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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

Contents:

The following documents are made available to consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Comments on the Appraisal Consultation Document from Bayer Healthcare**

3. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   a. UK Kidney Association and Association of British Clinical Diabetologists – a joint response

4. **Comments on the Appraisal Consultation Document received through the NICE website – No responses received**

5. **Evidence Review Group critique of company comments on the ACD**

6. **Company response to ERG request**

7. **EAG critique of company model post ACD**

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

Finerenone for treating chronic kidney disease in type 2 diabetes

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE 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 submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Company	Bayer	Bayer plc is disappointed that the NICE committee was minded not to recommend finerenone as an option for treating stage 3 and 4 chronic kidney disease with albuminuria associated with type 2 diabetes in adults. Despite standard of care therapy, and recent emerging therapies, overall, there remains a high residual risk of cardiorenal events in patients with chronic kidney disease (CKD) and type 2 diabetes (T2D). Therefore, as recognised by stakeholders to this appraisal, there is an unmet need for additional treatment options to further reduce cardiorenal morbidity and mortality in these patients. Current understanding of CKD and T2D suggests that three interrelated pathophysiological drivers promote CKD progression (1): • Metabolic factors (e.g. elevated blood sugar) • Haemodynamic factors (e.g. elevated blood pressure and/or intraglomerular pressure) • Inflammatory and fibrotic factors (e.g. pro-inflammatory cytokines and pro-fibrotic proteins). Metabolic and haemodynamic drivers of CKD in T2D are targeted by glucose-lowering agents and antihypertensive medications (e.g. angiotensin-converting enzyme inhibitors [ACEIs] and angiotensin receptor blockers [ARBs]). 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 (2, 3). However, despite existing therapies for CKD and T2D, there remains a residual risk of progression to more advanced CKD stages (4-7). Pathways that influence inflammation and fibrosis are complex, but pathological overactivation of the mineralocorticoid receptor (MR) remains a key driver of disease in the kidneys, heart, and vascular system (8-10). Finerenone is a non-steroidal, selective antagonist of the MR (11), addressing the third driver of disease progression. To optimise treatment outcomes, it is expected that all three drivers of disease progression should be addressed. Finerenone was demonstrated in the FIDELIO-DKD study (12), one of the largest contemporary studies to evaluate patients with CKD and T2D, to be efficacious in delaying the progression of kidney disease and reducing the risk of major CV events, on top of optimised background therapy, including a maximum tolerated labelled dose of either an ACEI or an ARB.	Comments noted. The recommendation in the FAD has been updated. Finerenone is recommended as an option for treating stage 3 and 4 chronic kidney disease (with albuminuria) associated with type 2 diabetes in adults. See section 1.1 of the FAD. The new analyses were considered by the committee during decision making. See relevant sections of the FAD.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Bayer presented a robust economic model which demonstrated that finerenone is a cost-effective use of NHS resources, compared to established NHS clinical practice with a base case ICER, using ERG preferred model assumptions of £13,626 (presented before the 1st committee meeting). Furthermore, there are aspects that have not been fully captured in the QALY calculation; 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 that were not fully captured in the economic model (13-15). In this response to the ACD, Bayer seeks to provide further information and analyses to the committee so that NICE reconsiders their draft decision and NHS clinicians are able to offer finerenone for appropriate patients with an unmet medical need. Specifically, the committee recommended that NICE request further clarification and analyses from Bayer, which should be made available for the second appraisal committee meeting, and should include: 1. a comparison of finerenone with sodium–glucose cotransporter-2 (SGLT2) inhibitors (see comment 3) 2. all data from the FIGARO-DKD and FIDELITY studies that are directly relevant to the decision problem in this appraisal (see comment 4) 3. updating the effectiveness data in the cost-effectiveness model with new point estimates from the additional clinical data (see comment 4) 4. cost-effectiveness scenario analyses of finerenone used at second line (compared with SGLT2 inhibitors in an SGLT2 inhibitor-naive population) and at third line (as an add-on to second-line SGLT2 inhibitors in an SGLT2 inhibitor-experienced population) (see comments 5 and 9) 5. comparisons of transition probabilities over time, and model predictions of time to events compared with empirical data from the trial (see comment 6) 6. base cases with both trial-based utilities and utilities from literature sources that are more recent and relevant than currently used in the model (see comment 2, 4, 5 and 7) 7. scenario analyses of alternative treatment waning effects for finerenone (see comment 7) 8. a valid probabilistic sensitivity analysis that includes accounting for parameter uncertainty in transition probabilities to reflect CKD progression (see comment 8) We take each of these points and address them in our response below.	
2	Company	Bayer	Firstly, further to the 1st appraisal committee meeting, we have implemented the ERG/NICE preferred assumptions to the cost effectiveness model as follows:	Comments noted. The committee at

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
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Please respond to each comment</th></tr>
<tr><td></td><td></td><td></td><td>
1. Finerenone is discontinued if the eGFR falls below 15 ml/min/1.73 m^2, i.e. end stage renal disease, at the point where a patient requires renal replacement therapy (RRT) (this change was included in the updated CE model submitted before the 1st committee meeting),

2. The sources of the modelled utilities have been updated as a result of committee discussions. At the 1st committee meeting, two sets of utilities (based on FIDELIO-DKD and the literature) were discussed and compared with the utilities used in NICE TA775 (16). It was concluded that utilities for the CKD stages i.e., CKD 1/2, CKD 3, CKD 4 and CKD 5 without RRT obtained from FIDELIO-DKD were reliable taking into account the number of observations in the population most relevant for this submission. However, for disutilities applied for dialyses, kidney transplants, CV events and Other Health Events, it was considered that due to the low number of these events in the trial, their impact on quality of life could not have been robustly assessed based on FIDELIO-DKD. It was suggested at the committee meeting that the utilities for these events should be based on the most up to date literature. In line with that, Bayer includes the utilities from the recently published NICE guideline *Type 2 diabetes in adults: management* NG28 (17).

The final sources of modelled utilities are set out below and summarized in Table 1:

a. Utility for CKD 1 - CKD 5 without RRT based on the FIDELIO-DKD trial. Note that the ERG previously highlighted that the utility for CKD 1 / 2 did not exhibit clear face validity when compared to that obtained for CKD 3. To address this, the utility value for CKD 1/2 was assumed to be the same as for CKD 3. The value for CKD 3 has been selected as it was estimated based on a larger cohort from the FIDELIO-DKD trial.

b. Utility for dialysis and kidney transplant based on the recently published NICE guideline *Type 2 diabetes in adults: management* NG28 (17),

c. Utility for CV events based on NG28 (17),

d. Utility for Other Health Events based on a systematic literature review as presented during the appraisal process (except for a sustained decrease in eGFR of 40% or more from baseline, which is sourced from FIDELIO-DKD, as no alternative sources were identified in the literature).

Table 1. Utilities included in the CE model - summary
<table>
<tr><th></th><th>Value</th><th>Source</th></tr>
<tr><td>Utility</td><td></td><td></td></tr>
<tr><td>CKD1/2</td><td>[redacted]</td><td>FIDELIO-DKD trial (assumed as for CKD 3)</td></tr>
<tr><td>CKD3</td><td>[redacted]</td><td>FIDELIO-DKD trial</td></tr>
<tr><td>CKD4</td><td>[redacted]</td><td>FIDELIO-DKD trial</td></tr>
</table>
</td><td>first appraisal committee meeting acknowledged that finerenone would be stopped after renal replacement therapy is started. See section 3.16 of the FAD.

The committee considered the updated utility values were appropriate. See section 3.18 of the FAD.</td></tr>
</table>

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row			NICE Response Please respond to each comment
			CKD 5 w/o RRT	[redacted]	FIDELIO-DKD trial	
			Dialysis (acute)	0.595	NG28 (17)	
			Dialysis (post-acute)	0.595	NG28 (17)	
			Kidney Transplant (acute)	0.748	NG28 (17)	
			Kidney Transplant (post-acute)	0.748	NG28 (17)	
			Utility decrements associated with first CV event, acute			
			MI	-0.060	NG28 (17)	
			Stroke	-0.160	NG28 (17)	
			Hospitalization for HF	-0.110	NG28 (17)	
			Utility decrements associated with first CV event, post-acute			
			MI	-0.032	NG28 (17), incurred only by patient with no CV history at baseline (45.9% of patients had CV history in the FIDELIO-DKD)	
			Stroke	-0.087	NG28 (17), incurred only by patient with no CV history at baseline (45.9% of patients had CV history in the FIDELIO-DKD)	
			Hospitalization for HF	-0.060	NG28 (17), incurred only by patient with no CV history at baseline (45.9% of patients had CV history in the FIDELIO-DKD)	
			Utility decrements associated with Other Health Events			
			Hyperkalaemia, leading to hospitalisation	-0.030	Palaka 2020 (18)	
			Sustained decrease in eGFR ≥ 40% from baseline (over at least 4 weeks)	[redacted]	FIDELIO-DKD trial	
			New onset of atrial fibrillation / atrial flutter	-0.014	Rinciog 2019 (19)	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment

Hyperkalaemia, not leading to hospitalisation	-0.030	Palaka 2020 (18)

3. A different method for modelling transition probabilities has been introduced into the model.

   The ERG was concerned that the transition probabilities in the model were not subjected to any form of sensitivity analysis. In order to address this concern, Bayer had to change the approach for handling transition probabilities. Transition probabilities for background therapy (BT) remain unchanged (See Table 43 in the main submission), however were sampled in the PSA from the Dirichlet distribution.

   - Transition probabilities from the FIN + BT arm were obtained relative to the BT transitions, as they were for CV events and Other Health Events, by applying HRs from the FIDELIO-DKD study. Three HRs reflecting the impact of finerenone on CKD progression were available in the trial. These HRs correspond to the transitions to CKD 5 without dialysis, to acute dialysis and kidney transplant. However, no impact of treatment on transplantation was assumed due to the limited number of transplants in the trial. It was also confirmed by clinical experts that kidney transplant is dependent on other aspects including donor availability, rather than any kind of treatment. The HRs applied are presented in the table below.

Table 2. HRs for Renal Events for FIN + BT arm, FIDELIO-DKD label population

Description	HR: FIN + BT vs BT [95%CI]
Onset of eGFR decrease < 15 mL/min/1.73m^2 sustained over at least 4 weeks	[redacted]
Progression to dialysis	[redacted]
Progression to kidney transplant	[redacted]

*Assumed no differences based on the clinical validation

HRs were applied to the BT transition probabilities by using the following formula:

$$P_{Finerenone+BT} = 1 - (1 - P_{BT})^{HR}$$

Following the inclusion of HRs, the transitions were adjusted to sum to 1. This was performed by weighting, with weights being the transitions as in the BT matrix (Table 43 in the main submission).

The transition probabilities for FIN + BT arm are presented in the table below.

The committee acknowledged the company's updated approach to estimating health state transition probabilities which allows consideration for parameter uncertainty in the sensitivity analysis. However, it notes there are limitations with the updated approach. See section 3.14 of the FAD.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment

Table 3. Transition probabilities for FIN + BT, FIDELIO-DKD label population

From \ To	CKD1/2	CKD3	CKD4	CKD5 w/o 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 w/o 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]

This approach enabled a robust PSA to be conducted, with inclusion of the variability of applied HRs and sampling the BT probabilities from the Dirichlet distribution. The transition probability matrix contains multinomial data divided into several categories, with the single transition always in range between 0 and 1, and the sum of transitions from each category equal to 1. In line with that, according to standard approaches (20), the Dirichlet distribution (multivariate generalization of the beta distribution) has been chosen for transiting among model health states.

To test the impact of the new approach to the transition probabilities on the model estimates, the results of the modified model were compared with the last version of the model Bayer submitted to NICE.

The impact on the ICER, and number of different events has been presented in the table below (Table 4). The results of the new approach to the transition probabilities are consistent with the original approach and somewhat conservative.

Table 4. Model validation for different transition probabilities options

	Transition probabilities directly from FIDELIO-DKD trial	Transition probabilities for FIN + BT by applying relevant HRs to the BT transitions
Incremental costs, discounted	£1,796	£1,687
Incremental LYs, discounted	0.134	0.127

<table>
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<tr><td></td><td></td><td></td><td>
<table>
<tr><td>Incremental QALYs, discounted</td><td>0.132</td><td>0.127</td></tr>
<tr><td>ICER, discounted</td><td>£13,626</td><td>£14,049</td></tr>
<tr><td>Average number of CV events, undiscounted</td><td>-0.073</td><td>-0.075</td></tr>
<tr><td>Average number of CV deaths, undiscounted</td><td>-0.002</td><td>-0.002</td></tr>
<tr><td>Average number of LYs with no CV event</td><td>0.327</td><td>0.322</td></tr>
<tr><td>Average number of LYs without RRT</td><td>0.331</td><td>0.335</td></tr>
</table>

4. Applying the revised NHS list price of finerenone of £1.31/ day

The impact of the changes on the ICER, and step-by-step results are presented in the table below.

