone provides further risk reduction of cardio-renal endpoints when used as an add-on therapy to SGLT2i in people with diabetes and CKD, optimally treated with RAAS blocking agents. The mechanisms of action of finerenone and SGLT2i are completely different. Finerenone, a non-steroidal MRA, counteracts over-activation of mineralocorticoid receptors and thereby reduces inflammation and fibrosis in renal disease. On the other hand, SGLT2is act by reducing glomerular capillary pressure through the tubulo-glomerular feedback. This provides the pathophysiological justification for using the two agents together in DKD. Furthermore, finerenone may also be an option in those intolerant to SGLT2i.

Key Issue 3: Uncertainty in the clinical relevance of trial outcomes	Yes	We remain perplexed as to why there is concern about the outcome measures used in this study. Sustained decrease in eGFR ≥40% baseline is a recognised endpoint in clinical trials and accepted by FDA and EMA (GFR decline as an end point for clinical trials in CKD: a scientific workshop sponsored by the National Kidney Foundation and the US Food and Drug Administration. Am J Kidney Dis. 2014; 64: 821-835). The combination of kidney failure, a sustained decrease of at least 40% in the eGFR from baseline, or death from renal causes is a relatively hard endpoint. These criteria have been used in many other studies that have looked at progression of chronic kidney disease and indeed has also been used in the currently concluded EMPA Kidney study, stopped early for the efficacy of empaglifozin in people with CKD. Furthermore, similar benefit was observed in FIDELIO DKD exploratory analysis using eGFR decline ≥57% and CV death as composite endpoint (CREDENCE primary endpoint) [Nephrol Dial Transplant (2022) 0: 1–9; https://doi.org/10.1093/ndt/gfab336] Therefore, we believe the endpoint used in this study was appropriate. Moreover, changing the goalposts in relation to recognised criteria for progression of CKD is going to have a significantly damaging impact on development of new therapies for the management of CKD.
Key Issue 4: Model transitions subject to substantial limitations	No	We note the ERG concern about the modelling but are equally concerned that the absence of evidence is not evidence of absence. We have a very well conducted trial in people with diabetes and CKD and the beneficial outcome is equivalent to the major studies that were reported in 2001 and which determined the introduction of inhibition of the renin angiotensin

		system to treat diabetic kidney disease (RENAAL and IDNT studies). Both the UKKA and the ABCD believe that the data from this trial has demonstrated significant benefit in a very high-risk group of patients with diabetes and CKD. We also need to consider the high cost of hospitalisation for heart failure and CV events in people with DKD who are often frail and elderly.
Key Issue 5: Several influential model inputs lack clinical plausibility affecting overall face validity of model results	No	The statement “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” is not very clear. CV risk goes up exponentially with the stage of CKD (Go et al, N Engl J Med 2004; 351:1296-1305; DOI: 10.1056/NEJMoa041031)
Key Issue 6: Overall uncertainty in the results of the model is not adequately captured by the company’s sensitivity analyses	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses

Additional issues

All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Table 3 Additional issues from the ERG report

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 2: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Insert key issue number and title as described in the ERG report	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the ERG report	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.
Insert key issue number and title as described in the ERG report	…	…	[INSERT / DELETE ROWS AS REQUIRED]
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case
[PLEASE DESCRIBE HERE]

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Technical engagement response form

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About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	AstraZeneca UK Ltd
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Not applicable**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Key Issue 1: Uncertainty in the appropriate population	Yes/No	No comment
Key Issue 2: Missing comparison with SGLT-2i	Yes/No	Sodium-glucose cotransporter 2 inhibitors (SGLT-2is) were included as a comparator in the final scope for this appraisal as they were considered part of standard clinical practice in this patient population at that point. Since then, NICE have published a final clinical guideline and a technology appraisal guidance (TA775) which further reinforce the class as standard of care for patients with CKD and T2D. We therefore believe that all of the 5 criteria for selecting an appropriate comparator detailed in Section 6.2.2 of the 'Guide to the methods of technology appraisal 2013' are now met by SGLT2is, namely: 1) Established NHS practice in England 2) The natural history of the condition without suitable treatment 3) Existing NICE guidance 4) Cost-effectiveness 5) The licensing status of the comparator

		In February 2022, the NICE T2D guidelines (NG28) were updated to provide clear recommendations for the use of SGLT2is in individuals with CKD and T2D. The guidelines state that for those taking an ACE inhibitor or ARB, an SGLT2i should be offered if ACR >30 mg/mmol and they meet the criteria in the marketing authorisation. For those with an ACR or 3-30 mg/mmol who are already taking an ACEi/ARB, an SGLT2i should be considered.[1] These recommendations were based on evidence from well conducted RCTs for the two SGLT2is that are licensed to treat patients with T2D and CKD, dapagliflozin and canagliflozin. The trial data showed reduced risk of CKD progression, mortality and cardiovascular events in adults with T2D and CKD. The guidelines committee also concluded that SGLT2is were a cost effective use of NHS resources when used in these patient populations.[1] Many of the patients in whom SGLT2is would be prescribed according to these guideline recommendations would also fall within the inclusion criteria of the FIDELIO-DKD trial which included patients with T2D and diagnosed CKD on maximum tolerated label dose of ACEi/ARB, with at least one of the following criteria at run-in and screening visits: o persistent high albuminuria (UACR ≥30 (~3 mg/mmol) to <300 mg/g (~30 mg/mmol) and estimated glomerular filtration rate (eGFR) ≥25 but <60 mL/min/1.73 m² and presence of diabetic retinopathy or o persistent very high albuminuria (UACR ≥300 mg/g (~30 mg/mmol) and eGFR ≥25 to <75 mL/min/1.73 m² In March 2022, NICE published the Technology Appraisal Guidance (TAG) recommending the use of dapagliflozin in adults with CKD who are already taking an ACEi/ARB and have an eGFR 25-75 mL/min/1.73 m², with no restriction based on uACR for the T2D population.[2] The population for which access to finerenone is being sought in the current appraisal (ID3773) falls within the population for which NHS funding of dapagliflozin will be mandated from early June 2022. Therefore the NICE recommended SOC therapies for patients falling within the “label population” for finerenone are clearly ACEi/ARB plus an appropriate SGLT2i as per license.

