NICE National Institute for Health and Care Excellence

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

Lead team presentation

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Company: Bayer
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Key clinical issues

Data is from key clinical trial FIDELIO-DKD. Other relevant clinical evidence include FIGARO-DKD and FIDELITY studies not included in clinical evidence

- *Has all the relevant clinical data been presented?*

SGLT-2is are included in the scope and are recommended in NICE guidance (NG28 and TA775). But, company exclude SGLT2s (not considered to be established NHS practice)

- *Are SGLT-2is a relevant comparator?*

Licence is stage 3 to 4 CKD (defined as eGFR ***≥25*** to <60 **and** albuminuria).

- *Do these eGFR ranges align with those used in NHS practice?*

Hyperkalaemia is main adverse event observed with finerenone vs placebo (18.3% vs 9.0%)

- *Is hyperkalaemia a significant adverse event to consider?*

The primary outcome is a composite of 3 outcomes but only one component of this overarching outcome is statistically significant (≥40% decrease eGFR over at least 4 weeks)

- *Does the composite outcome (and its underpinning components) reflect an important outcome in NHS practice?*
- *Does the lack of statistical significance in some components of the composite outcome affect confidence in the primary outcome?*

Disease background

Chronic Kidney Disease (CKD): long-term condition affecting kidneys

Often caused by other conditions affecting kidneys:

- Diabetes, high blood pressure, high cholesterol, kidney infections
- With **diabetes**, excess glucose damages the small filters in the kidneys
- Severely reduced kidney function may need dialysis or transplant

CKD and type 2 diabetes:

- ≈20% of the ≈3 million people with type 2 diabetes will need kidney disease treatment
- >10,000 people in UK have end-stage kidney failure from diabetes
- >1 in 3 people who need kidney dialysis or transplant have diabetes

CKD severity:

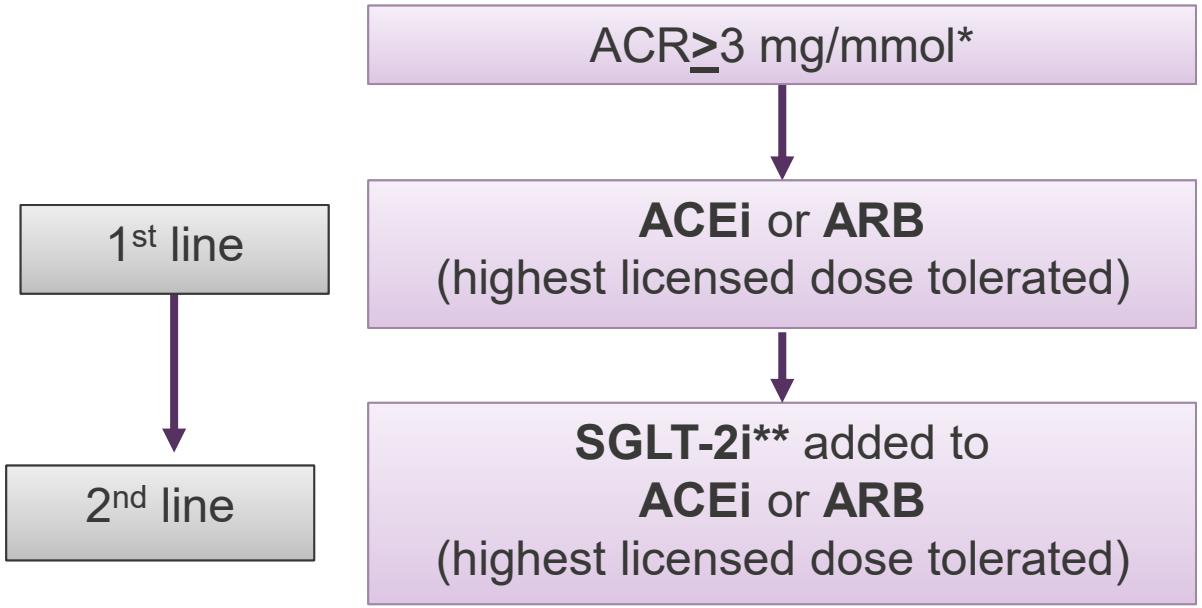
- 6 categories of **estimated glomerular filtration rate (eGFR)**: normal → mild reduction → mild to moderate → moderate to severe → severe → kidney failure
- 3 categories of albumin to creatinine ratio (ACR): normal to mild increase → moderate increase → severe increase
  - ACR>3 mg/mmol indicate albuminuria (increased urine protein from kidney damage)

Symptoms:

- Do not usually have early stage symptoms
- Include: weight loss, poor appetite, swollen ankles/feet/hands, shortness of breath, tiredness, feeling sick, itchy skin

Treatment pathway – CKD & type 2 diabetes

Finerenone as an add-on to existing treatment pathway and at max dose ACEi/ARBs



Finerenone?
(Stage 3 or 4 CKD with albuminuria)

*If ACR<3 mg/mmol monitor ACR, creatinine and blood pressure annually

- **NG28 recommends SGLT2i *offered* if ACR >30 mg/mmol & *considered* if 3-30 mg/mmol, & meets licence criteria inc. eGFR thresholds
- **TA775 recommends dapagliflozin (an SGLT-2i) as add-on to optimised care if eGFR 25 to 75 ml/min/1.73 m^2 at start of treatment **and** type 2 diabetes, **or** ACR ≥22.6 mg/mmol

- *Does this reflect the expected positioning of finerenone in NHS clinical practice?*
- *Will dapagliflozin use increase because of TA guidance?*
- *Would finerenone be used instead of, or in combination with, an SGLT2i? Or both?*
- *Would finerenone & comparators be given in primary or secondary care, or both?*

Abbreviations: ACEi: angiotensin-converting enzyme inhibitor; ACR: Urine albumin to creatinine ratio; ARB: angiotensin-receptor blocker; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; SGLT-2i: sodium-glucose-co-transporter-2 inhibitor

Patient organisation perspective

Kidney care UK:

Diagnosis:

- Type 2 diabetes leading cause of CKD worldwide – cases growing
- Progressed CKD needs specialist input → 'life changing treatment' – strict regimes; dietary restrictions

Treatment options limited for CKD with type 2 diabetes – can include dialysis/transplant

- New treatment option of significant interest to patients, give hope – especially where SGLT-2i not suitable

"Debilitating fatigue, significant pain, itching, swelling, restless leg syndrome, muscle cramps, sleep problems"

- Staying in work, maintaining relationships and quality of life can be *"severely compromised"*
- Physical and mental health effects: Up to 1 in 3 patients experience depression

"Symptoms of depression in people with early stage kidney disease increases risk of progressing to end-stage renal disease (need dialysis or transplant) and death. In transplant patients, depressive symptoms shown to increase the risk of death by 65%"

- Physical and emotional challenges for **carers** – including at-home dialysis

Considerations:

- **Hyperkalaemia** potential concern (adverse effect with finerenone)
- **Equality:** Some ethnic groups can be more sensitive to effects of proteinuria and hypertension
- **Younger people with diabetes** (<55 years)**:** 2X risk rapid progression compared with >65
  - So need closer monitoring, management of risk factors, early specialist review

Abbreviations: CKD: chronic kidney disease

Clinical expert perspective

Primary Care Diabetes Society and Association of British Clinical Diabetologists and UK Kidney Association Joint Committee

Aim to reduce co-morbidity frequencies; also eGFR decline rate – clinically significant → progressive decline ≥3.3% per year

Unmet need: CKD and type 2 diabetes have 'very high risk of morbidity and premature mortality'

- Increased CKD progression with diabetes (even with current treatment) – dialysis increasing
- DKD affects 40% people with type 2 diabetes and **most common cause of end-stage kidney disease** (30% people starting dialysis in UK who are high risk of CVD)
- People with type 2 diabetes and CKD have **significant additional risk of morbidity and pre-mature mortality** (higher CVD risk)

Current treatment: Focus on lifestyle changes (reducing weight, control blood pressure, glucose, increase exercise, smoking cessation), RAS inhibitors, SGLT-2i expected to increase

- Finerenone expected use in primary care (but initially secondary care and specialist clinics)
- Treatment pathway well defined but some variations across country

Innovative and substantial health benefits with finerenone

- Human, societal and economic impact of DKD in the UK
- Benefit for patients who cannot tolerate SGLT-2i

To consider:

- Monitoring serum potassium levels could increase primary care workload (also staff training)
- Some ethnicities have increase rates of kidney failure

Abbreviations: CKD: chronic kidney disease; CV: cardiovascular; CVD: cardiovascular disease; DKD: diabetic kidney disease; eGFR: estimated glomerular filtration rate; MI: myocardial infarction; RAS: renin-angiotensin-system