Table 5. Deterministic results
<table>
<tr><th>Preferred assumption</th><th>Cumulative ICER, £/QALY</th></tr>
<tr><td>Base case (as for the company model at the 1st committee meeting)</td><td>£13,626</td></tr>
<tr><td>#1 ERG/AC preferred assumption
Finerenone is discontinued if the eGFR falls below 15 ml/min/1.73 m^2, that is end stage renal disease (RRT)</td><td>£13,626 (already accounted for)</td></tr>
<tr><td>#2 Transition probabilities based of HRs</td><td>£14,049</td></tr>
<tr><td>#3 ERG/AC preferred assumption
Source of utility</td><td>£15,190</td></tr>
<tr><td>#4 Finerenone price (£1.31)</td><td>£5,464</td></tr>
</table>

By taking account of these preferred ERG/ NICE committee assumptions and applying the recently agreed NHS list price, Bayer considers this ICER i.e. £5,464 to be the revised base case. We address the requests for further clarification and analyses in the following comments and these are indeed informative, but we maintain, due to the limitations of this additional analysis that the base case ICER of £5,464 is the most robust to inform committee decision making

The base case deterministic results are supported with robust PSA presented further in comment 8.</td><td>The committee took in to account the cost-effectiveness results using the revised list price of £1.31/day for finerenone in its decision making. See section 2.3 of the FAD.</td></tr>
<tr><td>3</td><td>Company</td><td>Bayer</td><td>Bayer acknowledge the request from the appraisal committee to conduct a comparison to SGLT2i for this appraisal. However, Bayer retain the position that we have held throughout the process that SGLT2i are not an appropriate</td><td>Comments noted.

The committee</td></tr>
</table>

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			comparator in this appraisal and will not be presenting this analysis. We refer to the 2013 NICE Methods Guide in place at the time of making our submission (21) which states in section 6.2.2. that the committee must consider several factors, when selecting the most appropriate comparator(s) one of which is "established NHS practice in England". Additionally, section 6.2.3. states that the factors are not considered equally; rather, the committee will normally be guided by established practice in the NHS. Whilst Bayer accepts the comments made by experts at the committee meeting that SGLT2i use will inevitably increase as a result of recent guidelines and technology appraisal guidance, experts also stated that these drugs are not yet standard of care in clinical practice. Clinicians also commented during the meeting that it took 10 years after the landmark ACEI / ARB trials for them to become established in clinical practice in CKD. The ACD confirms the Committee's conclusion that SGLT2 inhibitors are not currently established NHS practice:" The committee recognised that SGLT2 inhibitors were not established NHS treatment for CKD during the FIDELIO-DKD and FIGARO-DKD trials but could still be ***considered a relevant comparator in the future.***" In addition, "The committee agreed that SGLT2 inhibitor use ***will*** increase and ***become*** incorporated into standard practice." Whether such products may become established treatments in the future is not of course the relevant test under NICE's Methods Guide and we respectfully submit that as it is accepted they are not currently established treatments, they cannot properly be considered as comparators for the purposes of this appraisal. The NICE website currently states that *"a comparator technology is one that is currently used in the NHS and could be replaced by the intervention, if recommended."(22)* An expert view stated at the appraisal committee meeting was that a choice would generally not be made i.e. that finerenone would not *replace* SGLT2i, and that with time, SGLT2i will form part of background therapy, with finerenone being used in combination with SGLT2i or in those unsuitable for SGLT2i. Finally, Bayer would like to point out that the delay in the NICE appraisal of finerenone introduced by NICE, lead to the appraisal committee for finerenone being held after, instead of before, the appraisal committee for dapagliflozin. If the original timelines been followed, then finerenone would have been appraised at committee prior to the decision being taken by NICE regarding dapagliflozin.	considered that finerenone could be given before or with SGLT2 inhibitors and concluded that SGLT2 inhibitors are a relevant comparator. It noted that the comparison of finerenone with SGLT2 inhibitors was still missing. So, finerenone could only be considered as an option in addition to SGLT2 inhibitors, or where these are unsuitable. See sections 3.3 and 3.4 of the FAD.
4	Company	Bayer	The Committee have expressed an interest in reviewing the overlapping data of the FIGARO-DKD study (23) with the FIDELIO-DKD study (12), matching the licensed population i.e. adults with chronic kidney disease (stage 3 and 4 with albuminuria*), * eGFR ≥25ml/min/1.73m^2. Bayer would like to address the comments made in the ACD regarding the results from FIDELIO-DKD being underpowered for the population matching the marketing authorisation. The FIDELIO-DKD label population represents approximately 90% of the entire FIDELIO-DKD population, resulting in a marginal loss of power. FIDELIO-DKD was powered at 90% and the results of the label population are very close to the results of the full FIDELIO-DKD population. This consequently highlights that the FIDELIO-DKD label population provides a solid basis for decision making by NICE.	Comments noted. The committee acknowledged that the clinical evidence from FIDELIO-DKD is relevant. However, it also considered there was overlap in the FIDELIO-DKD and FIGARO-DKD trial

<table>
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Bayer also presented the full analysis set (FAS) from FIDELIO-DKD in the submission and in scenario analysis this was shown to be cost-effective compared to standard of care, with a revised ICER after technical engagement of £11,976 (and corresponding ICER of £6,047 in line with the updated model presented in comment 2).

Bayer's position is that decision making should be based on the FIDELIO-DKD label dataset as this is reflective of the data on which the marketing authorisation was granted. Indeed, there are challenges in providing the overlapping FIDELIO-DKD and FIGARO-DKD data which generate concerns about its validity for decision making, which we set out below:

• The combined analysis of FIDELIO-DKD and FIGARO-DKD limited to the indication ("FIDELIO-label population") was not pre-specified

• Such analysis is combining a subgroup of FIDELIO-DKD with a subgroup from FIGARO-DKD and this is questionable from a statistical point of view

Despite these limitations, Bayer have updated the cost effectiveness model with the data from the FIDELITY analysis for the label population. The FIDELITY analysis (full analysis set) has been published (24) and represents the pre-specified pooled analysis of the FIDELIO-DKD and FIGARO-DKD trials. Bayer sourced data from our global statistical team for the FIDELITY data that matched the population in the marketing authorisation, the "label population" so that this could be applied in the updated cost-effectiveness model.

The inputs from the FIDELITY- label population are presented in Table 6.

The updated inputs include all clinical data available for finerenone, in the population of patients with CKD 3 and CKD 4 patients with albuminuria (i.e., eGFR ≥ 25 to <60ml/min/1.73m^2 at baseline) and type 2 diabetes.

Table 6. CE model inputs, FIDELITY- label population
<table>
<tr><th>Description</th><th>Value</th></tr>
<tr><td>Settings</td><td></td></tr>
<tr><td>Mean age [years]</td><td>[redacted]</td></tr>
<tr><td>Proportion of males</td><td>[redacted]</td></tr>
<tr><td>Cumulative risk of premature discontinuation at 4 years, finerenone</td><td>[redacted]</td></tr>
<tr><td>Proportion of patients with CKD1/2 at baseline</td><td>[redacted]</td></tr>
<tr><td>Proportion of patients with CKD3 at baseline</td><td>[redacted]</td></tr>
<tr><td>Proportion of patients with CKD4 at baseline</td><td>[redacted]</td></tr>
<tr><td>Proportion of patients with CKD 5 w/o RRT at baseline</td><td>[redacted]</td></tr>
</table>
</td><td>
populations. As the results from FIDELIO-DKD were underpowered for the marketing authorisation population, evidence from FIGARO-DKD could give further supportive evidence and reduce uncertainty. See section 3.6 of the FAD.

The committee considered that additional evidence from FIGARO-DKD supports the results of the primary composite outcome in FIDELIO-DKD, but has limitations. See section 3.9 of the FAD.
</td></tr>
</table>

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row		NICE Response Please respond to each comment
			Proportion of patients with Dialysis at baseline	[redacted]	
			Proportion of patients with Kidney Transplant at baseline	[redacted]	
			BT Main Events rates		
			Four-month risk of first modelled CV event, CKD1/2	[redacted]	
			Four-month risk of first modelled CV event, CKD3	[redacted]	
			Four-month risk of first modelled CV event, CKD4	[redacted]	
			Four-month risk of first modelled CV event, CKD 5 w/o RRT	[redacted]	
			Four-month risk of first modelled CV event, Dialysis (acute)	[redacted]	
			Four-month risk of first modelled CV event, Dialysis (post-acute)	[redacted]	
			Four-month risk of first modelled CV event, Kidney Transplant (acute)	[redacted]	
			Four-month risk of first modelled CV event, Kidney Transplant (post-acute)	[redacted]	
			BT other events rates		
			Four-month risk of hyperkalaemia leading to hospitalisation, no modelled CV event	[redacted]	
			Four-month risk of new onset of atrial fibrillation / atrial flutter, no modelled CV event	[redacted]	
			Four-month risk of hyperkalaemia not leading to hospitalisation, no modelled CV event	[redacted]	
			Four-month risk of subsequent CV event, post-CV event	[redacted]	
			Four-month risk of hyperkalaemia leading to hospitalisation, post-CV event	[redacted]	
			Four-month risk of new onset of atrial fibrillation / atrial flutter, post-CV event	[redacted]	
			Four-month risk of hyperkalaemia not leading to hospitalisation, post-CV event	[redacted]	
			BT mortality rates		
			Four-month CV mortality risk, CKD1/2	[redacted]	
			Four-month CV mortality risk, CKD3	[redacted]	
			Four-month CV mortality risk, CKD4	[redacted]	
			Four-month CV mortality risk, CKD5 w/o RRT	[redacted]	
			Four-month CV mortality risk, Dialysis (acute)	[redacted]	
			Four-month CV mortality risk, Dialysis (post-acute)	[redacted]	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment

Four-month CV mortality risk, Kidney Transplant (acute)	[redacted]
Four-month CV mortality risk, Kidney Transplant (post-acute)	[redacted]
Four-month renal mortality risk, CKD5 w/o RRT	[redacted]
HR finerenone	
HR: Onset of eGFR decrease < 15 mL/min, FIN+BT vs BT	[redacted]
HR: Progression to dialysis, FIN + BT vs BT	[redacted]
HR: CV death, FIN + BT vs BT	[redacted]
HR: Renal death, CKD 5 w/o RRT, FIN + BT vs BT	[redacted]
HR: First modelled CV event, FIN + BT vs BT	[redacted]
HR: Subsequent CV event, FIN + BT vs BT	[redacted]
HR: Hyperkalaemia leading to hospitalisation, FIN + BT vs BT	[redacted]
HR: Hyperkalaemia not leading to hospitalisation, FIN + BT vs BT	[redacted]
HR: New onset of atrial fibrillation / atrial flutter, FIN + BT vs BT	[redacted]
CV events distribution	
Proportion of first modelled CV events that are MI	[redacted]
Proportion of first modelled CV events that are IS stroke	[redacted]
Proportion of first modelled CV events that are ICH stroke	[redacted]
Proportion of first modelled CV events that are Hospitalisations for HF	[redacted]

[1]Assumed as weighted average across the FIDELITY-label population, not differentiated by CKD stage, as suggested by ERG (point 6.2.1 of the ERG report)

* The discontinuation has been recalibrated as suggested by the ERG (point 6.1 of the ERG report), to ensure the modelled proportion of patients on treatment at 4 years aligned with the proportion observed in the FIDELIO-DKD study.

The transition probabilities used in the updated model are presented below. The matrix for BT is taken directly from the FIDELITY-label population. For the FIN + BT arm the transition probabilities are obtained as in the new company base case i.e. based on the BT matrix by applying HRs from the FIDELITY-DKD trial. The HRs are presented in the table above (Table 6. CE model inputs, FIDELITY- label population).

The transition matrices are presented below (Table 7, Table 8).