		During this recently concluded NICE appraisal process of dapagliflozin for the treatment of CKD (TA775)[2], canagliflozin was not initially included in the final scope, however the NICE committee subsequently determined it to be an appropriate comparator for dapagliflozin in patients with CKD and T2D on an ACEi/ARB with an eGFR 25-75 mL/min/1.73 m². Given the overlap in the population now recommended dapagliflozin and the population included in this appraisal of finerenone, there seems to be no rationale for why both licensed SGLT2is wouldn't also be deemed relevant comparators in this instance. During the scoping phase for this appraisal of finerenone, a commentator noted that SGLT2is are not suitable for everyone and established clinical treatment without SGLT2is should be used as a comparator. Dapagliflozin is licensed and NICE recommended for individuals with CKD who fall within the finerenone "label population" for which access is sought. Although dapagliflozin might not be appropriate for every single patient that could receive finerenone, and vice versa, the significant overlap in eligible patient populations means it remains a relevant comparator and this is supported by precedent from TA775 in which canagliflozin was determined to be a relevant comparator by the NICE committee despite not being used or licenced in patients with CKD without T2D which were also included in the submission population. Another comment at scoping stage suggested that it would not be appropriate to compare finerenone with SGLT2is as no head-to-head trials have been conducted. It should be noted that whilst head-to-head trial evidence is always the preferred source of comparative efficacy data, there are a range of methods by which therapies can be compared indirectly and this is routinely conducted for the purposes of health technology assessments (HTAs). In the absence of a direct head-to-head trial, a feasibility assessment should have been conducted to identify relevant data sources and determine the appropriateness of conducting an Indirect

		Treatment Comparison (ITC); this assessment should be provided to the NICE committee and ERG. Overall, it's clear that NICE guidance, both clinical guidelines and the dapagliflozin CKD TAG (TA775), lists SGLT2is as relevant comparators for the patient population being considered in this appraisal of finerenone. Furthermore, NICE recently determined canagliflozin to be a relevant comparator in the T2D population in the dapagliflozin appraisal despite not including it in the original scope. It is therefore appropriate that licenced SGLT2is are included as comparators in the economic model and that an economic comparison is made, hence every effort should be made to investigate and execute this.
Key Issue 3: Uncertainty in the clinical relevance of trial outcomes	Yes/No	No comment
Key Issue 4: Model transitions subject to substantial limitations	Yes/No	No comment
Key Issue 5: Several influential model inputs lack clinical plausibility affecting overall face validity of model results	Yes/No	It is important that all health economic models used for the purposes of HTA are validated to ensure that the model has been appropriately designed, is technically sound and is referenced and documented clearly. AstraZeneca understands based on discussions with nephrologists and published literature that CV risk would increase as the CKD stages progress and there is no clear rationale as to why the utility values in CKD stage 3 would be greater than those for CKD stages 1 and 2. This is extensively supported in the literature, and simply illustrated in the KDIGO heatmap which shows risk increases incrementally as GFR declines and albuminuria increases.[3] Alternative model scenarios which fully explore the impact of the various inputs that clinical lack face validity should be conducted and provided by the company to ensure the impact on the ICER can be elucidated.
Key Issue 6: Overall uncertainty in the results of the model is not	Yes/No	No comment

adequately captured by the company's sensitivity analyses		

Additional issues

All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Table 3 Additional issues from the ERG report

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 2: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Insert key issue number and title as described in the ERG report	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the ERG report	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.
Insert key issue number and title as described in the ERG report	…	…	[INSERT / DELETE ROWS AS REQUIRED]
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case
[PLEASE DESCRIBE HERE]

References

1. National Institute for Health and Care Excellence. NG28: Type 2 diabetes in adults: management. 2022.
2. National Institute of Clinical Excellence. TA 775: Dapagliflozin for treating chronic kidney disease 2022.
3. KDIGO. Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease, 2012.

NICE National Institute for Health and Care Excellence

Technical engagement response form

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

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **Monday 14 March 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	UK Renal Pharmacy Group
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Nil**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Key Issue 1: Uncertainty in the appropriate population	No	I agree that the study population should reflect the proposed licensed indication for finerenone hence the company submission is appropriate but would ideally include data on those with eGRF <25 who could use the drug with caution. I would consider extrapolation of data is acceptable as only 10% of the patients fell outside the proposed licensed indication.
Key Issue 2: Missing comparison with SGLT-2i	No	I believe that the comparison with the SGLT-2i is key and I would recommend further investigation into the use of Finerenone as an alternative as well as an addition to SGLT-2i as baseline treatment. This evidence may be explored in the Figaro DKD study which was published after this submission was issued hence may provide more data to support Finerenone as an add on therapy. Alternatively, comparison with the clinical outcomes for the SGLT-2i used for the NICE submission could be used to establish the place for Finerenone and to compare cost effectiveness and efficacy for these two agents to inform a treatment guideline.
Key Issue 3: Uncertainty in the clinical relevance of trial outcomes	No	The clinical relevance of the efficacy of Finerenone would be supported by looking at the data from the Figaro DKD study hence increasing the population numbers included in the data. Increasing population numbers should help strengthen the evidence to support true clinical benefits of this novel therapy. Notwithstanding this the clinical relevance of avoiding a sustained decline in eGFR by >40%

		should translate into improved clinical outcomes and hence delay transition to RRT.
Key Issue 4: Model transitions subject to substantial limitations	No	I would support the recommendation to follow the modelling used in the NICE submission for the SLGT2i which should allow a better comparison between these two treatment options.
Key Issue 5: Several influential model inputs lack clinical plausibility affecting overall face validity of model results	Yes/No	No comment
Key Issue 6: Overall uncertainty in the results of the model is not adequately captured by the company's sensitivity analyses	Yes/No	No comment

Additional issues

All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Table 3 Additional issues from the ERG report

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Drug costs and additional costs associated with increased K+	Page 111 – table 26	No	I have concerns around the drug costs included in the company submission as well as the drug doses and therapeutic choices described in the submission. The company described the drugs selected as those most commonly seen throughout the trial although from experience, I would expect the most commonly used B Blocker to be bisoprolol and potassium binder to be sodium zirconium cyclosilicate or patiromer which have recently been approved by NICE. In addition, the doses described are very conservative (amlodipine 5mg, ramipril 5mg atorvastatin 10mg) hence I suspect do not reflect the optimum dose. I would anticipate that the hyperkalaemia seen with Finerenone might require a potassium binder to maintain the potassium below 6 and hence ensure ongoing optimal RAAS therapy – this will again add to the potential baseline costs of treatment.
Additional issue 2: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Insert key issue number and title as described in the ERG report	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the ERG report	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.
Insert key issue number and title as described in the ERG report	…	…	[INSERT / DELETE ROWS AS REQUIRED]
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case
[PLEASE DESCRIBE HERE]

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

A Single Technology Appraisal

ERG Review of Company's Response to Technical Engagement Response

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Produced by	**Peninsula Technology Assessment Group (PenTAG)** **University of Exeter Medical School** **South Cloisters** **St Luke's Campus** **Heavitree Road** **Exeter** **EX1 2LU**
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Rider on responsibility for document	The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.
This TE response is linked to ERG report	Crathorne L, Bullement A, Shaw N, Mann J, Wheat H, Kiff F, Melendez-Torres G.J.Finerenone for treating chronic kidney disease in people with type 2 diabetes [ID3773]. Peninsula Technology Assessment Group (PenTAG), 2021.