Finerenone (Kerendia, Bayer)

Marketing authorisation	Indicated for the treatment of chronic kidney disease (stage 3 and 4 **with** albuminuria) associated with type 2 diabetes in adults
Mechanism of action	• Non-steroidal, mineralocorticoid receptor (MR) antagonist, inhibiting steroidal hormones (aldosterone, cortisol) binding to MR in the heart, kidneys and blood vessels. • Over-activation of MR contributes to organ damage in chronic kidney disease, heart failure and hypertension because of pro-inflammatory and pro-fibrotic effects, sodium retention and endothelial dysfunction
Administration	• Oral tablet • Starting dose: 10 mg, once daily • (Maximum) recommended dose: 20 mg, once daily • Initiation and continuation dependent on serum potassium and eGFR
List price	£55.20 (30 tablets); £1.84 per tablet (indicative NHS list price) → for 10mg and 20mg tablet

Decision problem

Population narrower than scope; SGLT-2i not included as comparator

	Final NICE scope	Company	ERG comment
Population	Adults with type 2 diabetes and CKD	CKD (stage 3 and 4 with albuminuria*) associated with type 2 diabetes in adults *eGFR ≥25 to <60 mL/min/1.73 m^2	Population narrower than scope but in line with marketing authorisation
Intervention	Finerenone		In line with scope
Comparators	Established clinical management without finerenone, alone or in combination with ACEi, ARB or direct renin inhibitors; SGLT-2is	Standard of care established in clinical practice (ACEi/ARB) • Finerenone is an add-on therapy to ACEi/ARB • SGLT-2i not included	Comparators not aligned with scope; no finerenone vs SGLT-2i comparison
Outcomes	CV events *(non-fatal MI and stroke, heart failure hospitalisation);* subsequent CV events; CKD progression; mortality; sustained decrease of eGFR ≥40% from baseline; new onset of atrial fibrillation/atrial flutter; health-related quality of life; adverse events – hyperkalaemia		In line with scope

◉ *Spironolactone is an MR antagonist and is used for hypertension – is this a relevant comparator?*

Abbreviations: ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin-receptor blocker; CKD: chronic kidney disease; CV: cardiovascular; eGFR: estimated glomerular filtration rate; MI: myocardial infarction; SGLT-2i: sodium-glucose-co-transporter-2 inhibitor

Clinical effectiveness evidence

Overview of key clinical evidence

Company used **FIDELIO-DKD** trial to inform clinical effectiveness and in model:

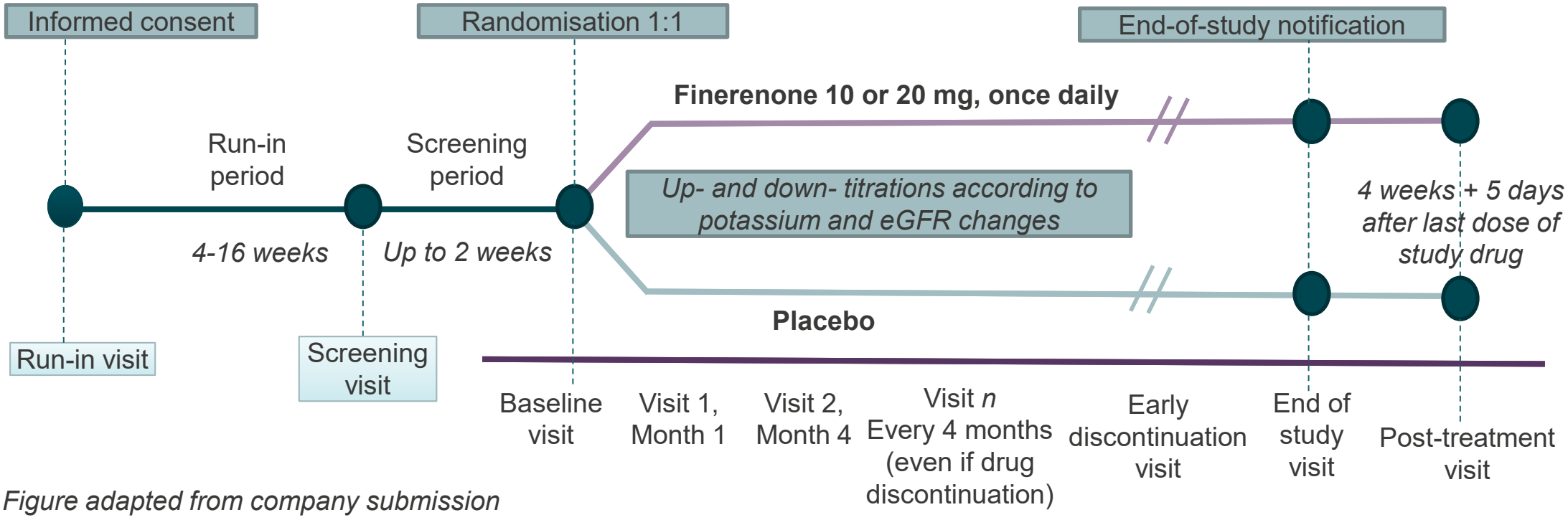


Figure adapted from company submission

Other relevant studies <u>not included in clinical evidence</u> but referred to in slides:

- **FIGARO-DKD:** Phase 3, randomised, double-blind clinical trial *to assess finerenone efficacy and safety on cardiovascular outcomes* – company excluded at literature search as full data not available (but available now)
- **FIDELITY:** Meta-analysis of individual patient data from FIDELIO- and FIGARO-DKD: *To evaluate relationship between kidney disease stage and finerenone efficacy on composite CV and renal endpoints*
- **CREDENCE trial**: *To assess canagliflozin effects (SGLT-2i) on renal outcomes in patients with type 2 diabetes and CKD with albuminuria*
- **Network meta-analysis:** SGLT-2i vs. finerenone for cardiorenal outcomes (Zhao et. al) for peer-review

◉ *Has all the relevant data been presented by the company?*

Abbreviations: eGFR: estimated glomerular filtration rate; SGLT-2i: sodium-glucose-co-transporter-2 inhibitor

Key clinical trial: FIDELIO-DKD

FIDELIO-DKD used to inform clinical evidence base and model

Study design	Phase 3, randomised, double-blind, placebo-controlled, parallel-group, multicentre, event-driven
Population	Adults with type 2 diabetes and clinical diagnosis of CKD
Intervention	Finerenone with standard care (maximum tolerated dose of ACEi/ARB) • 10 mg or 20 mg (the target), once daily – label population start on 10 mg
Comparator	Placebo in addition to standard care (see next slides)
Primary outcome	**Time to 1st event of composite endpoint:** kidney failure onset, sustained eGFR decrease ≥40% from baseline over at least 4 weeks, or renal death
Secondary outcomes	• **Time to first event of CV mortality and morbidity** (composite of: time to 1st event of CV death, non-fatal myocardial infarction, non-fatal stroke, or hospitalisation for heart failure (**key secondary endpoint**) • Time to all-cause mortality/hospitalisation • UACR change from baseline to 4 months • Secondary renal composite endpoint: Time to 1st event of kidney failure/sustained ↓eGFR ≥57% from baseline over min 4 weeks/renal death
Other outcomes	Components of primary and secondary outcomes, new diagnosis of atrial fibrillation or flutter, HRQoL (KDQOL-36, EQ5D-5L), adverse events
Follow up	Average 32 months from randomisation to primary outcome or censoring

Abbreviations: ACE: angiotensin-converting enzyme; ARB: angiotensin-receptor blocker; CKD: chronic kidney disease; CV: cardiovascular; eGFR: estimated glomerular filtration rate; EQ5D: EuroQol 5 Dimensions; HRQoL: health-related quality of life; KDQOL-36: Kidney Disease Quality of Life; UACR: urine albumin to creatinine ratio

Comparison of phase 3 trials in disease area

*2 Phase 3 clinical trials available **but only data from FIDELIO-DKD used by company***

Phase 3 clinical trials		FIDELIO-DKD (used for clinical effectiveness and in model)	FIGARO-DKD (excluded at literature search)
Primary endpoint		**Renal** (composite)	**Cardiovascular** (composite)
Secondary (key)		FIGARO primary endpoint	FIDELIO primary endpoint
Key inclusion criteria		Type 2 diabetes and chronic kidney disease; pre-treated with ACEi/ARB at max tolerated dose; serum potassium ≤4.8 mmol/l	
		ACR 30 to <300, eGFR ≥25 to **<60, and** diabetic retinopathy history • **Or** ACR ≥300 to ≤5000; eGFR ≥25 to **<75**	ACR 30 to <300 and eGFR 25 to **≤90** • **Or** ACR ≥300 to ≤5000, and eGFR **≥60**
ACR (mg/g), %	<30	0.4	2.7
	30-<300	12.1	46
	300-5000	87.4	51.2
eGFR (ml/min/1.73 m²), %	≥60	11.6	61.7
	45 to <60	33.5	20.9
	25 to <45	52.5	17
	<25	2.4	0.4