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment

Table 7. Transition probabilities for BT, FIDELITY label

From \ To	CKD1/2	CKD3	CKD4	CKD5 w/o 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 w/o 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]

Table 8. Transition probabilities for FIN + BT, FIDELITY label

From \ To	CKD1/2	CKD3	CKD4	CKD5 w/o 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 w/o 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]

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
Please insert each new comment in a new row</th><th>NICE Response
Please respond to each comment</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><td>Kidney Transplant (acute)</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>

The population-specific inputs have been included in line with the FIDELITY- label population as presented in Table 6, Table 7, and Table 8. All other inputs and assumptions, as they are not population-dependent, remain unchanged (as for the updated FIDELIO-DKD label base case in comment 2).

The deterministic results are presented in the table below (Table 9). The results are based on the updated model as presented in comment 2 (Table 5).

Table 9. Deterministic results, FIDELITY- label population
<table>
<tr><th>Incremental costs, undiscounted</th><th>Incremental costs, discounted</th><th>Incremental QALYs, undiscounted</th><th>Incremental QALYs, discounted</th><th>ICER, undiscounted</th><th>ICER, discounted</th></tr>
<tr><td>£1,102</td><td>£1,016</td><td>0.12</td><td>0.08</td><td>£9,167</td><td>£12,710</td></tr>
</table>
</td><td></td></tr>
<tr><td>5</td><td>Company</td><td>Bayer</td><td>As explained in comment 3 above, Bayer is not presenting a cost-effectiveness scenario analysis of finerenone used at second line (compared with SGLT2 inhibitors in an SGLT2 inhibitor-naive population). We have been advised by clinicians that they would like finerenone to be made available as an option for add-on to standard of care with ACEI/ARB in line with the marketing authorisation. Indeed, clinical experts stated during the meeting, as reflected in the ACD that “a range of therapies are needed to target different causes of kidney damage, and that all of these treatments will likely work together for better renal protection than any of them alone”.

We have been advised by experts however that finerenone will primarily be initiated in patients who are unsuitable for SGLT2i or as add-on to SGLT2i in those with high residual risk of adverse outcomes, in line with the marketing authorisation.

Further, clinicians have advised us that it is possible to define the patients who are unsuitable for, or who become intolerant of, SGLT2i. Whilst Bayer maintain the position that these drugs are not yet standard of care, we have been advised that for patients who cannot take SGLT2i, then finerenone addresses a “substantial unmet medical need” as the alternative for these patients is standard of care with ACEI/ ARB alone. Please see more detail regarding this group and the expert consensus statement leading to this definition in comments 9 and 10.

To address the request in the ACD (data for add-on to SGLT2 inhibitors), we set out below the supportive evidence for combined use of finerenone in addition to standard of care with ACEI/ARB plus SGLT2i with associated cost-effectiveness analysis.

Supportive evidence for combined use of finerenone and SGLT2i</td><td>Comments noted. The committee considered that finerenone could be given before or with SGLT2 inhibitors and concluded that SGLT2 inhibitors are a relevant comparator. It noted that the comparison of finerenone with SGLT2 inhibitors was still missing. So, finerenone could only be considered as an option in addition to SGLT2 inhibitors, or where these are unsuitable. See sections 3.3 and</td></tr>
</table>

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Analysis of FIDELIO-DKD data and FIDELITY data In the FIDELIO-DKD sub analysis considering baseline use of SGLT2i, the benefits of finerenone on kidney and CV outcomes in patients with CKD and T2D appeared consistent in the absence or presence of SGLT-2i use at baseline (interaction p-value 0.21 and 0.46, respectively), or at any time during the trial (25). Regarding safety, this was balanced with or without SGLT-2i use at baseline, with fewer hyperkalaemia events with finerenone in the SGLT-2i group (8.1% vs. 18.7% without) (25). An analysis of the relationship between finerenone exposure in the FIDELIO-DKD study and the time to reach the key composite kidney endpoint, including prognostic factor (PF) such as baseline use of SGLT-2is or non-use was conducted. The Kaplan-Meier (KM) curves indicated a time-to-event (TTE) approach when a Weibull hazard model was used to investigate the exposure/response (ER). Co-medications with SGLT-2is decrease the hazard for the primary endpoint by [redacted]% (95% CI: [redacted]%) indicating an additive effect on top of finerenone; SGLT2i use did not significantly modify the drug effect (26). The pre-specified FIDELITY analysis can provide more information on combination use of finerenone with SGLT2i. In this analysis set, 6.7% of patients were receiving SGLT2i at baseline and in the finerenone group, 11.8% of patients initiated SGLT2i after start of study drug (24). The benefits of finerenone on kidney and CV outcomes in patients with CKD and T2D in the FIDELITY analysis appeared consistent in the absence or presence of SGLT-2i use at baseline (interaction p-value [redacted] and [redacted], respectively), with the HRs [redacted] combined use of SGLT2i and finerenone. **UACR** Due to the low number of subjects with events in the FIDELIO-DKD trial, interpretability of subgroup data is limited, and UACR, a key predictor for CKD progression as strongly correlated with ESRD and a marker of CV risk, is perceived as the most applicable parameter to show efficacy (27). A similar reduction in UACR from baseline to month 4 in the FIDELIO-DKD study was observed after treatment with finerenone in those who received an SGLT-2i at baseline and those who did not, with a 25% and a 31% reduction versus placebo, respectively (ratio of least-squares means = 0.75, 95% CI = 0.62–0.90 with an SGLT-2i and 0.69, 95% CI = 0.66–0.71 without an SGLT-2i, $P_{interaction}$ = 0.31). The lower mean UACR observed with finerenone compared with placebo at month 4 was maintained for the duration of the study with no apparent effect of SGLT-2i treatment at baseline (25). The data reveal that finerenone improved UACR reduction in patients who were already receiving an SGLT-2i, i.e. a drug known to reduce UACR (25). **Figure 1: Line plot for least square means for ratio to baseline of UACR values by visit and by SGLT-2 inhibitor use at baseline = YES (FAS)(27)**	3.4 of the FAD. The committee considered the evidence presented for the scenario analyses for use of finerenone as add on to standard care including SGLT2 inhibitors in its decision making. See section 3.10 of the FAD.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			 BAY 94 – 8862 = Finerenone In 2018, a workshop led by the National Kidney Foundation, in collaboration with the FDA and EMA, evaluated whether changes in albuminuria or eGFR could be surrogate end points for kidney disease progression in clinical trials, and it was concluded that a UACR reduction of 21% to 27% is predictive of a benefit in clinical outcome in patients with UACR ≥30mg/g (28). As described above, finerenone was found in the FIDELIO-DKD study to reduce UACR by an additional 25% in those patients receiving SGLT2i at baseline. To further explore the benefit of finerenone added to SGLT-2i use over time, SGLT-2i use was applied as a time dependent covariate. Cox proportional hazards models including SGLT-2i intake as time-dependent covariate with and without variable selection for the primary renal endpoint demonstrated the [redacted] (27). In addition, SGLT-2i use was tested (*posthoc*) for its potential to modify the treatment effect of finerenone in popPK	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			analyses along with exposure versus time-to-event evaluations for the primary kidney composite endpoint based on FIDELIO-DKD data. [redacted] (27). A population pharmacokinetic/pharmacodynamics (popPKPD) model was developed to assess the finerenone dose-exposure-response relationship for urine albumin-to creatinine ratio (UACR) and eGFR and the impact of combined SGLT2i-finerenone use using patient level data from the FIDELIO-DKD trial. The popPKPD model adequately described effects of finerenone exposure in reducing UACR and slowing eGFR decline over time. The reduction in UACR achieved with finerenone during the first year predicted its subsequent effect in slowing progressive eGFR decline. SGLT2i use did not modify finerenone efficacy and indicated with 97.5% confidence that finerenone was at least 94.1% as efficacious in reducing UACR in patients using SGLT2i compared with patients not using an SGLT2i. The results demonstrate independent and additive effects of SGLT2i on top of finerenone (29, 30). A post hoc analysis of the CREDENCE trial reported that each 30% decrease in UACR over the first 26 weeks of canagliflozin treatment was independently associated with a lower hazard of cardiorenal events. It was also observed that there was a strong association between residual UACR at week 26 with cardiorenal outcomes; and residual albuminuria at week 26 of canagliflozin therapy was associated with similar cardiorenal risk as patients who received placebo (31). These findings underscore the likelihood that any therapies that confer further lowering of UACR on top of that from SGLT-2is, as is the case with finerenone, are likely to provide additional kidney and cardiovascular benefits beyond those of SGLT-2is alone (25). Indeed, clinical experts at the committee meeting advised that proteinuria is a “red flag” to be treated. **Summary** In summary, it can be concluded that co-administration of finerenone and SGLT-2i results in an independent and additive benefit on clinical outcomes. The additive effect is most evident from the additional UACR reduction of 25% in subjects already treated with an SGLT-2i at baseline, a treatment that is known to reduce albuminuria, and [redacted]. UACR is considered the most appropriate marker to show renal efficacy in smaller subgroups providing sufficient power due to its strong correlation to kidney failure. Complementary to the clinical data, [redacted] (27). **Cost-effectiveness analysis of combined use of finerenone and SGLT2i** Use of SGLT2 inhibitors as part of background therapy (BT) impacts the baseline risk of CKD progression and CV events among patients with CKD and T2D. To address this issue, an SGLT2is adjustment has been incorporated into the CE model, in order not to overestimate the absolute QALY gain with finerenone.	

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
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Please respond to each comment</th></tr>
<tr><td></td><td></td><td></td><td>
It has been assumed that the impact of SGLT2 inhibitors on modelled events is reflected by the HRs for CKD progression, CV death, and risk of first CV event according to the results of the DAPA-CKD study (32) (Table 10). Dapagliflozin has been selected as the SGLT2i for this analysis due to the recent publication of a NICE technology appraisal (16).

Table 10. HRs – dapagliflozin adjustment based on DAPA-CKD trial
<table>
<tr><th>Description</th><th>HR: Dapagliflozin + BT vs BT [95%CI]</th></tr>
<tr><td>Onset of eGFR decrease < 15 mL/min/1.73m2 sustained over at least 4 weeks (days)</td><td>0.73 [0.52;1.03]</td></tr>
<tr><td>Progression to dialysis</td><td>0.68 [0.47;0.98]</td></tr>
<tr><td>Progression to kidney transplant</td><td>1.00 [1.00;1.00]</td></tr>
<tr><td>First CV event (endpoint from DAPA-CKD study: CV death or hospital admission for HF)</td><td>0.70 [0.53;0.92]</td></tr>
</table>

The HRs, as presented in Table 10, were first used to calculate probabilities for non-SGLT2 inhibitors users and SGLT2 inhibitors users based on BT data from FIDELIO-DKD, in which 6.2% of patients used SGLT2 inhibitors. The probabilities were then weighted by the proportion of SGLT2 inhibitors users considered in the model (assumed 100%). This is further explained below.

The transition probabilities from FIDELIO-DKD for BT (for all patients i.e., SGLT2 inhibitors users and those who do not use SGLT2 inhibitors) were adjusted with the use of HRs from Table 10

• CKD progression: two publicly available HRs for SGLT2 inhibitors were used:
  o time to a sustained decrease in eGFR to <15mL/min/1.73 m^2
  o time to dialysis,
• CV events: HRs for time to CV death or hospital admission for HF.

The following formula is used to calculate the probability for all patients in the FIDELIO-DKD trial:

$$P_{ALL} = \%\ SGLT2 * (1 - (1 - P_{nonSGLT2})^{HR}) + (1 - \%\ SGLT2) * P_{nonSGLT2}$$
P_{ALL} – probability for all patients in FIDELIO-DKD, % SGLT2 – percentage of SGLT2 inhibitors users in
</td><td></td></tr>
</table>

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
Please insert each new comment in a new row</th><th>NICE Response
Please respond to each comment</th></tr>
<tr><td></td><td></td><td></td><td>
FIDELIO-DKD, HR – based on the clinical results for SGLT2 inhibitors (e.g., DAPA-CKD), $P_{nonSGLT2}$ – probability for patients who do not use SGLT2 inhibitors in FIDELIO-DKD.

Thus, a specific probability for patients who do not use SGLT2 inhibitors in FIDELIO-DKD is calculated. Based on this, and the HRs for SGLT2 inhibitors, the model calculates the weighted probability with the assumption that 100% of patients use SGLT2 inhibitors as part of BT.

The results from the model for the scenario that 100% of patients use SGLT2is as part of BT are presented in Table 11 below.