1. INTRODUCTION

This document provides the Evidence Review Group's (ERG's) critique of the company's response to the technical engagement report produced by the National Institute for Health and Care Excellence (NICE) for the appraisal of finerenone for treating chronic kidney disease (CKD) in people with type 2 diabetes (T2D) [ID3773]. Each of the issues outlined in the technical report are discussed in further detail in Section 3.

The company has also provided changes to the economic model. The ERG critique and the preferred ERG base case is presented in Section 2.

Finally, the company have presented some additional data, including cost-effectiveness estimates in alternative populations and cross-validation analyses for the economic model. These are addressed in the context of the key issues.

2. UPDATED COMPANY ALTERNATIVE ERG BASE CASE ANALYSES

In the company's technical engagement response, the company presented its revised base case analysis. The changes made by the company are described in brief below:

- The average risk of cardiovascular (CV) events and CV deaths has been re-calculated across all CKD stages, and then applied for all model health states
- Mortality has been adjusted where renal deaths are removed as a separate cause of death and combined with general population mortality
- Finerenone is assumed stop after initiation of renal replacement therapy (RRT), and then the treatment discontinuation curve is re-calibrated to account for competing risks
- Utility values from FIDELIO-DKD have been rejected, in favour of values from the literature
- Background therapy (BT) cost is aligned with the ERG's calculations
- A *"corrected implementation"* of CV event history has been incorporated, to account for 45.9% of patients with history of CV events
- Wastage for finerenone is now based on half a pack, as opposed to zero or one full pack

Ultimately, when combined and applied within the model, these changes caused the company's base case ICER to decrease from £17,552 to £13,626. The ERG's tentative preferred base case analysis, per the ERG's report, yielded an ICER of £23,706. As explained in the ERG's report, this analysis included several changes to the company's original base case analysis to address some (but not all) of the limitations highlighted in the ERG's report. These changes are described further both within the ERG's report, and in the context of Issue 5 in this response.

Similar to the point raised by the company in its response regarding a lack of access provided to the ERG's model, the ERG unfortunately does not have access to a copy of the company's model with these changes made so that they could be further investigated. Consequently, at this point in time, the ERG is only able to make one change to its base case analysis – to switch the wastage assumptions, which causes the ICER to decrease to [redacted]. Therefore, the ERG considered this ICER to serve as its current tentative preferred base case analysis, though its 'true' preferred base case analysis would likely include some additional edits that it is currently unable to make (discussed further in relation to Issue 5 of this response).

3. ERG REVIEW OF KEY ISSUES

Issue 1: Uncertainty in the appropriate population

In response to this key issue, the company reiterated their comments from the factual accuracy check; clarified any distinctions between the trial population, the label population and the scope; and provided their base case ICERs both with and without patients eGFR < 25ml/min/1.73m^2 in the model. The ultimate difference between discounted ICERs is ~£200, favouring the model inclusive of those with lower eGFR. Of note, the analysis provided by the company reflected the specific analysis requested by the ERG in their original report (Key Issue 1, p.16).

At this stage, the ERG would regard that the company have made appropriate efforts to address this uncertainty, and have clarified that the ultimate population for which approval is sought is adults with CKD (Stage 3 and 4 with albuminuria) and T2D, where Stage 3 and 4 is qualified as those adults with eGFR ≥25ml/min/1.73m^2. This population remains narrower than the NICE scope.

Issue 2: Missing comparison with SGLT-2i

In the original report, the ERG noted that a key uncertainty in the company's analysis was the exclusion of SGLT-2i agents as comparators. At the time, the ERG did not regard that the company's stated rationale for this was credible.

In response to this key issue at Technical Engagement, the company have reiterated the novel mechanism of action for finerenone as a mineralocorticoid receptor antagonist. This is not unto itself a credible argument for considering finerenone separately because different mechanisms of action between comparators have not previously precluded the assessment of comparators in the context of appropriately scoped decision problems. For example, platinum-based and taxane-based chemotherapies for cancers are frequently appraised alongside novel immunotherapies.

Subsequent to this, the company proposes six arguments for why SGLT-2i drugs should not be considered relevant comparators. Briefly, these arguments are that:

1. Due to recent changes in guidelines, few patients are receiving SGLT-2i drugs in clinical practice;

2. Not all patients would be receiving SGLT-2i drugs, even if they were a comparator;

3. Consultees on the draft scope commented that SGLT-2i drugs should not be considered a comparator;
4. The company previously commented that they do not regard SGLT-2i drugs to be comparators as defined in the NICE methods guide;
5. The mode of action between the two drugs are different; and
6. Differences in trial populations would limit comparability between comparators.

Not all of these arguments are credible. For example, the argument of distinctions between modes of action between the two drugs is, as discussed above, not invariably a preclusion to considering these comparators in the same decision problem (argument 5). The corollary argument to this (argument 2), that not all patients would be receiving SGLT-2i drugs even if these were fully integrated into routine clinical practice, is also not credible for this reason. Across a range of appraisals where multiple drugs are salient comparators including over diverse mechanisms of action (e.g. beta-interferons, S1P, monoclonal antibodies for relapsing multiple sclerosis; TNFi, JAK inhibitors and methotrexate for rheumatoid arthritis), patient choice and suitability are taken together with relevant cost-effectiveness considerations. Thus, a key limitation in this appraisal is that the company has not sought to present any credible estimates of comparative cost-effectiveness between finerenone and SGLT-2i drugs, nor any credible assertion with respect to their argument in the technical engagement response why patient choice is of central importance overtaking cost-effectiveness considerations, for example to address health inequalities.