- More earlier stage CKD in FIGARO-DKD

Abbreviations: ACEi: angiotensin-converting enzyme inhibitor; ACR: urine albumin to creatinine ratio; ARB: angiotensin-receptor blocker; eGFR: estimated glomerular filtration rate; SGLT-2i: sodium-glucose-co-transporter-2 inhibitor

FIDELIO-DKD baseline characteristics (1)

Baseline characteristics		Finerenone (n=[redacted])	Placebo (n=[redacted])
Median age (years)		[redacted]	[redacted]
Male (%)		[redacted]	[redacted]
Ethnicity (%)	White	[redacted]	[redacted]
	Asian	[redacted]	[redacted]
	Black or African American	[redacted]	[redacted]
	Other	[redacted]	[redacted]
Location (%)	Europe	[redacted]	[redacted]
	North America	[redacted]	[redacted]
	Latin America	[redacted]	[redacted]
	Asia	[redacted]	[redacted]
	Other	[redacted]	[redacted]
Diabetes duration (years)		[redacted]	[redacted]
Systolic blood pressure (mmHg)		[redacted]	[redacted]
Glycated haemoglobin (%)		[redacted]	[redacted]
Serum potassium (mmol/litre)		[redacted]	[redacted]

FIDELIO-DKD baseline characteristics (2)

Baseline characteristics		Finerenone (n=[redacted])	Placebo (n=[redacted])
Mean eGFR		[redacted]	[redacted]
45 to <60 ml/min/1.73m^2 (%)		[redacted]	[redacted]
25 to <45 ml/min/1.73m^2 (%)		[redacted]	[redacted]
Median Urine Albumin-to-Creatinine ratio (IQR)		[redacted]	[redacted]
30 to <300 mg/g (%)		[redacted]	[redacted]
≥300 mg/g (%)		[redacted]	[redacted]
Medications (%)	ACE inhibitor	[redacted]	[redacted]
	ARB	[redacted]	[redacted]
	Diuretic	[redacted]	[redacted]
	Statin	[redacted]	[redacted]
	*Potassium-lowering	[redacted]	[redacted]
	Glucose-lowering	[redacted]	[redacted]
	• Insulin	[redacted]	[redacted]
	• GLP-1 receptor agonist	[redacted]	[redacted]
	• SGLT-2i	[redacted]	[redacted]

*include sodium/calcium polystyrene sulfonate; potassium-binding agents

◉ *Is the medication profile consistent with the NHS? Are the baseline SGLT-2i representative?*

Abbreviations: ACE: angiotensin-converting enzyme; ARB: angiotensin-receptor blocker; eGFR: estimated glomerular filtration rate; GLP-1: glucagon-like peptide 1; IQR: inter-quartile range; SGLT-2i: sodium-glucose-co-transporter-2 inhibitor

Uncertainty in appropriate population – background

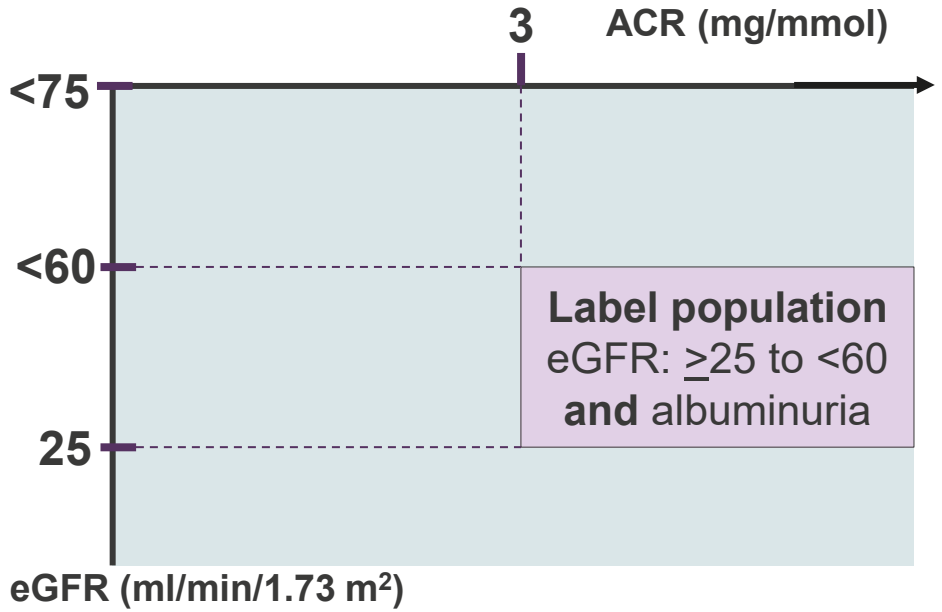
Label population best represents licence so used as basis of results where possible

- **Full analysis set:** eGFR ≤25 to ≥60 ml/min/1.73 m^2
- **Label population:** eGFR ≥25 to <60 **and** albuminuria (>3 mg/mmol); patients with eGFR 60 to 75 **and** very high albuminuria removed (approx. 11%)
- Label in line with licence but **differs from NHS stage 3 and 4 eGFR** in CKD (15≥ to <60)

eGFR reduction (ml/min/1.73 m^2)	**ACR increase** (mg/mmol)		
	A1 Normal to mild	**A2** Moderate	**A3** Severe
	< 3	3 to 30	>30
G1 Normal and high, ≥90	No CKD if no other kidney damage markers		
G2 Mild, 60-89			
G3a Moderate, 45-59			
G3b Moderate to severe, 30-44			
G4 Severe, 15-29			
G5 Kidney failure, <15			

Risk of adverse outcomes in adults by eGFR and ACR:

Low risk
Moderate risk
High risk
Very high risk



Abbreviations: ACR: urine albumin to creatinine ratio; eGFR: estimated glomerular filtration rate

Uncertainty in appropriate population

Population is narrower than NICE scope but in line with licence

Company: Do not consider uncertainty in the population using narrower label population

- FIDELIO-DKD lower limit of eGFR 25 at screening, but → 2.4% had lower eGFR at baseline following deterioration (excluded from label population but included in full analysis set)
- No evidence for interaction by baseline eGFR, but company conducted exploratory analysis using eGFR <25 which had limited (£200 reduction) impact on ICER

ERG: Consider uncertainty addressed appropriately with suggested analyses using broader population (>15 to <60 ml/min/1.73 m^2)

- Population for decision-making: **Adults with CKD (stage 3 and 4 with albuminuria) and type 2 diabetes** (narrower than scope) → Stage 3 and 4: eGFR ≥25 and <60 ml/min/1.73 m^2

Licence: Not recommended for eGFR <25

- For eGFR ≥15, can continue with dose adjustment based on serum potassium.
- eGFR measured 4 weeks after initiation
- But if progressed to end-stage renal failure (eGFR <15) then discontinue

Clinical expert and stakeholder comment: Finerenone may be effective in reducing cardio-renal endpoints at lower eGFR → **HR 0.48** (95%CI 0.22-1.03) from FIDELITY* study for eGFR<25 (81 patients in each arm)

- ◉ *Does the 'label' population best represent the population likely to receive finerenone in NHS?*
- ◉ *Why are eGFR ranges <25 and 60-75 excluded?*
- ◉ *Why were ACR ranges not considered in the population criteria?*

***FIDELITY:** Meta-analysis of individual patient data from FIDELIO-DKD (primary renal) and FIGARO-DKD (primary CV) endpoints*

Abbreviations: ACR: albumin-to-creatinine ratio; CKD: chronic kidney disease; CV: cardiovascular; eGFR: estimated glomerular filtration rate

All values rounded to 2 d.p.

Primary composite outcome results

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

Outcome	Incidence	Finerenone	Placebo	HR (95% CI)	P-value
Primary composite outcome	Crude, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Rate/100 patient-years (95%CI)	[redacted]	[redacted]		
Components of primary composite outcome:					
Kidney failure	Crude, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Rate/100 patient-years (95%CI)	[redacted]	[redacted]		
End-stage renal disease	Crude, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Rate/100 patient-years (95%CI)	[redacted]	[redacted]		
Sustained decrease in eGFR <15 ml/min/1.73 m^2	Crude, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Rate/100 patient-years (95%CI)	[redacted]	[redacted]		
Sustained decrease ≥40% eGFR from baseline	Crude, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Rate/100 patient-years (95%CI)	[redacted]	[redacted]		
Renal death	Crude, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: eGFR: estimated glomerular filtration rate

Primary composite outcome Kaplan-Meier

[redacted] in patients with CKD and type 2 diabetes with eGFR ≥25 and <60 ml/min/1.73 m^2 and albuminuria

- [redacted]

◉ *Has end-stage renal disease had enough time for a significant effect on results?*

Abbreviations: CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate

All values rounded to 2 d.p.