Table 11. Deterministic results, FIDELIO-DKD label – add-on to SGLT2I
<table>
<tr><th>Incremental costs, undiscounted</th><th>Incremental costs, discounted</th><th>Incremental QALYs, undiscounted</th><th>Incremental QALYs, discounted</th><th>ICER, undiscounted</th><th>ICER, discounted</th></tr>
<tr><td>£1,344</td><td>£1,216</td><td>0.14</td><td>0.09</td><td>£9,771</td><td>£12,984</td></tr>
</table>
As discussed in comment 2, Bayer considers that the FIDELIO-DKD data presented in our submission provides a solid basis for decision making, with the FIDELITY analysis subject to limitations when considering the label population. However, we present the same analysis below for the FIDELITY-label population.

Table 12. Deterministic results, FIDELITY- label – add-on to SGLT2I
<table>
<tr><th>Incremental costs, undiscounted</th><th>Incremental costs, discounted</th><th>Incremental QALYs, undiscounted</th><th>Incremental QALYs, discounted</th><th>ICER, undiscounted</th><th>ICER, discounted</th></tr>
<tr><td>£1,737</td><td>£1,528</td><td>0.10</td><td>0.07</td><td>£17,476</td><td>£23,432</td></tr>
</table>
Discussions with clinical experts indicate that finerenone would initially be added to an SGLT2i (and ACEI/ARB) in those patients at highest risk of adverse outcomes. Such a group would be those with persistent albuminuria.

A review paper considering the role of albuminuria in detecting cardio-renal risk and outcome in diabetes, reports that increased albuminuria promotes higher tubular albumin reabsorption, with consequent intra-renal trafficking, which in turn activates the release of several inflammatory and pro-fibrotic mediators accelerating renal damage. The review goes on to state that these mechanisms explain why albuminuria is now considered the principal risk factor predicting the faster progression of renal disease towards end-stage renal disease (ESRD) (33). Indeed, albuminuria is a strong predictor of the risk of adverse outcomes in CKD (28) and a higher ACR has been found to be significantly associated with mortality and ESRD in these patients (34).

In a paper that reports the results of an individual patient-level Bayesian meta-analysis of treatment comparisons
</td><td></td></tr>
</table>

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			from RCTs, it was found that across all studies, with a meta-regression slope of 0·89 (95% Bayesian credible interval [BCI] 0·13–1·70), each 30% decrease in geometric mean albuminuria by the treatment relative to the control was associated with an average 27% lower hazard for the clinical endpoint (composite of treated end-stage kidney disease, eGFR < 15ml/ min/ 1.73m^2, or doubling of serum creatinine), (95% BCI 5–45%; median R^2 0·47, 95% BCI 0·02–0·96). The association strengthened after restricting analyses to patients with baseline albuminuria of more than 30 mg/g (i.e. 3·4 mg/mmol; R^2 0·72, 0·05–0·99]) (35). Patients with CKD who fall within the eGFR category of G3a – G4 and have albuminuria levels that place them in the category A3 are all at very high risk of adverse outcomes according to the KDIGO classification (see figure below)(36). **Figure 2: Prognosis of CKD by GFR and albuminuria category (KDIGO)**	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment

Prognosis of CKD by GFR and albuminuria category

Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012

GFR categories (ml/min per 1.73 m²) Description and range			Persistent albuminuria categories Description and range: A1 Normal to mildly increased <30 mg/g <3 mg/mmol	A2 Moderately increased 30–300 mg/g 3–30 mg/mmol	A3 Severely increased >300 mg/g >30 mg/mmol
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.

In an as yet unpublished CPRD analysis of patients with T2D and CKD, [redacted] (37).

In addition to expert opinion, there is therefore biological plausibility that patients with high levels of albuminuria could be a priority group for further optimisation of therapy to reduce the risk of adverse renal and CV outcomes.

As described above, data from FIDELIO-DKD reveal that finerenone improved UACR reduction by 25% in patients who were already receiving an SGLT-2i, i.e. a drug known to reduce UACR (25)

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
Please insert each new comment in a new row</th><th>NICE Response
Please respond to each comment</th></tr>
<tr><td></td><td></td><td></td><td>Bayer have explored the cost-effectiveness of add-on therapy (to ACEI/ARB and SGLT2i), in a particularly high-risk subgroup, should NICE consider that finerenone cannot be recommended in a wider population. This subgroup defined by eGFR and UACR is as follows;

Patients from the label population from FIDELITY in the A3 category of albuminuria i.e. eGFR ≥ 25 – < 60 + A3 (i.e., albuminuria >= 300mg/g).

In line with the inclusion/exclusion criteria for the FIGARO-DKD and FIDELIO-DKD trials, this population comes exclusively from the FIDELIO-DKD trial.

The results are presented in the table below, Table 13

Table 13. Deterministic results, FIDELITY- label + A3 – add-on to SGLT2I
<table>
<tr><th>Incremental costs, undiscounted</th><th>Incremental costs, discounted</th><th>Incremental QALYs, undiscounted</th><th>Incremental QALYs, discounted</th><th>ICER, undiscounted</th><th>ICER, discounted</th></tr>
<tr><td>£748</td><td>£768</td><td>0.12</td><td>0.08</td><td>£6,249</td><td>£9,554</td></tr>
</table></td><td></td></tr>
<tr><td>6</td><td>Company</td><td>Bayer</td><td>An external validation was conducted to test the credibility of the cost-effectiveness model. The objective of the external validation step was to ensure that the model results are in line with the FIDELIO-DKD outcomes. The incidence of first CV events and CV deaths, as well as, the number of patients undergoing dialysis were compared with the model predictions. For each of the above-mentioned outcomes, a Kaplan–Meier curve for the observed cumulative event-free survival data from the trial was plotted against the cumulative event-free survival curve predicted by the model.

In order to test the null hypothesis of no difference between observed and predicted survival curves, Guyot's algorithm was used to produce patient level data from survival probabilities given by the model. The following statistical tests were then performed to assess whether the modelled survival coincided with that observed in the study:

- Log-rank test (using tests from survival and coin packages in R),

- Gehan-Breslow test.

The following assumptions were applied in the model for the purposes of this validation:

• A 48-month time horizon was considered (in line with FIDELIO-DKD follow-up period).

• Background mortality was not included.

• The increased mortality risk due to CKD stage as well as after the first CV event was not included.</td><td>Comments noted. The committee considered that structurally the company's model was suitable for decision making. However, it also considered that the company's updated transition probabilities are uncertain. See section 3.12 and 3.14 of the FAD.</td></tr>
</table>

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
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Half-cycle correction was not considered.
For the number of patients undergoing dialysis, no dialysis was initiated in the model in the first three cycles (to reflect the FIDELIO-DKD data)
No discontinuation was applied for the FIN+BT.

The model was validated on the overall population (ITT population) based on patient level data from FIDELIO-DKD.

The model results reflect the incidence of the first CV event observed in the FIDELIO-DKD trial. The model estimations for BT (Figure 3) are within the range of the FIDELIO-DKD confidence intervals (CIs).

The use of the HR in the model for the time to first CV event (0.87 in range [0.74;1.02]) for finerenone + BT vs. BT reflects the study results well (Figure 4).

The confidence intervals, determined by using lower and higher bounds of the HR from FIDELIO-DKD in the model, also coincide with the confidence intervals directly from FIDELIO-DKD (Figure 5).

The results of the statistical tests indicate no reason to reject the null hypothesis of no difference between observed and modelled curves. The estimated p-values are presented in the table below.

Table 14. P-values for statistical tests comparing first CV event-free survival curves
<table>
<tr><th>Test</th><th>Log rank (survival package)</th><th>Log rank (coin package)</th><th>Gehan-Breslow</th></tr>
<tr><td>BT</td><td>0.900</td><td>0.916</td><td>0.784</td></tr>
<tr><td>FIN+BT</td><td>0.800</td><td>0.831</td><td>0.782</td></tr>
</table>
</td><td></td></tr>
</table>

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Figure 3 Time to first CV event for BT: model vs. FIDELIO-DKD results 	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Figure 4. Time to first CV event for finerenone + BT: model vs. FIDELIO-DKD results 	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Figure 5. Time to first CV event for finerenone + BT with CIs for HR: model vs. FIDELIO-DKD results  The validation demonstrates that the model reflects the CV mortality from FIDELIO-DKD. The estimates generated for BT indicate that the model predictions are within the range of the CIs directly observed in FIDELIO-DKD (Figure 6). The use of the HR for the time to CV death (0.86 in range [0.68;1.08]) for finerenone + BT vs. BT in the model upfront to BT risks, also reflects the study results well (Figure 7). The confidence intervals, determined by applying the lower and higher bounds of the HR from FIDELIO-DKD (0.68 and 1.08) to the model, also coincide with the CIs directly from FIDELIO-DKD (Figure 8) Moreover, the results of the statistical tests indicate that there is no reason to reject the null hypothesis of no difference between observed and modelled curves. The estimated p-values are presented in the table below. **Table 15. P-values for statistical tests comparing CV death-free survival curves**	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment

Test	**Log rank** (survival package)	**Log rank** (coin package)	**Gehan-Breslow**
BT	0.700	0.711	0.756
FIN + BT	0.600	0.650	0.851

Figure 6. Time to CV death for BT: model vs. FIDELIO-DKD results

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Figure 7. Time to CV death for finerenone + BT: model vs. FIDELIO-DKD results 	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Figure 8. Time to CV death for finerenone + BT with CIs for HR: model vs. FIDELIO-DKD results  It should be noted that, at the beginning of the FIDELIO-DKD trial, very few patients were observed starting dialysis. In the model, the rate of dialysis per cycle was calculated as an average across the entire follow-up of FIDELIO-DKD. Therefore, visual inspection of validation results showed that the model slightly overestimated the incidence of dialysis when the average rate of dialysis was used in the first few cycles. However, at the end of the FIDELIO-DKD duration (four years), the incidence of dialysis observed in the trial was consistent with model predictions. 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. Validation results presented below were generated assuming no dialysis in the model in the first three cycles. With this assumption, the incidence of dialysis predicted by the model coincides with that observed in FIDELIO-DKD. The estimates generated for BT indicate that the model predictions fall within the range of CIs directly observed in FIDELIO-DKD (Figure 9). The estimates generated for finerenone + BT arm also reflect the study results well (Figure 10)	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Moreover, the result of statistical testing indicates that there are no reasons to reject the null hypothesis of no difference between observed and modelled curves. The estimated p-values are presented in the table below.	

Table 16. P-values for statistical tests comparing dialysis-free survival curves

Test	**Log rank** (survival package)	**Log rank** (coin package)	**Gehan-Breslow**
BT	0.700	0.709	0.590
FIN+BT	1.000	0.956	0.945

Figure 9. Time to dialysis for BT: model vs. FIDELIO-DKD results

-

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Figure 10. Time to dialysis for finerenone + BT: model vs. FIDELIO-DKD results -  The validation has been also conducted based on the FIDELITY-DKD data. The same approach has been undertaken, and the results are presented in the graphs below. The model estimations for BT (Figure 11) are within the range of the FIDELITY confidence intervals (CIs). The use of the HR in the model for the time to first CV event (0.88 in range [0.76; 1.03]) for finerenone + BT vs. BT reflects the study results well (Figure 12) The confidence intervals, determined by using lower and higher bounds of the HR from FIDELITY in the model, also coincide with the CIs directly from the study (Figure 13) The results of the statistical tests indicate no reason to reject the null hypothesis of no difference between observed and modelled curves. The estimated p-values are presented in the table below (Table 17).	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment

Table 17. P-values for statistical tests comparing first CV event-free survival curves.

Test	**Log rank** (survival package)	**Log rank** (coin package)	**Gehan-Breslow**
BT	0.600	0.651	0.857
BT + finerenone	0.500	0.550	0.911

Figure 11 Time to first modelled CV event for BT: model vs. FIDELITY results

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Figure12. Time to first modelled CV event for finerenone + BT: model vs. FIDELITY results  **Figure 13. Time to first modelled CV event for finerenone + BT with CIs for HR: model vs. FIDELITY results** 	

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
Please insert each new comment in a new row</th><th>NICE Response
Please respond to each comment</th></tr>
<tr><td></td><td></td><td></td><td>

CV death

The validation demonstrates that the model reflects the CV mortality from FIDELITY. The estimates generated for BT indicate that the model predictions are within the range of the CIs directly observed in the FIDELITY study (Figure 14).

The estimated modelled number of cardiovascular deaths based on the HR for the time to CV death (0.88 in range [0.76; 1.02]) for finerenone + BT vs. BT, also reflect the study results (Figure15).

The confidence intervals, determined by applying the lower and higher bounds of the HR from FIDELITY to the model, also coincide with the CIs directly from the trial (Figure 16).