Argument 6 is not credible on the basis that a comparison being difficult does not mean it should not be undertaken. There was no attempt to provide such a comparison in order to then critique its feasibility and utility for decision-making.

Arguments 1, 3 and 4 relate to what 'counts' as a comparator. Argument 3 is not unto itself credible to the extent that the draft scope was published before considerable changes to clinical guidance and guidelines in respect of this population; specifically, as noted by the company, positive NICE recommendations relating to SGLT-2i drugs in T2D and CKD. It is also the case that at the time the company previously commented that they did not regard SGLT-2i drugs were relevant comparators (argument 4), these positive recommendations were not in evidence. What remains, then, is the argument that due to small market share, SGLT-2i drugs cannot be considered standard clinical practice. Ultimately, this is a point for committee to consider. It is

certainly plausible that, for example, 'historical' comparators for a given patient population and decision problem may no longer be considered relevant because they are unacceptable to patients and clinicians and have been superseded by better alternatives; but that is not the situation here. And, indeed, it is possible that over the remaining lifetime of this appraisal, SGLT-2i drugs could become standard clinical practice such that they would meet this standard to be considered as a comparator. It is ultimately for the appraisal committee to decide whether SGLT-2i drugs should be considered comparators in light of their recent positive recommendation, and what might be reasonably expected to become routine clinical practice in the UK as measured by prescribing volume rather than by NICE guidance.

Issue 3: Uncertainty in the clinical relevance of trial outcomes

This key issue ultimately relates to the value of surrogate outcomes (specifically, the use of eGFR) for assessing the value of health technologies and the interpretation of a significant impact on composite endpoints as compared to a non-significant impact on components of the endpoints.

In response to this key issue, the company has provided additional commentary on the value of eGFR. This commentary, which also integrates statistical tests of risk of kidney failure before and after eGFR reduction, is persuasive. However, what is less persuasive is the company's argument in respect of interpretation of the individual endpoint components. The company presents a test of heterogeneity of the composite efficacy endpoint by the endpoint components, interpreting a non-significant p-value as evidence of no heterogeneity. However, if the study was not powered on the endpoint components, it would not be reasonable to expect a significant test on an interaction-based test of heterogeneity. The company also noted a significant impact on delaying sustained decrease in eGFR of ≥57% from baseline over at least four weeks. While this is probative, it is not dispositive in respect of the interpretation of the range of endpoint components. Ultimately, the company's view is that interpretation of effects on endpoint components should be undertaken by 'pattern-matching' a signal of positive, albeit non-significant, results across endpoint components. While this may be useful in a global view of the drug's impact, it is not useful in understanding the specific effectiveness of finerenone and, thus, the clinical relevance of FIDELIO-DKD's findings, in respect of the endpoint components.

Issue 4: Model transitions subject to substantial limitations

In response to this key issue (related to how transitions/risks are reflected within the company's model), the company has undertaken a cross-validation exercise and has obtained independent

feedback from an external health economic expert. These are discussed in turn in the response that follows.

Cross-validation

It was beyond the scope of the ERG's review to perform this type of cross-validation, and so the ERG appreciates the efforts made by the company to undertake this exercise. Nevertheless, the ERG considers it important to acknowledge how much this exercise is able to practically reveal about differences in modelling approaches and potential impacts on results. In the cross validation, expected event rates are compared for the BT arm only, and so the possible influence in terms of how these would compare for finerenone (both on an absolute scale, and relative to BT), as well as how this would impact cost-effectiveness results, remain unknown. The ERG expects that it would be very difficult to conduct a cross-validation exercise to robustly compare these findings without effectively re-building the SHARP CKD-CVD model.

The ERG highlights that it did not recommend that the SHARP CKD-CVD model could (or should) be used instead of the company's model to inform this appraisal. The company correctly highlights a number of limitations of the SHARP CKD-CVD model that limit its ability to perform the cross-validation exercise (and by extension, would mean it is not possible to use to inform this appraisal). Rather, the ERG highlights that some aspects of the SHARP CKD-CVD model and other published models (e.g., the NICE guideline model) or model structures (e.g., multi-state modelling) would allow for the ability to capture time-varying transitions/risks. The ERG's perspective on this point remains unchanged, and while the results from the cross-validation may imply similar projections in terms of CV events, this should not be confused with an expectation that incorporating time-varying transitions/risks within the company's model would have a negligible impact on the ICER.

External validation

The ERG notes the findings from an external validation of the company's submission and the ERG's report. The external reviewer comments that the ERG has focused predominantly on the data available from the FIDELIO-DKD study in determining its judgements with respect to model face validity and the plausibility of its inputs. This is correct – the FIDELIO-DKD study comprises the main source of data to inform the model, and so the ERG's commentary focuses mostly on this study. However, the ERG disagrees with the implication that there was an absence of logic applied in its analysis that would have (undoubtedly) benefitted results in favour of finerenone.

As noted within the ERG's report (Section 4.2.6.1), the risk of some events occurring within the company's model appear to be counterintuitive in light of the summary measures of effect for finerenone and/or clinical plausibility. This was highlighted in the following excerpt from the ERG's report: *"… 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"* (Section 4.2.6.1). Here, the ERG acknowledges that some of these inputs appear illogical (in this case, related to transition probabilities), and it was noted that this is likely to be (at least partially) a consequence of how the model parameters were estimated. Nonetheless, without any alternative analyses to populate the model, the ERG was left unable to produce an improved version of the transition probabilities. The company's edits made to the model are discussed further in response to Key Issue 5.

The ERG does not agree that resolving these apparent errors in logic would *"undoubtedly* [benefit] *the cost effectiveness"* of finerenone (company's TE response, Key Issue 4). This is because all the transition probabilities included within the model are inherently linked – changing one value would likely affect all other values, and therefore the impact on cost-effectiveness is unknown (particularly in the context of a model which has some complex features, particularly when considering long-term costs and treatment effects). It may be the case that if a more formal analysis of transition probabilities was conducted in which a treatment effect was explicitly modelled (e.g., through a multi-state modelling approach as acknowledged in the ERG's report), then the ICER could reasonably be lower, higher, or very similar to the current ICER. The ERG considers speculation concerning the likely direction of travel for the ICER were the transition probabilities edited to be unhelpful for decision-making.