Key secondary composite outcome results

Secondary composite outcome: Time to 1st event of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalisation for heart failure

Outcome	Incidence	Finerenone	Placebo	HR (95% CI)	P-value
Key secondary composite outcome	Crude, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Rate/100 patient-years (95%CI)	[redacted]	[redacted]		
Components of secondary composite outcome:					
• *Cardiovascular death*	Crude, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Rate/100 patient-years (95%CI)	[redacted]	[redacted]		
• *Non-fatal myocardial infarction*	Crude, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Rate/100 patient-years (95%CI)	[redacted]	[redacted]		
• *Non-fatal stroke*	Crude, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Rate/100 patient-years (95%CI)	[redacted]	[redacted]		
• *Hospitalisation for heart failure*	Crude, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Rate/100 patient-years (95%CI)	[redacted]	[redacted]		

Key secondary composite outcome Kaplan-Meier

All values rounded to 2 d.p.

Other secondary outcome results

Exploratory statistical analysis

	Incidence	Finerenone	Placebo	HR (95% CI)	P-value
Death (any cause)	Crude, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Rate/100 patient years (95% CI)	[redacted]	[redacted]		
Hospitalisation (any cause)	Crude, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Rate/100 patient years (95% CI)	[redacted]	[redacted]		
Secondary composite kidney outcome*	Crude, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Rate/100 patient years (95% CI)	[redacted]	[redacted]		
Change in urine albumin: creatinine ratio from baseline to 4 months		Next slide			

*kidney failure or sustained decrease in eGFR ≥57% (equivalent of doubling serum creatinine) from baseline over at least 4 weeks, or renal death

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Abbreviations: eGFR: estimated glomerular filtration rate

Other secondary outcome results – UACR

[redacted]

Urinary albumin-to-Creatinine ratio covariance analysis from baseline to month 4						
Treatment	N	Least-squares mean	95%CI for least-squares mean	P-value of F-test	Ratio of means	95%CI for ratio of least-squares means
Finerenone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]			

Exploratory analysis: [redacted]

NICE

Abbreviations: UACR: urine albumin to creatinine ratio

Clinical relevance of trial outcomes

ERG: [redacted] on *composite* outcome [redacted]

[redacted]

- [redacted]

Company after TE: consider outcomes as clinically relevant and supported by regulators

- Study powered to show significance on composite endpoint not components
- CKD progression usually slow – so general acceptance of surrogate measures
  - ↓eGFR and ↑albuminuria predictors of ↑CV events, mortality and kidney disease progression (NKF with EMA and FDA accept surrogacy in trials)
  - Observational studies show strong link between ↓eGFR and end-stage kidney disease
- EPAR: primary endpoint appropriate, inline with CHMP scientific advice, clinically relevant
- Cox model developed to assess heterogeneity between treatment and individual component: No heterogeneity found (p-value [redacted])
- Proportional hazards Cox model used in post-hoc analyses to find risk of developing kidney failure after sustained eGFR decrease: [redacted] than before
- Secondary renal endpoint (≥57% eGFR): relate to 2x serum creatinine – predictor of ESRD

ERG: Statistical tests of eGFR reduction is useful but 'pattern-matching' with endpoint components less useful to understand effectiveness of finerenone

Clinical experts: Surrogate outcome is accepted by FDA and EMA and considered appropriate

◉ *Are the surrogacy outcomes appropriate in evaluating finerenone for decision-making?*

Abbreviations: CHMP: committee for medicinal products for human use; CKD: chronic kidney disease; CV: cardiovascular; eGFR: estimated glomerular filtration rate; EMA: European medicines agency; EPAR: European public assessment reports; ESRD: end-stage renal disease; FDA: food and drug administration; NKF: national kidney foundation

Adverse events (1)

Adverse events from **safety analysis set** (of full-analysis set): Minimum 1 dose of drug ([redacted] finerenone; [redacted] placebo)

Higher %

FIDELIO-DKD Safety Analysis Set	Finerenone, N=2827	Placebo, N=2831
Any adverse event (%)	[redacted]	[redacted]
Any TEAE (%)	**87.3**	**87.5**
Drug-related TEAE (%)	22.9	15.9
TEAE leading to discontinuation of drug (%)	7.3	5.9
Any serious TEAE (%)	**31.9**	**34.3**
Serious drug-related TEAE (%)	1.7	1.2
Serious TEAE leading to discontinuation of drug (%)	2.7	2.8
TEAE resulting in death* (%)	[redacted]	[redacted]

*excluding efficacy outcome events

Of TEAEs in ≥5% patients:

- **More common in finerenone** than placebo: Hyperkalaemia (15.8% vs. 7.8%) and decrease in GFR (6.3% vs. 4.7%)
- **More common in placebo** than finerenone: Peripheral oedema, hypertension, hypoglycaemia, pneumonia, constipation

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Abbreviations: TEAE: treatment-emergent adverse event

Adverse events (2)

Overall finerenone plus BT well-tolerated but main risk is hyperkalaemia

Hyperkalaemia incidence %	Finerenone	Placebo
All treatment-emergent investigator reported	18.3	9
Serious	1.6	0.4
Hospitalisation	1.4	0.3
Discontinuation	2.3	0.9
Development of end-stage kidney disease	4.2	4.9

Hyperkalaemia:

- 2x as frequent in finerenone than placebo (18.3% vs 9.0%)
- Leading to discontinuation higher for finerenone than placebo (2.3% vs 0.9%)
- No fatal hyperkalaemia events reported

Company: Most treatment-emergent hyperkalaemia: [redacted]

- Hyperkalaemia inherent risk with population because of underlying disease (serum potassium tends to increase with low eGFR) and background care (ACE-i/ARB)
- Hyperkalaemia associated with mode of action of finerenone and mineralocorticoid
- **Manageable with flexible dose-titration based on serum potassium and eGFR**

% new concomitant medication after start of study drug (FAS)	Finerenone	Placebo
Potassium-lowering (% at baseline)	10.8 (2.5)	6.5 (2.3)
Potassium supplements	[redacted]	[redacted]

- *Is the level of hyperkalaemia acceptable?*
- *Is the increase in potassium-lowering medications as expected?*

Abbreviations: FAS: full-analysis set

Missing comparison with SGLT-2i (1)

Company compares finerenone with background therapy only

Company: SGLT-2i not included as relevant comparator

- Trial: at baseline only 4.5% treated with SGLT-2i. Increased during trial but remained <10%
- Trial designed to take into account polypharmacy nature of clinical practice
- Sales data estimate market share SGLT-2i< [redacted] compared with oral or parental hypoglycaemics
  - SGLT-2i not embedded in UK clinical practice (NICE recommendation Nov 2021)
  - SGLT-2i a variable in background therapy compared with ACEi/ARBs
  - SGLT-2i not suitable for all patients
  - Not known how much of market share for SGLT-2i is for both CKD and type 2 diabetes – for comparison market share by volume for biguanides approx. [redacted]
- Finerenone not replacing existing therapies, instead is independent and different mode of action
- Comparison limited by differences in trial population and methodology

ERG: SGLT-2i is a relevant comparator and included in final scope

- Suggest comparison either as standard of care PLUS:
  1. Finerenone vs SGLT-2i
     (indirect comparison but challenges with different populations and endpoints used) → but still possible,
  2. Finerenone vs finerenone + SGLT-2i
     using trial data (don't need indirect comparison but small sample size from trial)
- SGLT-2i can increase from current level (TA775 dapagliflozin; NG28 recommending SGLT-2i)
- Different mechanism of action doesn't mean comparator not considered
- Patient choice/suitability should be considered with cost-effectiveness estimates

Abbreviations: ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin-receptor blocker CKD: chronic kidney disease; SGLT-2i: sodium-glucose-co-transporter-2 inhibitor

Subgroup analysis (1)

Company did exploratory subgroup analyses on primary/secondary efficacy variables and some safety variables for 44 pre-specified subgroups