Moreover, the results of the statistical tests indicate that there is no reason to reject the null hypothesis of no difference between observed and modelled curves. The estimated p-values are presented in the table below (Table 18).

Table 18. P-values for statistical tests comparing CV death-free survival curves.

Test	**Log rank** (survival package)	**Log rank** (coin package)	**Gehan-Breslow**
BT	0.600	0.636	0.597
BT + finerenone	0.600	0.636	0.795

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Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Figure 14. Time to CV death for BT: model vs. FIDELITY results  **Figure 15. Time to CV death for finerenone + BT: model vs. FIDELITY results** 	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Figure 16. Time to CV death for finerenone + BT with CIs for HR: model vs. FIDELITY results  ***Number of patients undergoing dialysis*** The incidence of dialysis predicted by the Bayer model coincides with that observed in FIDELITY. The estimates generated for BT (Figure 17) indicate that the model predictions are mostly within the range of the FIDELITY confidence intervals (CIs). The immediate application of the HR for the time to dialysis (0.82 in range [0.65; 1.03]) for finerenone + BT vs. BT in the model reflects the study results well (Figure 18). The confidence intervals, determined by applying the lower and higher bounds of the HR from FIDELITY to the model, are also consistent with the CIs directly from the FIDELITY analysis (Figure 19). Moreover, the results of the statistical tests indicate that there are no reasons to reject the null hypothesis of no difference between observed and modelled curves. The estimated p-values are presented in the table below (Table 19). **Table 19. P-values for statistical tests comparing dialysis-free survival curves.** **Test** | **Log rank** (survival | **Log rank** (coin | **Gehan-Breslow**	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment

	package)	package)	
BT	0.100	0.124	0.199
BT + finerenone	0.500	0.492	0.686

Figure 17. Time to dialysis for BT: model vs. FIDELITY results

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Figure18. Time to dialysis for finerenone + BT: model vs. FIDELITY results  **Figure 19. Time to dialysis for finerenone + BT with CIs for HR: model vs. FIDELITY results** 	

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
Please insert each new comment in a new row</th><th>NICE Response
Please respond to each comment</th></tr>
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Furthemore, in order to further validate the model estimates, a comparison of patients' distribution across the modelled health states with the trial data has been performed, as requested in the ACD.

The comparison has been made between:

• The percentage of patients in each CKD stage, at the end of each 4-month period, based on the trial data for FIDELIO-DKD - label population (separately for BT, and FIN+BT arm)

• The percentage of patients in each CKD stage, at the end of each 4-month cycle in the CE model for finerenone

The model includes all assumptions as for the external validation (presented at the beginning of this section). Results of the performed comparison are presented in the tables below (Table 20, Table 21).

Table 20. Percentage of patients in each CKD stage, at the end of each 4-month period, BT arm
<table>
<tr><th>Months</th><th>0</th><th>4</th><th>8</th><th>12</th><th>16</th><th>20</th><th>24</th><th>28</th><th>32</th><th>36</th><th>40</th><th>44</th><th>48</th></tr>
<tr><td>FIDELIO-label</td></tr>
<tr><td>CKD 1/2</td><td>0%</td><td>5%</td><td>5%</td><td>5%</td><td>4%</td><td>4%</td><td>3%</td><td>3%</td><td>3%</td><td>3%</td><td>2%</td><td>3%</td><td>4%</td></tr>
<tr><td>CKD 3</td><td>88%</td><td>80%</td><td>75%</td><td>73%</td><td>69%</td><td>67%</td><td>63%</td><td>59%</td><td>56%</td><td>54%</td><td>53%</td><td>49%</td><td>49%</td></tr>
<tr><td>CKD 4</td><td>12%</td><td>15%</td><td>18%</td><td>20%</td><td>24%</td><td>26%</td><td>29%</td><td>30%</td><td>31%</td><td>33%</td><td>34%</td><td>36%</td><td>34%</td></tr>
<tr><td>CKD 5</td><td>0%</td><td>0%</td><td>0%</td><td>1%</td><td>1%</td><td>2%</td><td>3%</td><td>4%</td><td>5%</td><td>4%</td><td>5%</td><td>5%</td><td>5%</td></tr>
<tr><td>Dialysis</td><td>0%</td><td>0%</td><td>0%</td><td>0%</td><td>1%</td><td>1%</td><td>2%</td><td>3%</td><td>3%</td><td>4%</td><td>4%</td><td>6%</td><td>8%</td></tr>
<tr><td>Transplant</td><td>0%</td><td>0%</td><td>0%</td><td>0%</td><td>0%</td><td>0%</td><td>0%</td><td>0%</td><td>0%</td><td>0%</td><td>0%</td><td>0%</td><td>0%</td></tr>
<tr><td>CE model</td></tr>
<tr><td>CKD 1/2</td><td>0%</td><td>2%</td><td>3%</td><td>4%</td><td>4%</td><td>4%</td><td>4%</td><td>4%</td><td>4%</td><td>4%</td><td>3%</td><td>3%</td><td>3%</td></tr>
<tr><td>CKD 3</td><td>88%</td><td>79%</td><td>73%</td><td>69%</td><td>65%</td><td>63%</td><td>61%</td><td>59%</td><td>58%</td><td>57%</td><td>55%</td><td>54%</td><td>53%</td></tr>
<tr><td>CKD 4</td><td>12%</td><td>18%</td><td>22%</td><td>25%</td><td>27%</td><td>29%</td><td>29%</td><td>30%</td><td>30%</td><td>30%</td><td>30%</td><td>30%</td><td>30%</td></tr>
<tr><td>CKD 5</td><td>0%</td><td>1%</td><td>1%</td><td>2%</td><td>3%</td><td>3%</td><td>4%</td><td>4%</td><td>4%</td><td>4%</td><td>4%</td><td>4%</td><td>5%</td></tr>
<tr><td>Dialysis</td><td>0%</td><td>0%</td><td>0%</td><td>0%</td><td>1%</td><td>1%</td><td>2%</td><td>3%</td><td>4%</td><td>5%</td><td>6%</td><td>7%</td><td>8%</td></tr>
<tr><td>Transplant</td><td>0%</td><td>0%</td><td>0%</td><td>0%</td><td>0%</td><td>0%</td><td>0%</td><td>0%</td><td>0%</td><td>0%</td><td>0%</td><td>0%</td><td>0%</td></tr>
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Table 21. Percentage of patients in each CKD stage, at the end of each 4-month period, Finerenone+BT arm
<table>
<tr><th>Months</th><th>0</th><th>4</th><th>8</th><th>12</th><th>16</th><th>20</th><th>24</th><th>28</th><th>32</th><th>36</th><th>40</th><th>44</th><th>48</th></tr>
<tr><td>FIDELIO-label</td></tr>
<tr><td>CKD 1/2</td><td>0%</td><td>3%</td><td>3%</td><td>2%</td><td>2%</td><td>2%</td><td>2%</td><td>2%</td><td>3%</td><td>2%</td><td>2%</td><td>2%</td><td>2%</td></tr>
<tr><td>CKD 3</td><td>89%</td><td>77%</td><td>74%</td><td>72%</td><td>69%</td><td>66%</td><td>64%</td><td>60%</td><td>59%</td><td>58%</td><td>56%</td><td>55%</td><td>58%</td></tr>
<tr><td>CKD 4</td><td>11%</td><td>19%</td><td>22%</td><td>25%</td><td>27%</td><td>28%</td><td>29%</td><td>31%</td><td>30%</td><td>31%</td><td>32%</td><td>32%</td><td>30%</td></tr>
<tr><td>CKD 5</td><td>0%</td><td>0%</td><td>0%</td><td>0%</td><td>1%</td><td>1%</td><td>2%</td><td>3%</td><td>4%</td><td>4%</td><td>4%</td><td>4%</td><td>5%</td></tr>
</table>
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</table>

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment

Dialysis	0%	0%	0%	0%	1%	1%	2%	2%	3%	4%	5%	6%	5%
Transplant	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
CE model													
CKD 1/2	0%	2%	3%	4%	4%	4%	4%	4%	4%	3%	3%	3%	3%
CKD 3	88%	79%	72%	68%	64%	61%	59%	57%	56%	55%	53%	52%	51%
CKD 4	12%	18%	22%	25%	27%	28%	29%	29%	30%	30%	29%	29%	29%
CKD 5	0%	0%	1%	2%	2%	3%	3%	3%	4%	4%	4%	4%	4%
Dialysis	0%	0%	0%	0%	1%	1%	2%	2%	3%	4%	5%	6%	6%
Transplant	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%

Please find below the graphs corresponding tothe results in Table 20 and Table 21.

Figure 20. Percentage of patients in each CKD stage, at the end of each 4-month period, BT arm