The external expert also comments on the utility values used within the company's model. As with the transition probabilities, the ERG focused its review on the available evidence which came from an analysis of the FIDELIO-DKD study, given that this was the primary data source chosen by the company to inform its model (which the ERG agrees is likely the best source of data available for this population in general, but certainly for this population treated with finerenone). The ERG accepts that, in theory, small differences in utility values by health state may mean that delayed progression with finerenone could under-estimate QALY gains. However, it could also be argued that lower utility values in more advanced disease states could mean that total QALYs reduce for both arms, meaning that the absolute incremental QALY gain for finerenone could be smaller than the current results, and so it could also be the case that the current model may over-estimate QALY gains (notwithstanding the company's view that some

elements of the model are deemed to be conservative). The company has edited its preferred utility values within its revised base case analysis which is discussed further in response to Key Issue 5.

The ERG accepts that it would have been possible for the company to develop either a simpler or a more complex model as part of its submission, and that ultimately there will be a tipping point at which additional complexity may no longer be justified by the expected impact on the cost-effectiveness results. However, it is the ERG's view that some of the simplifications made in the company's model may still have an important impact on model results, though the directional effect on the ICER itself is, and remains, unclear, even in light of the cross-validation the company has undertaken. In the ERG's report, it is stated with respect to Key Issue 4: *"The effect of addressing some of* [the limitations of the model with respect to transitions and the risk of events] *on the ICER is unclear, and theoretically could cause the ICER to either increase or decrease"* (ERG report, Section 1.5, Key Issue 4 summary table).

Additional ERG commentary

For completeness, the ERG highlights that the company has not commented on the following other related topics associated with Key Issue 4:

- The feasibility of re-analysing transition probabilities to address the apparent logical errors highlighted by the ERG within its report (see ERG report Section 4.2.6.1)
- The feasibility of re-analysing utility data to address the apparent logical errors highlighted by the ERG within its report (see ERG report Section 4.2.7.2)
- The suitability of other model features or structures, other than the SHARP CKD-CVD model used to inform the company's cross-validation (see ERG report Sections 1.5 and 4.2.6.1)

Conclusion

Overall, the ERG is keen to highlight that the presence of limitations in the modelling approach does not necessarily mean that the model should be irrefutably rejected as a basis from which to determine the likely cost effectiveness of finerenone. The results from the cross-validation are somewhat helpful, in that the results show that similar projections of events are modelled for the BT arm over time. However, at the same time, it would be remiss of the ERG not to highlight what it considers to be important limitations of the company's model, and the true impact of

including time-varying risks into the model (when accounting for the relative effect of finerenone) on the results required for decision making (i.e., the ICER) is still unclear.

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

In response to this key issue (related to how some model inputs lack clinical plausibility in the company's model), the company has opted to amend each of the ERG's preferred assumptions (*"Bayer revision of the ERG preferred model assumptions"* – see Table 6 of the company's TE response for a summary of the edits made). In the ERG's response below, each topic is addressed in turn, with a summary position of the ERG highlighted at the end of each sub-section for simplicity. Of note, the ERG did not have access to a version of the company's revised model at the time of preparing its response, and so the ERG's understanding of changes made to the model are based on written description provided by the company. Furthermore, the ERG was unable to verify any of the reported ICERs.

#1: ERG-corrected company's base case // Setting finerenone to be stopped after RRT and calibrating discontinuation (revision of #1 ERG assumption)

The ERG acknowledges that in addition to the edit made by the ERG to treatment discontinuation, in clinical practice patients may discontinue treatment upon initiation of RRT (linked to the wording of the SmPC for finerenone which states that treatment should be stopped in patients that have progressed to end-stage renal disease). However, the ERG was unclear whether or not this treatment stopping rule was mandated in the FIDELIO-DKD study. In terms of discontinuation in the FIDELIO-DKD study, the CS states: *"Patients were monitored and followed for efficacy and safety events until the study end, even if study drug treatment had been discontinued. Patients who experienced a health event considered for the pre-specified primary or secondary endpoints, were encouraged to continue study drug until the trial was completed provided there were no safety grounds for discontinuing treatment" … "Permanent discontinuation of study drug was recommended if a recurrent hyperkalaemia event was experienced soon after a previous hyperkalaemia event with interruption of study drug if there was no explanation for the recurring event other than intake of study drug."* (CS Section B.2.3).

Summary: In the absence of information to determine whether or not patients in FIDELIO-DKD discontinued treatment upon initiation of RRT, the ERG prefers its approach to adjusting treatment discontinuation in which treatment with finerenone is theoretically permitted after patients initiate RRT. However, if finerenone was discontinued upon initiation of RRT in the

FIDELIO-DKD study, the ERG would prefer the company's additional edit to discontinuation in the model.

#2: Set risk of CV events to be independent of CKD stage // Calculating the average risk of CV events for all CKD stages and applying it in all model health states (revision of #2 ERG assumption)

Both the ERG and the company's revised base case analyses include the risk of CV events which are independent of CKD stage. This change was originally made by the ERG in light of the fact that there was a risk of double-counting the "cardio-protective" effect of finerenone, given that the finerenone arm were also subjected to a hazard ratio which reduced the risk of CV events for each CKD stage (yet finerenone also delays progression through CKD stages).

The company's revised base case analysis includes this edit, but instead of using the value for the CKD3 health state, the company prefers to instead make use of data from all states to determine the average risk of a CV event in the model. The ERG notes that owing to limited data available in the company's model and submission, it was unable to perform this calculation itself, and so the value for CKD3 was used as a proxy for the state wherein the majority of data were expected to lie. However, the ERG agrees that the company's revised approach is likely preferred over the arbitrary selection of the CKD3 value per the original company model. However, one caveat to this is that the ERG is currently unable to sense check the value produced, but the ERG accepts the company's approach in principle.

Summary: In principle, the ERG accepts the company's revised approach to implement CV risk within the model as an improvement upon the ERG's original approach, but ideally the ERG would have been able to "sense check" the resultant value applied within the model for completeness.

#3: Amend application of renal deaths // Remove renal deaths from the model and add them back to general mortality (revision of #3 ERG assumption)

Based on the ERG's understanding of the company's TE response, the company does not appear to have made any edits to the ERG's suggested approach to adjusting mortality within the model (except related to CV deaths, which are described separately in the text below). Therefore, the ERG does not comment on this further, but would appreciate clarity from the company that this interpretation is correct (i.e., that the company has not made any alternative edits to the ERG's suggested approach to remove renal deaths from the model).