Key subgroup analyses (from 44 pre-specified groups)	
• Region	• eGFR category at screening/baseline
• Age at run-in visit	• Baseline serum potassium value
• Sex	• UACR at baseline
• Race	• Haemoglobin A1C
• History of CV disease	• Systolic blood pressure at baseline
• Type of albuminuria at screening/baseline	• SGLT-2i treatment at baseline
• Baseline BMI	GLP-1 agonists treatment at baseline

ERG: Subgroup of particular interest **(key issue)** → next slide

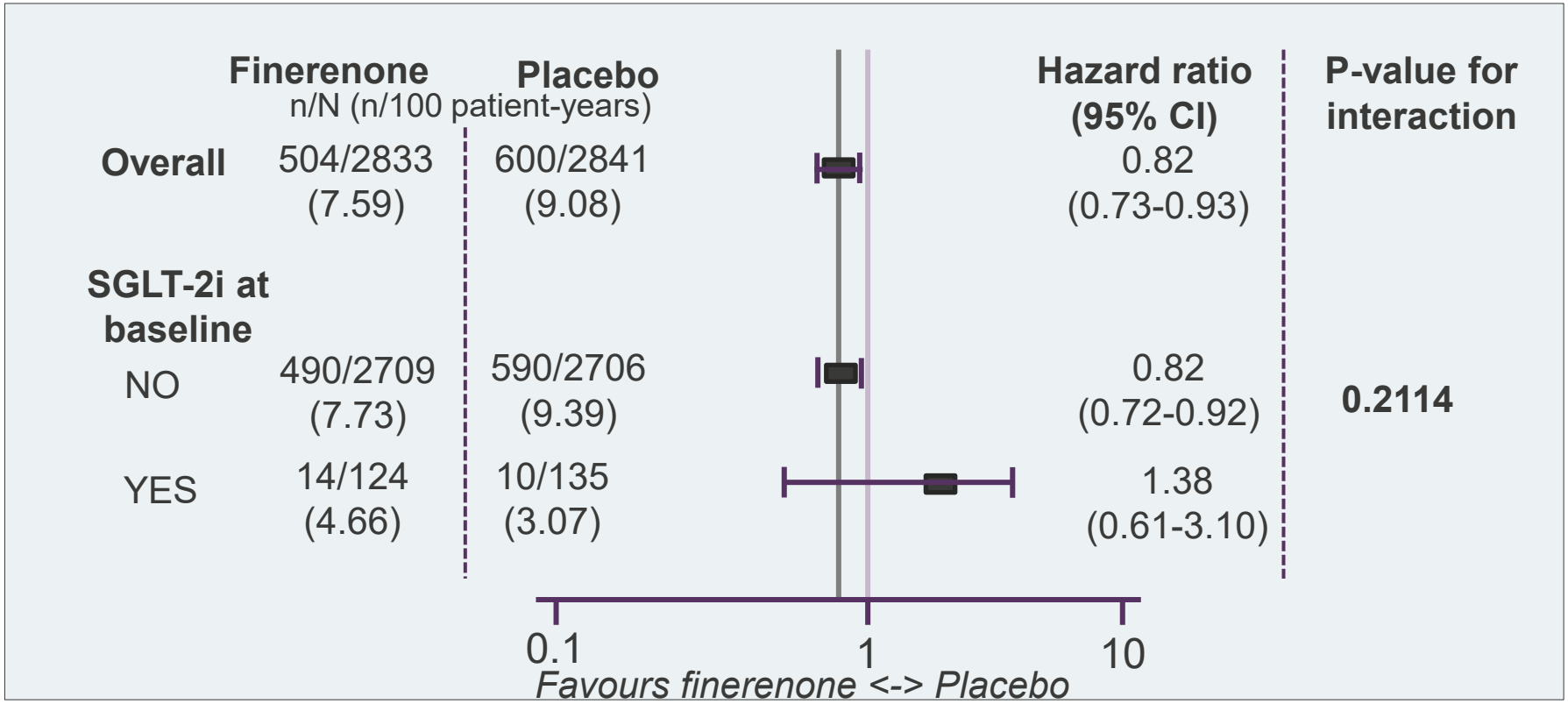
Company conclusions from subgroup analysis:

- **Consistent results** across a range of demographic and baseline characteristics for primary and secondary endpoints
- **Primary renal composite outcome:** estimates generally consistent with overall population – majority <1 hazard ratios
- **Subgroups with secondary outcomes reported:** [redacted]

Abbreviations: BMI: body-mass index; CV: cardiovascular; eGFR: estimated glomerular filtration rate; GLP-1: glucagon-like peptide; SGLT-2i: sodium-glucose-co-transporter-2 inhibitor; UACR: urine albumin to creatinine ratio

Subgroup analysis (2) – SGLT-2i subgroup

Forest plot to show estimated treatment effects, 95%CI and statistical test for interaction of primary composite outcome* according to *SGLT-2i treatment at baseline* subgroup



Company: Few clinical endpoint events in a small subgroup so no meaningful conclusions from subgroup time-to-event efficacy endpoint analyses (wide confidence intervals)

ERG: 259 SGLT-2i at baseline (124 finerenone, 135 placebo)

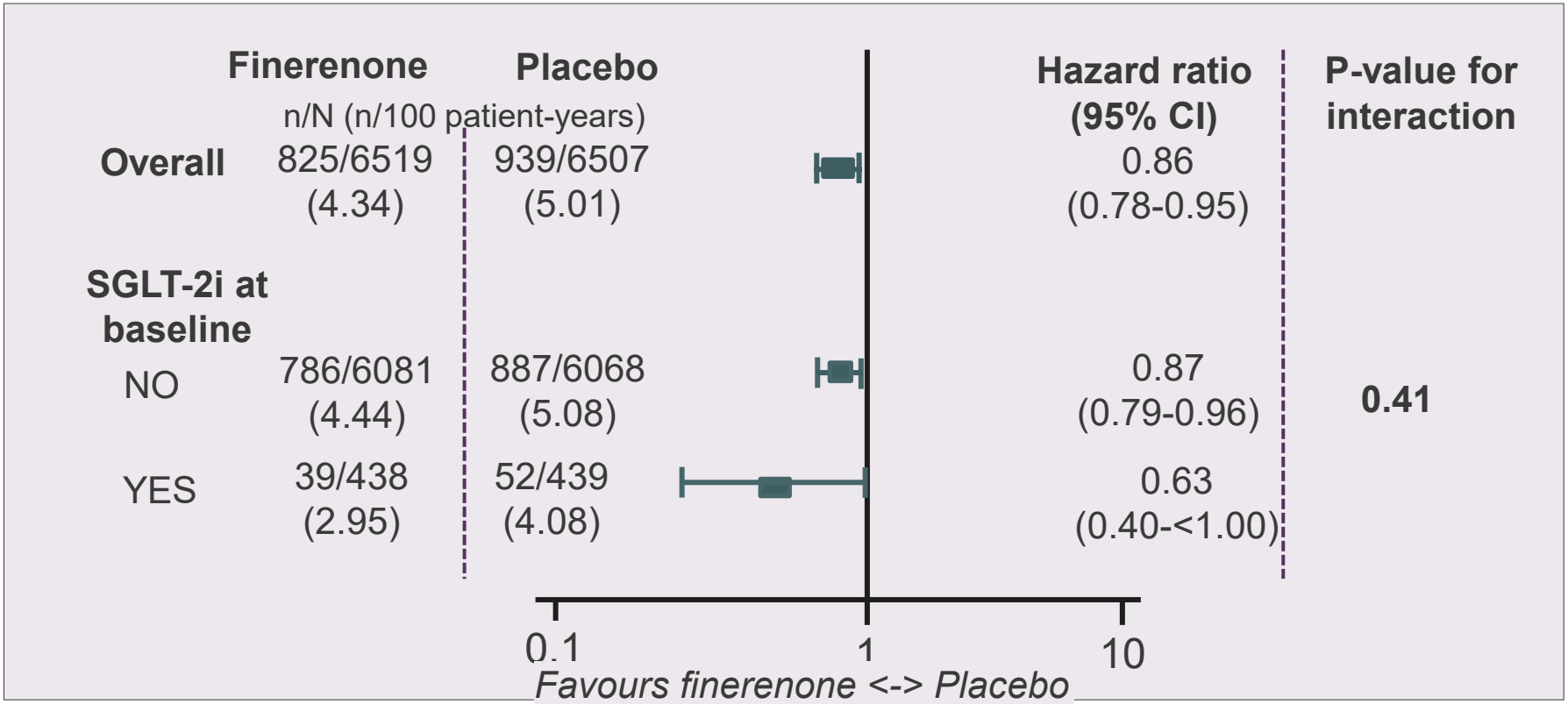
- **With** SGLT-2i: **No statistically significant effect** of finerenone on primary outcome
- **Without** SGLT-2i: **Reduction** in primary outcome