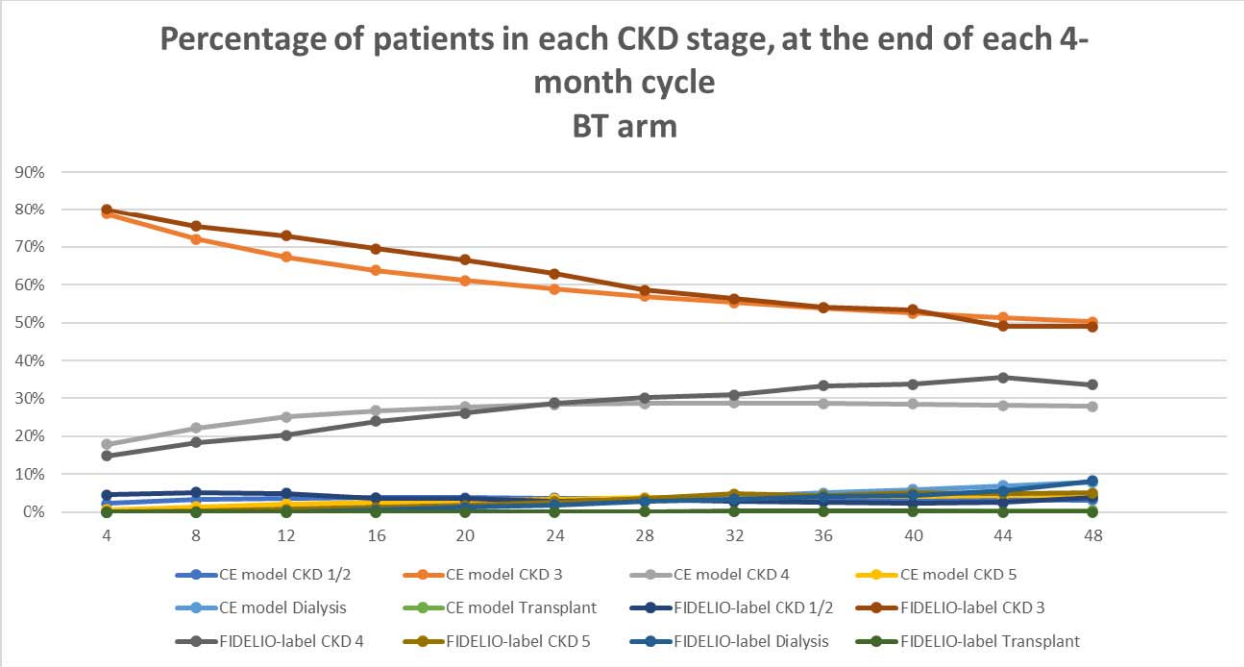
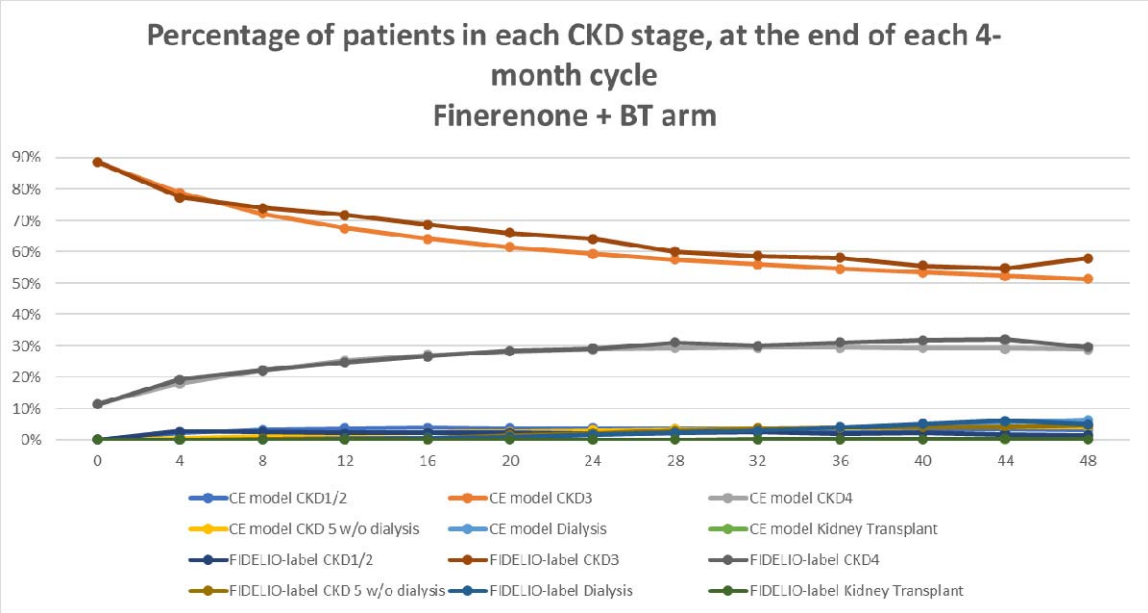
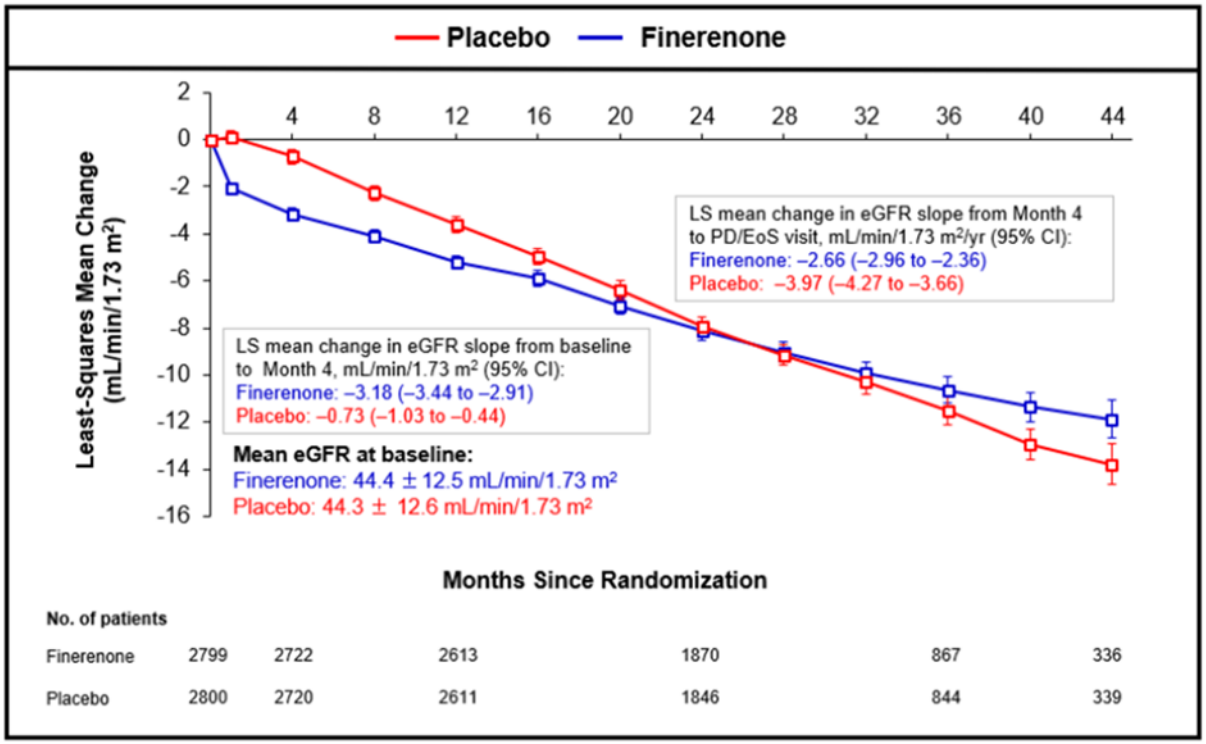
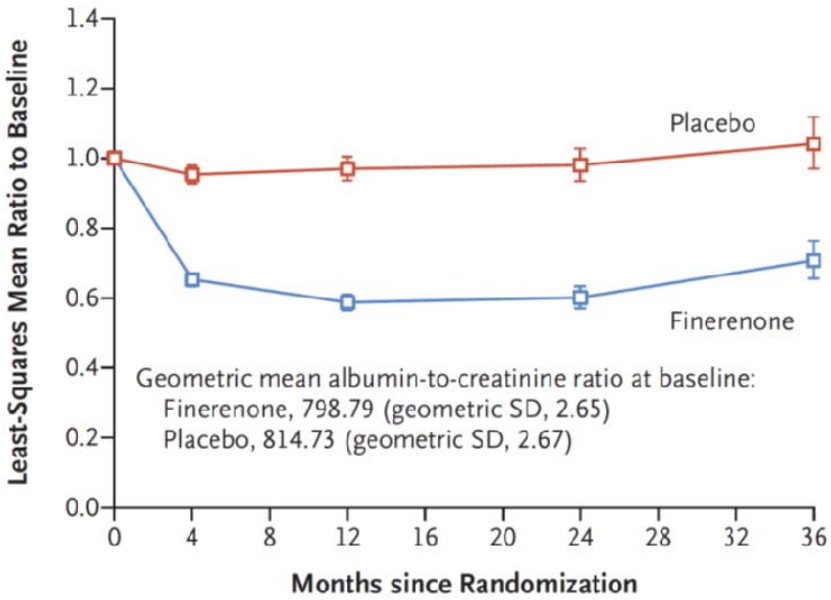


Figure 21. Percentage of patients in each CKD stage, at the end of each 4-month period, BT arm

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
				
7	Company	Bayer	Bayer are asked to explore the potential for a waning of effect for finerenone. Bayer do not consider this to be appropriate for the reasons as set out below. With continued use, the effect of finerenone treatment is persistent and the FIDELIO-DKD data supports the treatment effect of finerenone during a median follow-up of 2.6 years. Bayer provided as an appendix to the main submission (Appendix L) the proportional hazard assumption justification i.e. demonstrating that there is no evidence that the proportional hazard assumption was not met. In summary, the plausibility of the proportional hazard's assumption can be assessed by visually examining: - the plot of the log of the negative log of Kaplan-Meier estimates of the survival function versus the log of time for evidence of non-parallelism; - the smoothed plot of the scaled Schoenfeld residuals to directly visualise the log hazard ratio; - by including a time-treatment interaction term in the Cox model (time log transformed).	Comments noted. The committee considered that uncertainty around the treatment waning effect was inherent beyond the trial period. It also considered that extrapolating relative treatment effects beyond the 4 years seen in the trial was uncertain, but that the company had

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			The significance of the interaction was tested at the 5% type I error level. If the interaction is significant and there is strong evidence of non-proportionality from the plots, time-dependent hazard ratios should be estimated within the model that includes the interaction term. Two outcomes from FIDELIO-DKD were considered: - Time to onset of kidney failure, a sustained decrease of eGFR 40% or renal death (days) (primary outcome from FIDELIO-DKD); - Time to first occurrence of non-fatal CV event (days) (component of key secondary outcome from FIDELIO-DKD). It was determined that there was no evidence against the proportional hazards assumption. Further analysis was also presented by Bayer in response to ERG clarification question A8. When the potential for waning of treatment effect was discussed at committee, the clinical expert opinion was that biologically there is no reason why finerenone benefits would decline over time. There was a suggestion that patients would have better results the longer that they are on treatment and therefore the relative benefit may increase over time. Indeed, in the FIDELIO-DKD study, a more pronounced effect of finerenone on the key composite kidney outcome has been shown in the on-treatment population (all events whilst on treatment and ≤30 days after the last dose of study medication following permanent discontinuation) compared with the ITT population (HR: 0.78 (95% CI: 0.68-0.89) vs HR: 0.82 (95% CI: 0.73–0.93, respectively). A similar effect has been confirmed for the key composite cardiovascular outcome (HR: 0.78 (95% CI: 0.66–0.92) vs HR: 0.86 (95% CI: 0.75–0.99) for the on-treatment analysis and ITT analysis, respectively)(12). A constant treatment effect was observed for finerenone based on the least-squares mean change from the baseline in the eGFR slope in the FIDELIO-DKD study. Aside from the initial decrease in eGFR in the first month, which was more pronounced, treatment with finerenone was associated with a consistently slower decrease in eGFR compared with placebo over the whole study follow-up (up to 44 months). This may imply that the trajectory would continue in a linear fashion. **Figure 22: Effect of finerenone and placebo on eGFR; FIDELIO-DKD study**	made a reasonable attempt to explore this. See section 3.15 of the FAD.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			 Further support for a persistence of effect comes from the analysis of change in UACR during the FIDELIO-DKD study. 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 (see figure 23 below). **Figure 23: Urinary albumin-to-creatinine ratio (FAS) (12)**	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			 **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 In the pre-specified CSR analyses for FIDELIO-DKD, Bayer tested for a potential time-dependent treatment effect on all primary and secondary time-to-event endpoints, but none of the corresponding tests indicated that this was the case. If the p-value for the interaction of time and treatment is found to be small this would indicate that the treatment effect isn't constant over time; this has not been found. Please see below for the analysis for the primary endpoint which does not indicate a waning of treatment effect over the course of the study:	

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
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Please respond to each comment</th></tr>
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Despite not agreeing that a waning effect should be applied, Bayer have conducted scenario analyses as set out below.

The key HRs which have a major impact on the cost-effectiveness results (as presented in the DSA results, presented in comment 8 below) were selected to provide the scenario of treatment waning. These are as follows:

• Onset of eGFR decrease < 15 mL/min/1.73m^2 sustained over at least 4 weeks,
• Progression to dialysis,
• CV death,
• First CV event.

The scenario assumes treatment effect waning as presented in the table below:

Table 22. Treatment effect waning – FIDELIO-DKD label – assumptions applied
<table>
<tr><th rowspan="2">Time in model [years]</th><th colspan="2">Onset of eGFR decrease < 15 mL/min/1.73m2 sustained over at least 4 weeks</th><th colspan="2">Progression to dialysis</th><th colspan="2">CV death</th><th colspan="2">First CV event</th></tr>
<tr><th>HR</th><th>Source/ Assumption</th><th>HR</th><th>Source/ Assumption</th><th>HR</th><th>Source/ Assumption</th><th>HR</th><th>Source/ Assumption</th></tr>
<tr><td>0-4</td><td>0.85</td><td>FIDELIO-DKD</td><td>0.85</td><td>FIDELIO-DKD</td><td>0.93</td><td>FIDELIO-DKD</td><td>0.87</td><td>FIDELIO-DKD</td></tr>
<tr><td>4-8</td><td>0.89</td><td>25% reduction</td><td>0.88</td><td>25% reduction</td><td>0.94</td><td>25% reduction</td><td>0.90</td><td>25% reduction</td></tr>
<tr><td>8-12</td><td>0.92</td><td>50% reduction</td><td>0.92</td><td>50% reduction</td><td>0.96</td><td>50% reduction</td><td>0.93</td><td>50% reduction</td></tr>
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<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
Please insert each new comment in a new row</th><th>NICE Response
Please respond to each comment</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><td>12-16</td><td>0.96</td><td>75% reduction</td><td>0.96</td><td>75% reduction</td><td>0.98</td><td>75% reduction</td><td>0.96</td><td>75% reduction</td></tr>
<tr><td>16+</td><td>1.00</td><td>100% reduction</td><td>1.00</td><td>100% reduction</td><td>1.00</td><td>100% reduction</td><td>1.00</td><td>100% reduction</td></tr>
</table>

The results of the base case in the model with assumed waning of the treatment effect are presented below (Table 23).

Table 23. Treatment waning – FIDELIO-label – deterministic results
<table>
<tr><th>Incremental costs, undiscounted</th><th>Incremental costs, discounted</th><th>Incremental QALYs, undiscounted</th><th>Incremental QALYs, discounted</th><th>ICER, undiscounted</th><th>ICER, discounted</th></tr>
<tr><td>£991</td><td>£891</td><td>0.13</td><td>0.09</td><td>£7,461</td><td>£9,471</td></tr>
</table>

Finerenone remains a cost-effective treatment despite inclusion of a waning of treatment effect.
</td><td></td></tr>
<tr><td>8</td><td>Company</td><td>Bayer</td><td>
Bayer has updated the sensitivity analyses (both DSA and PSA) in order to address the limitations raised by ERG/NICE.