Summary: No change has been made to the ERG's approach to adjusting mortality to remove the impact of renal deaths, as it is the ERG's understanding that the company has accepted the ERG's approach without further revision.

#4: Set risk of CV death to be independent of CKD stage // Calculating the average risk of CV death for all CKD stages and applying it in all model health states (revision of #4 ERG assumption)

The issue related to the implementation of CV death is very similar to that of how CV events are captured in the model. As per the ERG's view related to CV events, the ERG accepts the company's revised approach *in principle*, pending a sense check of the resultant value applied within the model.

Summary: In principle, the ERG accepts the company's revised approach to implement CV death within the model as an improvement upon the ERG's original approach, but ideally the ERG would have been able to "sense check" the resultant value applied within the model for completeness.

#5: Assume 45.9% of patients enter post-CV event sub-model // Corrected implementation of 45.9% of patients with history of CV events (revision of #5 ERG assumption)

Both the company and the ERG agree that 45.9% of patients in FIDELIO-DKD enter the model with CV event history. However, as highlighted by the company, there is a distinction to be made with respect to the model for how CV event history is modelled. The company explains that as the model is structured around CV event history *after entering the study*, patients should not enter the 'post CV event' sub-model at baseline, as *"all the benefits of finerenone in terms of reducing the risk of CV events are modelled from this perspective"* (company's TE response, Key Issue 5).

Conversely, in the ERG's preferred base case analysis patients were permitted to enter the 'post CV event' sub-model at baseline. This was justified in the ERG's report on the following basis: *"Given that some elements of the model related to prior CV event history 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."* (ERG report Section 6.2.3). Here, the ERG refers to the fact that after a CV event has occurred, patients are modelled to experience an increased risk of death due to CV event history obtained from external data.

The ERG considers both the company's and the ERG's approaches to be imperfect, as the two different definitions of CV event history (one defined based on patient history, and the other since entering the FIDELIO-DKD study) mean that at some aspects of the model are applied inappropriately. The ERG holds the view that mortality is of paramount importance to be modelled appropriately and given that other-cause mortality is informed by external data it takes the view that a proportion of patients should enter in the 'post CV event' sub-model.

Summary: The ERG maintains its preference for 45.9% of patients to enter post-CV event sub-model at baseline, which is driven primarily because of implications related to other-cause mortality within the model.

#6: Remove all death costs // Remove all death costs (revision of #6 ERG assumption)

Based on the ERG's understanding of the company's TE response, the company does not appear to have made any edits to the ERG's suggested approach to capturing death costs within the model. Therefore, similar to the adjustment of mortality, the ERG does not comment on this further but would appreciate clarity from the company that this interpretation is correct (i.e., that the company has not made any alternative edits to the ERG's suggested approach to capturing death costs).

Summary: No change has been made to the ERG's approach to capturing death costs, as it is the ERG's understanding that the company has accepted the ERG's approach without further revision.

#7: Edit BT cost to ERG's calculations // Edit BT cost to ERG's calculations (revision of #7 ERG assumption)

Based on the ERG's understanding of the company's TE response, the company does not appear to have made any edits to the ERG's suggested approach to capturing BT costs within the model. Therefore, similar to both the adjustment of mortality and capturing death costs, the ERG does not comment on this further but would appreciate clarity from the company that this interpretation is correct (i.e., that the company has not made any alternative edits to the ERG's suggested approach to capturing BT costs).

Summary: No change has been made to the ERG's approach to capturing BT costs, as it is the ERG's understanding that the company has accepted the ERG's approach without further revision.

#8: Include one additional pack of finerenone to reflect wastage // Include additional half of the pack of finerenone to reflect wastage (revision of #8 ERG assumption)

The ERG included a cost of a full pack of finerenone as wastage as a plausible "upper bound", noting that the company's original base case wherein no wastage was modelled represented a plausible "lower bound".

The ERG accepts that its analysis is likely biased against finerenone, but this was acknowledged within the ERG's report; namely: *"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."* … *"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"* (ERG report, Section 6.2.6).

The ERG considers the company's suggestion of applying a half-pack cost to capture wastage as a reasonable alternative application of drug wastage in the model, though the ERG highlights that the 'true' wastage could be less than, or greater than, this cost (in line with the content of the ERG's report).

Summary: The ERG accepts this revision to capturing drug wastage within its revised base case analysis.

#9: Assume utility for CKD1/2 is 0.80 and #10. Assume post-acute disutility is half of acute disutility // Assume utilities from the literature (revision of #9 and #10 ERG assumptions)

The ERG notes that the company has revised its preferred specification of utility values to be those reported in a previous NICE appraisal (TA358: Tolvaptan for treating autosomal dominant polycystic kidney disease),[1] published in October 2015. However, the most relevant values reported in this submission (for the CKD-based health states) were attributed to a study by Gorodetskaya *et al.*, (2005).[2] This study considers a sample of n=205 people with CKD, of whom an estimated 46% also had T2D (estimated based on Table 1 of this study).[2] Recruitment for this study began in May 2002, and the last follow-up visit was conducted in June 2004.[2] Patients completed several questionnaires including SF-12 and HUI-3, but not the EQ-5D.[2]

Within the timeframe available to prepare the ERG's response, the ERG could not verify the methodological approach used to derive the disutilities from this study based on information provided in this submission, the original TA358 committee papers that are available online, and this published study. However, providing the methodological approach taken was suitable, the ERG maintains its preference for the modifications made to the company's values derived from FIDELIO-DKD given that they are (i) EQ-5D values, (ii) in the correct population (per the FIDELIO-DKD study), (iii) collected recently (versus the published study which provides utility values collected nearly 20 years ago).

Furthermore, the company makes repeated reference to the fact that the FIDELIO-DKD study was not designed, nor powered to make conclusions based on health-related quality of life (HRQoL). The ERG acknowledges this concern, but highlights that trials used to inform HTA submissions would not be expected to be designed specifically with HRQoL outcomes in mind. Therefore, the ERG rejects the implication that utility values from the FIDELIO-DKD study, or indeed any other study used to inform an HTA submission, would be inappropriate for informing the model.

Summary: The ERG maintains its preference for its modified trial-based utility values, given that the alternative source of utility data provided by the company is subject to a number of important limitations.