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

Abbreviations: CI: confidence interval; SGLT-2i: sodium-glucose-co-transporter-2 inhibitor

Subgroup analysis (3) – SGLT-2i subgroup in FIDELITY pooled analysis

Forest plot to show composite cardiovascular outcomes according to SGLT-2i at baseline subgroup from FIDELITY study



***FIDELITY:** Meta-analysis of individual patient data from FIDELIO-DKD (primary renal) and FIGARO-DKD (primary CV) endpoints*

NICE **Abbreviations:** CI: confidence interval; SGLT-2i: sodium-glucose-co-transporter-2 inhibitor

Missing comparison with SGLT-2i (2)

Company compares finerenone with background therapy only

Clinical experts and stakeholders:

- Patients on optimum ACEi/ARB with SGLT-2i have important cardiorenal residual risk – **Finerenone as add-on therapy reduces risk**
- **Some cannot tolerate SGLT-2i**
- **Mechanisms of action different** – appear not to compete with each other
- **FIDELITY analysis: Finerenone with SGLT-2i** at baseline **reduced risk** of composite **cardiovascular** endpoints by **37%** (HR: 0.63 [95%CI: 0.40 to <1.0]) vs placebo
- Exploratory post-hoc analysis of FIDELIO-DKD* with CREDENCE* results:
  - Relative risk reduction of **cardiorenal** endpoints **26%** (HR: 0.74 [95%CI 0.63 to 0.87]) with finerenone compared with **30%** with canagliflozin (HR:0.70 [95%CI 0.59 to 0.82])
- Finerenone reduced ACR by 25% when already on SGLT-2i

Stakeholders:

- Guideline *NG28 (type 2 diabetes in adults: management)* and TA775 *(dapagliflozin for treating CKD)* give SGLT-2i as relevant comparators for this population
- Canagliflozin a relevant comparator in type 2 diabetes population in TA775 dapagliflozin
- Indirect treatment comparison is a possibility

◉ *Is finerenone plus standard care vs standard care alone the most relevant comparison?*

- ***FIDELITY:** Meta-analysis of individual patient data from FIDELIO- and FIGARO-DKD
- ***CREDENCE trial**: Assess canagliflozin effects on renal outcomes in patients with type 2 diabetes, CKD, albuminuria

Abbreviations: ACEi: angiotensin-converting enzyme inhibitor; ACR: urine albumin-to-creatinine ratio; ARB: angiotensin-receptor blocker; CKD: chronic kidney disease; CI: confidence interval; HR: hazard ratio; SGLT-2i: sodium-glucose-co-transporter-2 inhibitor

Key clinical issues

Data is from key clinical trial FIDELIO-DKD. Other relevant clinical evidence include FIGARO-DKD and FIDELITY studies not included in clinical evidence

- *Has all the relevant clinical data been presented?*

SGLT-2is are included in the scope and are recommended in NICE guidance (NG28 and TA775). But, company exclude SGLT2s (not considered to be established NHS practice)

- *Are SGLT-2is a relevant comparator?*

Licence is stage 3 to 4 CKD (defined as eGFR ***≥25*** to <60 **and** albuminuria).

- *Do these eGFR ranges align with those used in NHS practice?*

Hyperkalaemia is main adverse event observed with finerenone vs placebo (18.3% vs 9.0%)

- *Is hyperkalaemia a significant adverse event to consider?*

The primary outcome is a composite of 3 outcomes but only one component of this overarching outcome is statistically significant (≥40% decrease eGFR over at least 4 weeks)

- *Does the composite outcome (and its underpinning components) reflect an important outcome in NHS practice?*
- *Does the lack of statistical significance in some components of the composite outcome affect confidence in the primary outcome?*

Cost-effectiveness evidence

Key cost issues

Modelled background therapies include 1 representative from each class of drug

- *Are these drugs/doses representative of NHS practice for this population?*
- *Would finerenone and comparators be commissioned in primary care, secondary, or both?*

Model uses time-invariant transition probabilities, so may over-simplify the patient journey

- *Are time-invariant transitions acceptable for decision-making?*

Some model inputs have clinical uncertainty:

- ERG prefer using modified utilities from FIDELIO-DKD trial; company propose using utilities from the literature
  - *What utilities are the most appropriate to use?*
- The company prefer for patients with CV event history not to start in post-CV sub-model
  - *Are CV events modelled appropriately?*

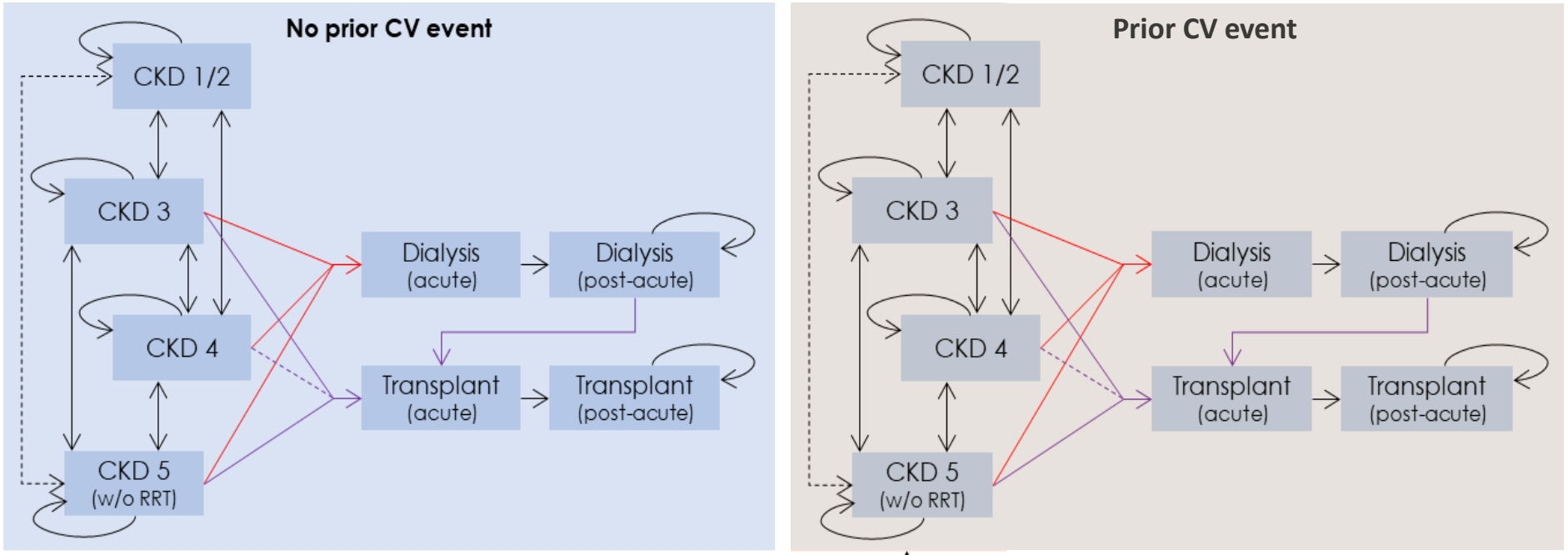
There is uncertainty in the deterministic and probabilistic sensitivity analyses

- *Have the issues been sufficiently addressed for a robust ICER?*

Company's economic model (1) – characteristics

Model type	*De novo,* cohort-level, state-transition Markov model
Time horizon	Lifetime (33.4 years)
Model cycle	4 months – inline with trial
Population	Adults with stage 3 or 4 CKD (eGFR ≥25 ml/min/1.73m^2) with type 2 diabetes
Intervention	Finerenone plus background therapy
Comparators	Background therapy alone
Health states	CKD1/2, CKD3, CKD4, CKD5 without dialysis, dialysis, transplant, death
Utility values	EQ5D-5L from trial (mapped on 3L) • Utilities from literature used in scenarios
Health events (if significant differences in trial and non-negligible impact on costs/QALYs)	Hyperkalaemia, new onset of atrial fibrillation/flutter, sustained decrease of eGFR ≥40% from baseline, subsequent CV event
Treatment effect waning	No – considered constant over time

Company's economic model (2) – structure



From any health state, with differential risk based on CV event history

From any health state, with differential risk based on CV event history

Dead

Occurrence of a CV event

Impacts costs & outcomes, patients remain in previous health state

- Non-fatal stroke
- Non-fatal myocardial infarction
- Hospitalisation for heart failure

Source: ERG adapted model

- Transitions technically permitted in company model but for at least 1 treatment arm, this probability is = 0 (effectively removing it from the model)
- States patients can progress to dialysis
- States patients can progress to kidney transplant