The ERG was concerned that the transition probabilities in the model were not subjected to any form of sensitivity analysis. To address this issue, Bayer changed the approach for handling transition probabilities (this has been described in the comment 2). This approach enabled a robust PSA to be conducted, with inclusion of the variability of applied HRs and sampling the BT probabilities from the Dirichlet distribution.

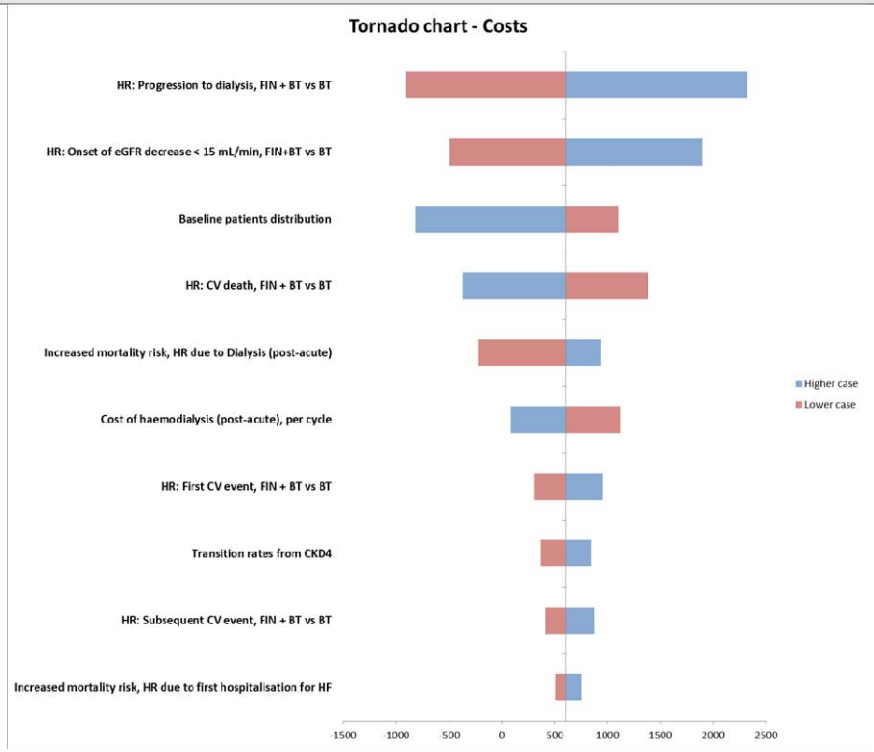
The list of inputs which have been added to the DSA and PSA are presented in the table below (Table 24)

Table 24. List of inputs and variables of the cost-effectiveness analysis included in the DSA and PSA
<table>
<tr><th>Variable</th><th>Value</th><th>Measurement of uncertainty and distribution: CI (distribution)</th></tr>
<tr><td>Transition rates from CKD1/2</td><td rowspan="8">As presented in Table 43 of the main submissio n</td><td>Dirichlet [redacted]</td></tr>
<tr><td>Transition rates from CKD3</td><td>Dirichlet [redacted]</td></tr>
<tr><td>Transition rates from CKD4</td><td>Dirichlet [redacted]</td></tr>
<tr><td>Transition rates from CKD5</td><td>Dirichlet [redacted]</td></tr>
<tr><td>Transition rates from Dialysis (acute)</td><td>Dirichlet [redacted]</td></tr>
<tr><td>Transition rates from Dialysis (post-acute)</td><td>Dirichlet [redacted]</td></tr>
<tr><td>Transition rates from Transplant (acute)</td><td>Dirichlet [redacted]</td></tr>
<tr><td>Transition rates from Transplant (post-acute)</td><td>Dirichlet [redacted]</td></tr>
<tr><td>HR: Onset of eGFR decrease < 15 mL/min, FIN+BT vs BT</td><td>[redacted]</td><td>CI ([redacted]) LogNormalY (μ,σ)</td></tr>
<tr><td>HR: Progression to dialysis, FIN + BT vs BT</td><td>[redacted]</td><td>[redacted]) LogNormalY (μ,σ)</td></tr>
</table>
</td><td>Comments noted. The committee considered the updated approach to sensitivity analysis was an improvement, the outputs of these remained uncertain. It concluded that the results of the updated sensitivity analyses should be interpreted with caution. See section 3.19 of the FAD.</td></tr>
</table>

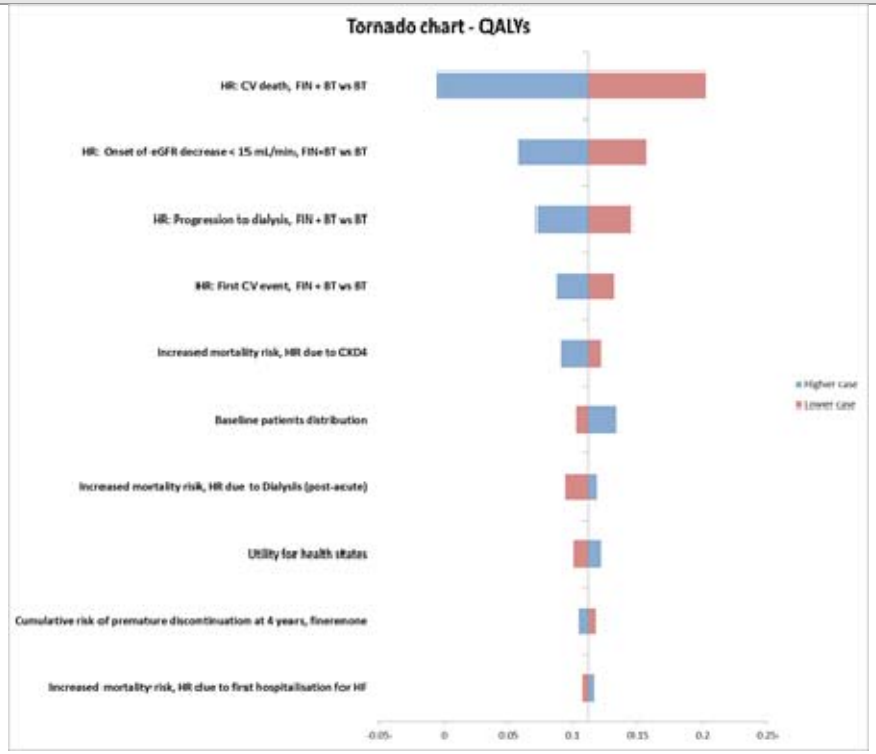
Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment

CKD1/2 utility	[redacted]	[redacted] Beta (μ,σ)
CKD3 utility	[redacted]	[redacted] Beta (μ,σ)
CKD4 utility	[redacted]	[redacted] Beta (μ,σ)
CKD 5 w/o RRT utility	[redacted]	[redacted] Beta (μ,σ)
Dialysis (acute) utility	0.595	CI(0.536;0.653) Beta (μ,σ)
Dialysis (post-acute) utility	0.595	CI(0.536;0.653) Beta (μ,σ)
Kidney Transplant (acute) utility	0.748	CI(0.673;0.816) Beta (μ,σ)
Kidney Transplant (post-acute) utility	0.748	CI(0.673;0.816) Beta (μ,σ)
Utility decrement associated with first MI (acute)	-0.060	CI(-0.055;-0.065) Beta (μ,σ)
Utility decrement associated with first MI (post-acute)	-0.032	CI(-0.029;-0.037) Beta (μ,σ)
Utility decrement associated with first stroke (acute)	-0.160	CI(-0.145;-0.176) Beta (μ,σ)
Utility decrement associated with first stroke (post-acute)	-0.087	CI(-0.079;-0.095) Beta (μ,σ)
Utility decrement associated with first hospitalisation for HF (acute)	-0.110	CI(-0.099;-0.122) Beta (μ,σ)
Utility decrement associated with first hospitalisation for HF (post-acute)	-0.060	CI(-0.055;-0.065) Beta (μ,σ)
Utility decrement associated with hyperkalaemia leading to hospitalisation	-0.030	CI(-0.026;-0.034) Beta (μ,σ)
Utility decrement associated with hyperkalaemia not leading to hospitalisation	-0.030	CI(-0.026;-0.034) Beta (μ,σ)
Utility decrement associated with sustained decrease in eGFR >=40% from baseline	[redacted]	[redacted] Beta (μ,σ)
Utility decrement associated with new onset of atrial fibrillation / atrial flutter	-0.014	CI(-0.014;-0.014) Beta (μ,σ)

The results of the DSA, for the base case as described in comment 2, are presented below in the form of two tornado charts. Total incremental costs and the number of QALYs gained are displayed in separate tornado charts (please see graphs below).

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
				

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment



It is visible that the two HRs included in the transition probabilities (i.e., HR of onset of eGFR decline <15 and HR for progression to dialysis) as well as the HR for CV death have the biggest impact on the incremental costs and incremental QALYs.

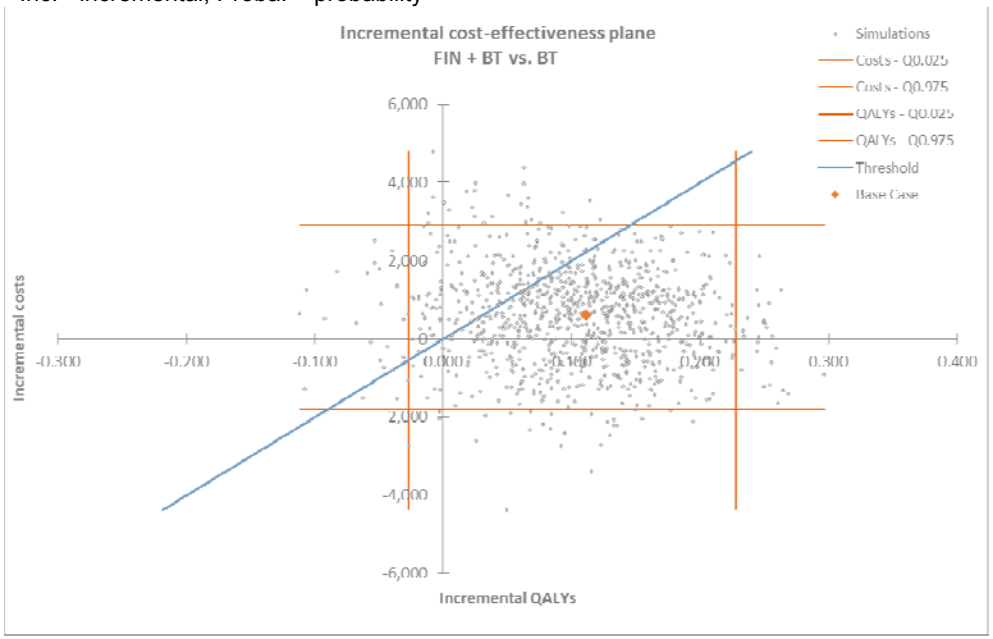
The results of the PSA, for the base case as described in comment 2 are presented below.

	Inc. costs	Inc. QALYs	ICER
Base Case	**607**	**0.111**	**5,464**
Mean	573	0.103	5,557
Std Deviation	1,216	0.066	188,822
Median	637	0.106	5,284
Min	-4,368	-0.112	-850,073

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment

Q 0.025	-1,811	-0.027	-88,728
Q 0.975	2,907	0.228	116,420
Max	4,802	0.297	5,056,355
Proba. CE Threshold			80.0%
Proba. Dominant			28.9%
Proba. Dominated			4.9%

Inc. - incremental; Proba. – probability



The mean ICER of the PSA is very close to the deterministic result. The inclusion of the variability in the transition probabilities did not cause the results to deviate from the base case.