Conclusion

To summarise, the ERG agrees with the following edits made by the company (some of which are in principle, pending confirmation once the ERG can verify these edits in the company's model):

- Change to CV event risk
- Change to CV death
- Change to wastage

The ERG is still unclear with respect to whether or not patients in FIDELIO-DKD discontinued treatment upon initiation of RRT. If this is true, then the ERG would accept the company's edit to treatment discontinuation in favour of the ERG's original edit. However, if this is not the case, the ERG maintains that both the company's revised approach and the ERG's original edit may be suitable scenarios for decision making.

The ERG disagrees with the company's revisions to edits concerned with:

- Change to patients entering with CV event history
- Change to source of utility values

Due to the information currently available to the ERG, the only edit possible for it to make within the model is to adjust for wastage. Changing from assuming a full pack of wastage to half a pack of wastage causes the ERG's preferred ICER to decrease from £23,706 to [redacted]. The ERG would be willing to implement the changes for CV event risk and CV death pending receipt of the necessary values from the company.

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

In response to this key issue (related to how uncertainty is reflected within the company's sensitivity analyses), the company has provided commentary and made some amendments to the programming of sensitivity analyses within its model. Relevant aspects are discussed in turn below.

Grouping of parameters in the DSA

The ERG is still unclear what can realistically be inferred from the DSA for grouped parameters – for example, grouped characteristics by CKD stage were included in the company's analysis where the "lower bound" was set as 100% CKD3, and the "upper bound" was set as 100% CKD4. It is the ERG's view that these are not suitable bounds of uncertainty. For utility values, the ERG does not consider it appropriate to draw inferences from "lower bound" and "upper bound" values which are clearly clinically implausible (e.g., health state utility value lower bounds were in the region of [redacted] to [redacted]). Furthermore, the ERG highlighted that the combination of lower bound values does not appear to consider the plausible "lower bound(s)" of differences *between* values, which is arguably why varying these values should not be considered within this type of DSA. Overall, this issue remains unresolved.

Inclusion of utility values within sensitivity analysis

In choosing to use the published values from the literature (see company's response to Key Issue 5), the company's revised base case sensitivity analyses include independent sampling of utility values by health state with some parameters requiring assumed uncertainty (SE assumed to be 10% of the mean value). This is a clear limitation of using published utility values to inform

the model, and further renders aspects of the company's sensitivity analyses subject to important limitations (most notably, the PSA). Therefore, this resolves one issue (of spurious imprecision reflected in the PSA for utility values) but replaces it with a different issue (of sampling correlated parameters independently).

Plausibility of width of confidence intervals

The ERG highlighted within its report that some confidence intervals appeared to be unrealistically wide, which could lead to misinterpretations concerning the 'true' parameter uncertainty in model results. The company's TE response states: *"Nevertheless, it should be noted that the sensitivity analyses results presented in the original submission considered higher uncertainty. If the bounds are more precisely calculated the sensitivity analyses results would have been closer to the base case value. Therefore, the results in the original submission can be considered conservative regarding the estimated probability of finerenone being cost-effective in comparison to BT."* (company TE response to Key Issue 6).

The ERG disagrees with the assertion that because uncertainty has been over-estimated, this means that the estimated probability of finerenone being cost-effective has been conservatively estimated. It is the ERG's view that inappropriate programming of sensitivity analyses leads to results that are potentially misleading and/or unsuitable to understand the uncertainty in results. For example, by running PSA with extreme values, this could lead to simulations where finerenone is modelled to be cost saving or associated with a QALY loss (both of which are seen in the PSA scatterplot). The ERG argues that were more suitable parameter bounds available, the chance of seeing such extreme results would be reduced, and ultimately the DSA/PSA results would be a more suitable basis to understand uncertainty in the company's model.

Use of Gamma distribution for costs

The ERG acknowledges the company has amended its PSA to use the Normal distribution.

Duration of sustained decrease in eGFR >=40%

The ERG notes that the company has now omitted this parameter from both the DSA and PSA owing to a lack of information to inform a suitable range of uncertainty, and its limited impact on model results if it was excluded entirely. The ERG accepts this has a limited impact on results, but ideally this would be populated using empirically derived confidence interval limits and the

ERG is unclear precisely why this was not possible. In spite of this, the ERG considers this parameter being omitted from the DSA and PSA to be acceptable.

Lack of parameter uncertainty captured within model transitions

The company does not comment on this important limitation of the PSA (and also the DSA) – that individual transition probabilities are assumed fixed and are therefore not varied in any sensitivity analysis. This issue was explicitly highlighted in the ERG's report: *"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"* (ERG report Section 5.1.3). This issue remains unresolved.

Conclusion

The ERG's view that findings from the DSA are not relevant for decision making remains unchanged. This is because of the implausible limits set for key parameters, meaning the resultant ICERs are unrealistic. The ERG's view of the PSA being unsuitable is also unchanged, given that transition probabilities are still not varied within this analysis.

4. REFERENCES

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2. Gorodetskaya I, Zenios S, McCulloch CE, Bostrom A, Hsu CY, Bindman AB, et al. Health-related quality of life and estimates of utility in chronic kidney disease. Kidney International. 2005;68(6):2801-8.

Finerenone for treating chronic kidney disease in people with type 2 diabetes [ID3773]: Addendum #1

A Single Technology Appraisal

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1. INTRODUCTION

Following technical engagement (TE), the company has provided a copy of its updated economic model. The ERG has therefore revisited the changes made by the company in its revised base-case analysis with a view to edit the ERG's tentative preferred base-case analysis such that it is aligned with edits made by the company that the ERG agrees with, limiting outstanding issues to areas of disagreement between the company and the ERG. A summary of the key issues highlighted discussed in the company's TE response is provided in Table 1.