◉ *Is the model considered appropriate for decision-making?*

Abbreviations: CKD: chronic kidney disease; CV: cardiovascular

Background therapies used in model

Max dose of each drug from its class used in background therapy

Drug *(example)*
ACE-is *(Ramipril 5 mg)*
ARBs *(Losartan 50 mg)*
Beta-blockers *(Carvedilol 12.5 mg)*
Diuretics *(Furosemide 40 mg)*
Calcium antagonists *(Amlodipine 5mg)*
Statins *(Atorvastatin 10 mg)*
PAIs *(Acetylsalicylic acid 75 mg)*
Glucose-lowering therapies
Insulin *(Insulin glargine)*
Metformin *(Metformin 1,500 mg)*
Acarbose *(Acarbose 150 mg)*
Sulfonylurea *(Gliclazide 40 mg)*
DPP-4 inhibitors *(Linagliptin 5 mg)*
GLP-1 agonists *(Liraglutide 1.2 mg)*
SGLT-2i *(Canagliflozin 100 mg)*

Background therapy: 1 representative drug per class used in this disease area (max dose assumed)

- Based on most frequently administered drug within each class from trial
- Pooled distribution seen as appropriate by company

ERG agree with approach to identify common background therapies:

- Drugs appear well-balanced between arms
- Large sample from trial
- Considered broadly representative of UK population

Clinical expert: Some low doses (losartan, atorvastatin)

- Acarbose rarely used in UK
- Insulin and liraglutide typically secondary care

Stakeholder: Low doses (amlodipine, ramipril, atorvastatin)

- Expect bisoprolol as most common beta-blocker
- Hyperkalaemia may need potassium binder
  - ➢ Expect sodium zirconium cyclosilicate (TA599) or patiromer (TA623) – will add to background costs

◉ *Are background therapies appropriate and examples representative of NHS practice?*
◉ *Would finerenone and other modelled drugs be given in primary or secondary care, or both?*

Abbreviations: ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin-receptor blocker; DPP-4: dipeptidyl peptidase-4; GLP-1: glucagon-like peptide-1; PAI: platelet aggregation inhibitor; SGLT-2i: sodium-glucose-co-transporter-2 inhibitor

Model transitions subject to limitations (1)

ERG: Model limited in how it reflects patient journey over lifetime

- Most transitions are **time-invariant**, dependent only on current stage (same transitions used over time) – may **oversimplify** overall disease progression estimation
- **CV event risks** based on stage, not risk equations
- Suggest alternative modelling with **time-varying risks** (e.g. multi-state model) /**risk equations**

Company after TE: consider model structure and transitions as relevant after validation

- Risk equations: Limited major events in trial, so limiting data available to estimate
- Model focus on already established relationship with CKD stage & (CV) events (fatal or not)
- **Study of Heart and Renal Protection (SHARP) CKD-CVD Markov for cross-validation**
  - Comparison of CV event or death, CV death and renal replacement therapy endpoints
- Modelled clinical progression appears aligned with SHARP CKD-CVD model but uncertainty because of wide ranges and only 1 model comparison
- SHARP used CKD 3b at baseline (for comparison: FIDELIO [redacted])

Validation by external expert: results of company model based on averages from whole trial population and SHARP CKD-CVD presents expectation of single patient so SHARP may be more representative for the median than mean

- Model driven by data – some logic not inline with progressive disease nature – effect uncertain

ERG: Agree with limitations of SHARP model, but this along with other published models or model structures (NICE guideline model; multi-state modelling) could allow time-varying transitions/risks

- Results show similar CV events predictions but adding time-variations would impact ICER

Abbreviations: CKD: chronic kidney disease; CV: cardiovascular; ICER: incremental cost-effectiveness ratio

SHARP-CKD-CVD validation results with model (2)

Results for comparison with SHARP CKD-CVD for patients using standard of care alone (i.e. background therapy arm of company model)

- Risk equations used, varying in each cycle, for CKD progression and CV events
- Additional parameters tested to generate ranges of the estimates *(smoking status, BMI, albumin, haemoglobin, phosphate, ACR, renal diagnosis)*

	Major CV event or CV death	**RRT initiation**	**CV death**
Cumulative probabilities per 1,000 participants, **at 5 years**			
SHARP-CKD-CVD (ranges)	236 (155-316)	276 (41-413)	92 (55-135)
Company model (95% CI)	273 (247, 297)	106 (103, 107)	87 (73, 104)
Cumulative probabilities per 1,000 participants, **at 10 years**			
SHARP-CKD-CVD (ranges)	431 (283-549)	670 (156-820)	244 (137-349)
Company model (95% CI)	541 (491, 587)	249 (241, 255)	181 (147, 214)

◉ *Are time-invariant transitions appropriate in the model?*

Abbreviations: ACR: albumin-to-creatinine ratio; CKD: chronic kidney disease; CV: cardiovascular; RRT: renal replacement therapy

Clinical plausibility of model inputs

Company originally had all model inputs directly from FIDELIO-DKD but ERG concluded lack of clinical plausibility in parts of the model affecting overall face validity of results

ERG preferred assumption	Company revision after technical engagement	ERG comment
• Set risk of CV **events** independent of CKD stage – used value [redacted]	Calculating average risk of CV events for all CKD stages and applying in all model health states • Using value [redacted]	**Resolved:** Accept company revised approach
• Set risk of CV **death** independent of CKD stage – used value [redacted]	Calculating average risk of CV death for all CKD stages and apply in all model health states • Using value [redacted]	
• Include 1 additional pack of finerenone for wastage	Include additional half pack of finerenone for wastage	**Resolved:** Accept company revision – 'true' wastage could be < or > this
• Amend renal deaths application	Remove renal deaths from model and add back to general mortality	**Resolved:** Company and ERG application align
• Remove all death costs	Remove all death costs	
• Edit background therapy costs to ERG calculations	Edit background therapy cost to ERG's calculations	£0.01 difference in cost per day from rounding error (£2.34 company vs £2.33 ERG) – unlikely material impact on ICER but ERG prefer its cost in base-case

Abbreviations: CKD: chronic kidney disease; CV: cardiovascular

Clinical plausibility of model inputs

ERG preferred assumption	Company revision after TE	ERG comment
• Stopping finerenone after RRT and re-calibrating constant risk of discontinuation to prevent overestimation – 4-year discontinuation to [redacted]	Stopping finerenone after RRT and 4-year discontinuation lowered to [redacted]	**Unclear preference:** • If finerenone permitted after initiating RRT then prefer adjusting treatment discontinuation • But if finerenone discontinued after RRT in trial then prefer company's additional edit to discontinuation • £2,207 decrease ICER with stopping rule and post-technical engagement revisions
• Assume 45.9% patients with history of CV events enter post-CV event sub-model	Post-acute costs reduced by a factor equivalent to the proportion of patients without CV event history	**Unresolved:** Both agree 45.9% patients enter model with CV history but how this is modelled depends on CV event history definition. ERG prefer proportion of trial cohort with CV history to enter 'post CV event' sub-model at baseline
• Assume utility for CKD1/2 is 0.80 • Doubled acute disutilities; assume post-acute disutility: 1/2 acute disutility	Assume all utilities and disutilities based on literature (TA358 tolvaptan)	**Unresolved:** ERG preference for modified trial-based utility values

◉ *Do the committee agree with stopping finerenone after RRT or continuing?*

Abbreviations: CKD: chronic kidney disease; CV: cardiovascular; ICER: incremental cost-effectiveness ratio; RRT: renal replacement therapy

Unresolved issue – Modelling post-CV events

Company and ERG agree 45.9% patients in FIDELIO-DKD enter the model with prior CV history

- 2 definitions of CV event history, so modelled differently:
  1) Since entering FIDELIO-DKD (company preference); 2) Based on patient history (ERG);

Company disagree with these patients entering 'post-CV event' part of the model at baseline

- 'Post-CV' states correspond to incidence of first event in FIDELIO-DKD and all benefits of finerenone to reduce risk of CV events modelled from this perspective
- All patients should **start in 'no-CV event' states**
- Prior CV history can have post-acute costs/disutilities from CV events before entering model
- Acute consequences of CV events assumed to be the same regardless of history of CV event – so should not be amended for this group
- Company scenario: not applying post-acute consequences of CV events to 45.9% patients with history of CV events to account for ERG suggestion to consider CV event history

ERG: allowed *a proportion* of patients to enter 'post-CV event' part of model at baseline

- Some parts of model related to prior CV event history based on published literature so considered broader view of CV history
- After CV event happens, patients modelled to see an increase risk of death because of CV event history from external data
- Other-cause mortality informed by external data and mortality is of significant importance to be modelled appropriately – so maintain its modelling preferences