Table 1: Comparison of assumptions (by issue) ERG vs Company

Company revision of the ERG preferred model assumptions	ERG report base-case approach	Company's revision post TE	ERG view in light of company's TE response	Resolved post TE
Setting finerenone to be stopped after RRT and calibrating discontinuation (revision of #1 ERG assumption)	4-year discontinuation lowered to [redacted] (previously [redacted])	4-year discontinuation lowered to [redacted], but switch to stop finerenone upon initiation of RRT now enabled	Per TE response, depends on whether stopping upon initiation of RRT was allowed in FIDELIO-DKD	×
Calculating the average risk of CV events for all CKD stages and applying it in all model health states (revision of #2 ERG assumption)	Used value of [redacted]	Used value of [redacted]	Company's change accepted by ERG	✓
Remove renal deaths from the model and add them back to general mortality (revision of #3 ERG assumption)	Removed renal deaths from model	Removed renal deaths from model	Same application – Company's change accepted	✓
Calculating the average risk of CV death for all CKD stages and applying it in all model health states (revision of #4 ERG assumption)	Used value of [redacted]	Used value of [redacted]	Company's change accepted by ERG	✓
Corrected implementation of 45.9% of patients with history of CV events (revision of #5 ERG assumption)	45.9% of patients enter the 'post CV event' sub-model at baseline	Changed post-acute costs such that these are reduced by a factor equivalent to the proportion of patients without CV event history	ERG preference maintained. It is the ERG's view that the company's approach does not adequately address the ERG's concerns with respect to CV event history	×
Remove all death costs (revision of #6 ERG assumption)	Set all death costs to £0	Set all death costs to £0	Same application – Company's change accepted	✓
Edit BT cost to ERG's calculations (revision of #7 ERG assumption)	Cost per day calculated to be £2.33	Cost per day calculated to be £2.34	Difference in cost per day is caused by rounding error. The ERG maintains its preferred cost in its base-case analysis, but difference of £0.01 unlikely to have a material impact on the ICER	✓

Company revision of the ERG preferred model assumptions	ERG report base-case approach	Company's revision post TE	ERG view in light of company's TE response	Resolved post TE
Include additional half of the pack of finerenone to reflect wastage (revision of #8 ERG assumption)	1 full pack of wastage	½ pack of wastage	Company's change accepted by ERG	✓
Assume utilities from the literature (revision of #9 and #10 ERG assumptions)	Used company's original values, except assumed a value of 0.80 for CKD ½. ERG also doubled acute disutilities, and halved post-acute disutilities for face validity	Changed all utilities (including disutilities) to be based on the literature	ERG does not accept this change. The ERG considers there to be a number of issues associated with the published values, and so the ERG's previous preferred set of utility values are preferred	×

Key: No difference between preference of company and ERG; ERG accepts the implementation preferred by the company; ERG unclear if this is preferred or not (pending committee discussion); ERG does not accept company's preferred application

The ERG sense-checked the company's revised inputs in its updated model (with parameter changes mostly related to Key Issue 5). The ERG accepts the company's changes to the constant risk of CV events and CV deaths, and so these edits are incorporated into the ERRG's tentatively preferred base-case analysis. However, the ERG highlights that this base-case analysis should be viewed while also considering the other outstanding issues highlighted within the ERG's report, including issues with the model structure and a lack of a comparison to SGLT-2 inhibitors.

To summarise the changes made to the ERG's base-case analysis since the ERG's report was prepared, please consider the information below:

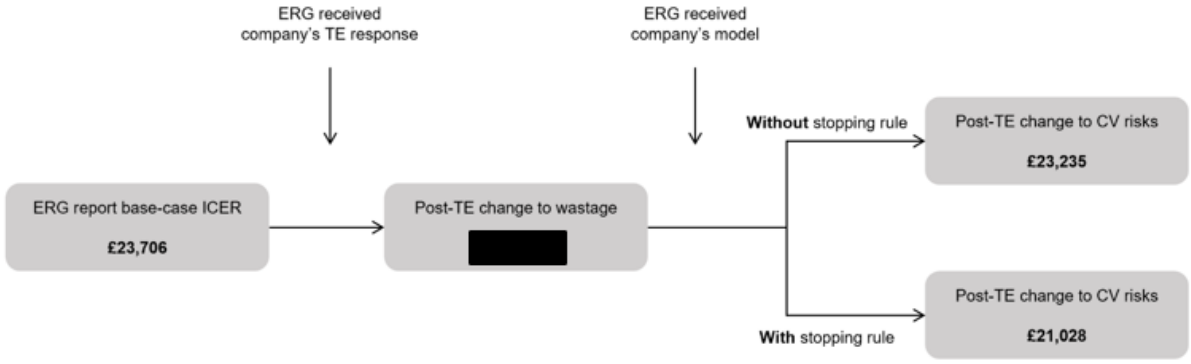
- ERG received company's updated base-case in response to TE, but did not initially receive a copy of the model to incorporate updated parameters in the ERG's preferred base-case analysis
  - These affected the risk of CV events, the risk of CV deaths, and (in a scenario) a re-calibration of discontinuation to account for discontinuation upon initiation of RRT
- Before these changes were made, the ERG's tentative preferred base-case analysis was [redacted]

  [redacted]
- Based on the company's response at TE, the ERG's revised post-TE tentative base-case analysis now includes the following changes:
  - Updated constant risk of CV events by CKD stage (previously [redacted], now [redacted])
  - Updated constant risk of CV death by CKD stage (previously [redacted], now [redacted])
  - A scenario including re-calibrated discontinuation over 4 years to account for RRT initiation (previously [redacted] without RRT initiation as a stopping rule, now [redacted] plus enabling the "Finerenone is stopped after initiation of RRT" setting in the model)
- The combined impact of these edits causes the ERG's tentative preferred base-case ICER to be:

- £23,283, if the stopping rule is disabled
- £21,047, if the stopping rule is enabled

Figure 1 shows the changes to the ERG's preferred base-case ICER:

Figure 1: Changes to ERG's base case ICER



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

A summary of ERG's preferred assumptions and resulting ICER is provided in Table 2.

Table 2: Summary of ERG's preferred assumptions and ICER: post TE

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)

Scenario #*	Preferred assumption	Incremental cost	Incremental QALYs	ICER (change from ERG-corrected company base case)
#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 report base case**	[redacted]	**0.08**	**£23,706 (+£5,824)**
TE edit 1	Include half an additional pack of finerenone to reflect wastage	[redacted]	0.08	£23,376 (+£5,494)
NA	**ERG critique of company's TE response**	[redacted]	**0.08**	**£23,376 (+£5,494)**
TE edit 2	Use company's value for average risk of CV events for all CKD stages	[redacted]	0.08	£23,283 (+£5,731)
TE edit 3	Use company's value for average risk of CV death for all CKD stages	[redacted]	0.08	£23,235 (+£5,683)
TE edit 4	Stop finerenone upon initiation of RRT and re-calibrate discontinuation	[redacted]	0.09	£21,028 (+£3,476)
NA	**ERG post-TE base-case without stopping rule**	[redacted]	**0.08**	**£23,235 (+£5,683)**
NA	**ERG post-TE base-case with stopping rule**	[redacted]	**0.09**	**£21,028 (+£3,476)**

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

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.