◉ *Should patients with prior CV history enter the 'post-CV event' sub-model at baseline?*

Abbreviations: CKD: chronic kidney disease; CV: cardiovascular

Unresolved issue – Utilities in the model (1)

Company base-case uses updated utilities from literature rather than FIDELIO-DKD

ERG: Agree with using specific health state utilities based on CKD stage but concerns with face validity

- Patients with stage 3 CKD estimated with 0.001 increase in utility compared with stage 1 or 2 CKD

Company after technical engagement: acknowledge limitations with utilities from trial – new base case uses utilities from systematic literature review sources

- **TA358** (tolvaptan for treating autosomal dominant polycystic kidney disease) used because all utilities needed for CKD health states reported here and previously accepted by NICE
- **Meads (2014)** used for CV events because utilities based on UK studies (using EQ-5D) and focusing on MI and stroke with short- and long-term impact
- **McEwan (2020)** used for disutility due to hospitalisation for heart failure – disutilities were from pooled analysis of individual patient-level EQ-5D data from DAPA-HF trial

ERG: Literature utilities used CKD-based health utilities from TA358 attributed from Gorodetskaya et al (2005)

  - N=205 sample with CKD and 46% with type 2 diabetes too
  - Did not include EQ-5D
- Prefer modified trial-based utilities than values from literature

Abbreviations: CKD: chronic kidney disease; DAPA-HF: dapagliflozin and prevention of adverse-outcomes in heart failure; EQ-5D: EuroQol-5 dimension; MI: myocardial infarction

All values rounded to 2 d.p.

Unresolved issue – utilities in the model (2)

Company base-case uses updates utilities from literature rather than FIDELIO-DKD

Original company submission used multi-variate regression analysis for utilities from trial; updated base-case uses utilities from literature

Health state utilities (no CV event)	**Mean utility (95%CI)** (multi-variate analyses of FIDELIO-DKD)	**Utilities used in updated model** (TA358 tolvaptan)	**Mean utility in TA775 dapagliflozin for comparison**
CKD 1/2 *(EQ-5D-5L utility directly from FIDELIO-DKD)*	[redacted]	[redacted](FIDELIO-DKD)	[redacted] (DAPA-CKD, 2021)
CKD 3	[redacted]	[redacted]	[redacted] (DAPA-CKD, 2021)
CKD 4	[redacted]	[redacted]	[redacted] (DAPA-CKD, 2021)
CKD 5 without RRT	[redacted]	[redacted]	[redacted] (DAPA-CKD, 2021)
Dialysis	[redacted]	[redacted](acute and post-acute)	0.46 (Lee *et al*., 2005)
Post-dialysis	[redacted]		
Transplant	[redacted]	[redacted] (acute)	0.71 (Lee *et al*., 2005)
Post transplant	[redacted]	[redacted] (post-acute)	

NICE

Abbreviations: CKD: chronic kidney disease; RRT: renal-replacement therapy

All values rounded to 2 d.p.

Unresolved issue – utilities in the model (3)

Company base-case uses updates utilities from literature rather than FIDELIO-DKD

Utility decrement from event		Mean disutility (95%CI) (multi-variate analyses of FIDELIO-DKD)	Disutility from literature (updated base case)
Myocardial infarction	Acute	[redacted]	-0.14 (Meads, 2014)
	Post-acute		-0.07 (Meads, 2014)
Stroke	Acute	[redacted]	-0.16 (Meads, 2014)
	Post-acute		-0.08 (Meads, 2014)
Hospitalisation for heart failure (HF)	Acute	[redacted]	-0.32 (McEwan, 2020)
	Post-acute		-0.03 (McEwan, 2020)
Average utility decrement from 1st CV event	Acute	[redacted]	-0.25
	Post-acute	[redacted]	-0.03
New onset atrial fibrillation/flutter		[redacted]	-0.01 (Rinciog, 2019)
Hyperkalaemia (based on all hyperkalaemia in trial)		[redacted]	-0.03 (Palaka, 2020)
Sustained decrease eGFR ≥40%		[redacted]	FIDELIO-DKD
Subsequent CV event*		[redacted]	-0.25**

**Weighted average MI, stroke, HF hospitalisation* from multivariate analysis – FIDELIO-DKD CV event distribution
**Weighted average of acute MI/stroke, HF hospitalisation

◉ *Should modified utilities from FIDELIO-DKD or utilities from literature inform the model?*

Overall uncertainty of results in sensitivity analyses not adequately captured (1)

ERG identify issues of uncertainty in company deterministic (DSA) and probabilistic sensitivity analyses (PSA)

Issue	Company response	ERG comment
Grouping parameters rationale e.g. baseline patient distribution and utilities grouped; specific risks and utility decrements separate	Varies for DSA and PSA, e.g. baseline patient distribution grouped because interrelated • Grouping utilities helps issue with higher utilities in more advanced health states	Unclear inference from DSA for grouped parameters - some combined 'lower-bounds' clinically implausible e.g. lower bound 100% CKD3; upper: 100% CKD4 - Combination does not consider possible lower bounds between values - **unresolved**
Wide parameter bounds	Agree some high bounds with Alva et al. source → suggest fixed +/-30% from base case for costs from Alva et al. But consider overall that SA are conservative	PSA with extreme values can lead to misleading results **–** don't agree that over-estimation means conservative ICERs
Distribution used	Applied ERG suggestion of normal distribution instead of gamma for costs	**Resolved**

Abbreviations: CKD: chronic kidney disease; ICER: incremental cost-effectiveness ratio; SA: sensitivity analysis

Overall uncertainty of results in sensitivity analyses not adequately captured (2)

Issue	Company response	ERG comment
Removed duration of sustained decrease in eGFR ≥40% from baseline parameter	Removed parameters sampled from user-specified limits (i.e. eGFR ≥40% decline from baseline) in DSA and PSA because no credible ranges to test – scenario analysis excluding parameter: £302 increase in ICER	Acceptable but ideally used empirically derived confidence interval limits
Utilities: range of values in sensitivity analyses over-estimate volume of uncertainty in values (e.g. [redacted] CKD3 utilities, range: [redacted] and [redacted])	Updated utility source and separate DSA and PSA for new base-case with independent sampling of utilities by health states with some assumed uncertainty (10% of mean value)	Limitations of using published utilities (affecting PSA) and independent sampling; but resolved issue of imprecision in PSA for utilities
Fixed transition probabilities		Company did not comment – individual transition probabilities are assumed fixed – limitation of PSA and DSA

◉ *Are any of the limitations in the sensitivity analyses of particular concern?*

Abbreviations: CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; ICER: incremental cost-effectiveness ratio

Cost-effectiveness results

All cost-effectiveness results are presented in private PART 2 slides because of confidential comparator PAS discounts

Outstanding issues after technical engagement

Key issues	Impact on ICER	Slides
Uncertainty in appropriate population		15-16
Uncertainty in clinical relevance of trial outcomes		17-23
Missing comparison with SGLT-2i		26-30
Model transitions subject to substantial limitations		37-38
Several influential model inputs lack clinical plausibility affecting overall face validity of model results		39-44
Overall uncertainty in results of model not adequately captured by company's sensitivity analyses		45-46

 Model driver

 Unknown impact

 Small/Moderate impact

NICE

Other considerations

Innovation:

- Company consider finerenone innovative in treating CKD in type 2 diabetes as a treatment in addition to current standard of care, and a distinct mechanism of action
- Non-steroidal structure of finerenone allows more selective targeting of inflammatory/fibrotic features of CKD progression
- Benefits kidney, heart and blood vessels, and prevents tubular injury in kidney and cardiac hypertrophy

Aspects in QALY calculation:

- Can delay progression to kidney failure and dialysis
- Substantial benefit for patient and carers to be considered

Equalities:

- CKD progression can be more rapid in specific groups (e.g. socio-economic), and also specific backgrounds e.g. Bangladeshi
  - Likely due to more sensitivity to combined effects of proteinuria and hypertension than in other ethnic groups
- Rapid progression of CKD in people with diabetes is more common in people aged under 55 years, compared to people aged 55 and over

Abbreviations: CKD: chronic kidney disease

Key cost issues

Modelled background therapies include 1 representative from each class of drug

- *Are these drugs/doses representative of NHS practice for this population?*
- *Would finerenone and comparators be commissioned in primary care, secondary, or both?*

Model uses time-invariant transition probabilities, so may over-simplify the patient journey

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There is uncertainty in the deterministic and probabilistic sensitivity analyses

- *Have the issues been sufficiently addressed for a robust ICER?*