9	Company	Bayer	Bayer would also like to highlight to the committee that there is a patient group with a particular unmet need, which will become apparent as more patients are considered for an SGLT2i. This group are those patients who are unsuitable for SGLT2i or who permanently discontinue SGLT2i e.g. for intolerance. Indeed, this group was highlighted by both the clinical experts during the committee and the patient expert submission. To help define this patient group, the unmet need, and the applicability of the FIDELIO-DKD data to this population,	Comments noted. The committee considered that finerenone could be given before or with SGLT2 inhibitors and

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Bayer convened a multidisciplinary panel of UK experts. The description of the methodology and the outputs – "The Consensus Statement" can be found as Appendix A. (Comment 10). The group discussed the characteristics and factors that could result in a patient with CKD progression associated with T2D being unsuitable for SGLT2i, those in whom SGLT2is may be used with caution, and in identifying those who are intolerant to treatment with SGLT2is. Although each advisor had specific clinical reasons why they would consider not treating a patient with SGLT2is or using them with caution, only factors where there was consensus were recorded. The outputs of the discussion were both reviewed and agreed by the participants at the conclusion of the working group meeting and in reviewing the final report. The group also reported on the unmet need for such patients whose standard of care is ACEI/ARBs, which is associated with a significant residual risk of CKD progression. Finally, the group considered that finerenone would be suitable for patients who were SGLT2i unsuitable/ intolerant and set out their rationale. Importantly, the advisors could not identify any plausible biological or clinical rationale for why the FIDELIO-DKD data would not be applicable to these patients. A conclusion of the consensus statement is set out below: *"There is strong clinician support to ensure that Kerendia be made available for adult patients with CKD and T2D who are unsuitable for or intolerant to treatment with SGLT2is."* Utilising the consensus statement as a framework, Bayer has conducted a thorough evaluation of the size of the SGLT2i unsuitable population. Extensive desk research has been supplemented with expert opinion where insufficient information was available in the literature. Expert opinion was also utilised to estimate the degree of overlap both within and between categories of patients. For example, a single patient may have two or more risk factors that invoke ineligibility for SGLT2i prescription. In the same manner, a single patient may have two or more risk factors that cause caution to be expressed about the initial prescription of an SGLT2i. Likewise, there will exist some degree of overlap between those in whom caution is expressed and those who are ultimately prescribed and discontinue or do not adhere to SGLT2i. For the latter situation, an assumption has been made about degree of overlap. Finally, there will also exist a proportion of ineligible patients with one or more caution characteristics in their medical history. Utilising the same approach, a degree of overlap in medical history has been accounted for when estimating patient numbers. Bayer therefore estimate that the number of patients in England who are likely to be unsuitable, intolerant or where caution may be exercised in the prescription of SGLT2i is approximately 20k in 2023. This represents approximately 20% of the eligible population that Bayer presented in the budget impact assessment for the full label population.	concluded that SGLT2 inhibitors are a relevant comparator. It noted that the comparison of finerenone with SGLT2 inhibitors was still missing. So, finerenone could only be considered as an option in addition to SGLT2 inhibitors, or where these are unsuitable. See sections 3.3 and 3.4 of the FAD. The committee considered the evidence presented for the scenario analyses for use of finerenone as add on to standard care including SGLT2 inhibitors in its decision making. See section 3.10 of the FAD.
10	Company	Bayer	**Establishing the potential of Kerendia (finerenone) to delay chronic kidney disease progression associated with type 2 diabetes in adult patients who are unsuitable for, or intolerant to, treatment with SGLT2 inhibitors.**	Comments noted. The committee considered that finerenone could be given before or

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			INTRODUCTION Kerendia (finerenone) is a novel, non-steroidal, selective mineralocorticoid receptor antagonist (MRA) that has been extensively investigated in adult patients with chronic kidney disease (CKD) associated with type 2 diabetes (T2D). Kerendia was approved in the US (September 2021)[1] and in Europe for the treatment of CKD progression associated with T2D (February 2022).[2] Subsequent to the date of this expert group meeting (22 February 2022), Kerendia has received MHRA authorisation in the UK with the following indication (March 2022):[3] • Kerendia is indicated for the treatment of chronic kidney disease (stage 3 and 4 with albuminuria) associated with type 2 diabetes in adults.[2,3] In the last 2 years, the sodium-glucose co-transporter 2 inhibitors (SGLT2is), canagliflozin and dapagliflozin,[4,5] have been authorised for the treatment of CKD progression associated with T2D (and dapagliflozin for CKD progression not associated with T2D) and are now increasingly being considered an integral part of the current standard of care (SoC) in combination with angiotensin converting enzyme inhibitors (ACEis) or angiotensin receptor blockers (ARBs). Guidelines have recently been updated for T2D, CKD and heart failure which suggest the earlier use of SGLT2is to improve outcomes, regardless of glycaemic control, and concerns about prescribing SGLT2is are decreasing.[6-8] SGLT2is have been demonstrated to improve cardiovascular and renal outcomes for many patients with T2D; however, there are some people who may not benefit from SGLT2is because they are either contraindicated, or unable to tolerate SGLT2is due to other patient-related factors or patient preferences. These patients remain at risk of CKD progression, and for these patients there is a need for an effective alternative treatment. Kerendia could meet the needs of these patients. Bayer convened an expert working group of specialists working in CKD and T2D to build consensus on the potential use of Kerendia to delay CKD progression associated with T2D in adult patients who are unsuitable for or intolerant to treatment with SGLT2is. This included defining the particular patient population who are unsuitable for or intolerant to treatment with SGLT2is and understanding whether currently available data are applicable to this patient population. Authors and working group participants: [redacted] [redacted] [redacted]	with SGLT2 inhibitors and concluded that SGLT2 inhibitors are a relevant comparator. It noted that the comparison of finerenone with SGLT2 inhibitors was still missing. So, finerenone could only be considered as an option in addition to SGLT2 inhibitors, or where these are unsuitable. See sections 3.3 and 3.4 of the FAD. The committee considered the evidence presented for the scenario analyses for use of finerenone as add on to standard care including SGLT2 inhibitors in its decision making. See section 3.10 of the FAD.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			[redacted]	

METHODOLOGY

Selection – The selection of advisors was based on specialty knowledge and expertise, differing skills, practice types representing secondary and primary care centres and geography (ensuring that as much regional representation as possible was secured).

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			Research – Each advisor considered their patient population and current clinical practice. The advisors reviewed the literature for RCTs of SGLT2is and Kerendia (CREDENCE, DAPA-CKD, and FIDELIO-DKD),[9-12] SPCs[4,5] and MHRA Drug Safety Updates,[13-15] clinical practice guidelines,[6-8] and papers on the safe and effective use of SGLT2is,[16] and discontinuation rates and reasons for discontinuation with SGLT2is from real word evidence.[17,18] ***Discussion and consensus*** – The group discussed the characteristics and factors that could result in a patient with CKD progression associated with T2D being unsuitable for or intolerant to treatment with SGLT2is. Although each advisor had specific clinical reasons why they would consider not treating a patient with SGLT2is or using them with caution, only factors where there was consensus have been recorded and the results below were both reviewed and agreed at the conclusion of the working group meeting and in reviewing the final report. **RESULTS** The group concluded that while differences in clinical practice exist across the country, a consensus could be reached that defined the clinical factors determining if a patient with CKD associated with T2D would be unsuitable for SGLT2is, those in whom SGLT2is may be used with caution, and in identifying those who are intolerant to SGLT2is. Discussions included knowledge of recent guidelines[6-8] and other clinical pathways not necessarily available in formal guidelines. The recommendations below highlight the criteria which either would lead to a clear and absolute decision that SGLT2is would be unsuitable, or where clinical judgement combined with guideline recommendations could lead to a clinical decision that SGLT2is may be unsuitable for a particular patient. **Consensus on criteria for patient unsuitability for SGLT2is** 1. Patients who should not receive SGLT2is ● History of unprovoked diabetic ketoacidosis (DKA) ● In patients where there has been a very rapid progression to insulin (within 12 months of diagnosis of T2D) ● In patients during an acute (and dehydrating) illness, though they may be considered for an SGLT2i at a later date ● History of recurrent mycotic genital infections, especially those with poorly controlled glycaemia ● Urinary sepsis resulting in recurrent hospital admissions ● Pancreatic disease ● History of Fournier's gangrene ● Women of reproductive age who are not using reliable contraception and there is pregnancy potential	

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			2. Patients with whom to exercise caution with initial prescribing of SGLT2is (but still offer an SGLT2i) ● Complex stone disease (including staghorn calculus) ● Overactive bladder, prostatitis, and recurrent urinary tract infections ● Previous lower limb amputation ● Active peripheral vascular disease (ulceration, or intermittent claudication) ● Potential drug interactions ● Very high HbA1c levels (>86 mmol/mol or 10%) ● Low body weight (BMI <23) ● Significant frailty ● History of fragility fractures or osteoporosis ● People with dietary restrictions, e.g., those who fast/on a ketogenic diet/very low-calorie diet 3. Patients who choose not to take an SGLT2i ● People may choose not to take an SGLT2i due to concern about certain known side effects with SGLT2is, such as Fournier's gangrene **Patients who should not continue on SGLT2is** 1. Patients who develop intolerance after an initial trial of an SGLT2i (5–10% of patients) ● Recurrent genital infections (men are less likely to tolerate recurrent infections than women) ● Patients who suffer symptomatic hypotension on an SGLT2i ● Urinary symptoms – frequency and recurrent infections ● Idiosyncratic adverse events 2. Patients who do not adhere to treatment with SGLT2is ● Patients who start and discontinue SGLT2i treatment for any reason (10–20% of patients) ○ For example, real world evidence shows discontinuation of dapagliflozin within 3 months in approximately 10% of patients (N=149/1663)[18] ■ One-quarter of those patients discontinued due to elevated HbA1c, increased body	

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			weight or increased appetite ■ Half of those patients discontinued due to adverse events (two major side effects were genital and urinary tract infections). **Identified unmet need** The advisors identified the unmet need for the 'SGLT2i unsuitable or intolerant' patient population as follows: ● The current optimal SoC (ABCD) provides insufficient protection ○ A – ACEi/ARB at maximal doses ○ B – Blood pressure targeting ○ C – Cardiovascular risk factor reduction ○ D – Diabetes, glycaemic control - utilising agents that have cardio-renal benefit preferentially ● In the placebo arm of the SGLT2i studies and FIDELIO-DKD trial, patients were on optimal SoC but there was still progression of CKD ● For SGLT2i ineligible patients, the current SoC is ACEi/ARBs and there is significant residual risk of CKD progression for T2D patients on ACEi/ARBs ○ In studies of ARBs in patients with T2D and proteinuria, the relative risk reduction was only 16–20% (RENAAL and IDNT studies)[19,20] **Rationale for Kerendia as an alternative to SGLT2is** The advisors considered that Kerendia would be suitable to use in an 'SGLT2i unsuitable or intolerant' patient population for the following reasons: ● FIDELIO-DKD, DAPA-CKD and CREDENCE studies included broadly the same patient population; the baseline characteristics between the clinical trials are comparable[9-11] ● Although SGLT2i intolerant patients were not specifically recruited to studies of Kerendia, Kerendia may be expected to provide similar kidney protection irrespective of whether the patient is SGLT2i tolerant or not as none of the reasons for SGLT2i intolerance would be expected to interfere with Kerendia's mechanism of action ● Kerendia has a different mechanism of action to the SGLT2is: ○ SGLT2is primarily target haemodynamic (elevated blood pressure and/or intraglomerular pressure) and metabolic factors (poor glycaemic control)[21-25]	

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			○ Kerendia targets the mineralocorticoid receptor (MR); there is a growing body of evidence that MR overactivation leads to inflammation and fibrosis and is a key driver of CKD progression[26-30] ○ In clinical studies, Kerendia was associated with reduced albuminuria versus placebo, despite only modest reductions in blood pressure and no effect on glycaemic control in patients with CKD and T2D.[12,30,31] Albuminuria is a significant risk factor for rapid decline in kidney function[6] ● An SGLT2i-excluded cohort would have similar characteristics as those patients recruited for FIDELIO-DKD ● Patients are SGLT2i intolerant predominantly for metabolic reasons, or due to complications either from insulinopenia or septic complications of glycosuria ● A higher proportion of SGLT2i intolerant patients may be insulinopenic and more type 1 diabetes-like; however, there is no biological reason to suggest that these patients would not respond to Kerendia. These patients would usually be prescribed an ACEi/ARB ● The FIDELIO-DKD, DAPA-CKD and CREDENCE studies resulted in similar renal outcomes (decline in eGFR or doubling of serum creatinine) for similar patient populations ○ Hard outcomes for example, end-stage kidney failure and renal death are most important for HTA bodies; however, the numbers of patients who go into kidney failure in the studies has been small due to the medium term follow up duration ● Patients with lesser degrees of albuminuria need to be monitored carefully and may be considered for Kerendia in the future if there is evidence of deteriorating albuminuria and progressive diabetic kidney disease. **CONCLUSIONS** The expert group was able to reach consensus in defining the clinical factors that would result in an adult patient with T2D and CKD being unsuitable for SGLT2is, those in whom SGLT2is may be used with caution, and in identifying those who are intolerant to SGLT2is. The group advised that a substantial unmet medical need to reduce the risk of CKD progression remains for people who are 'SGLT2i unsuitable or intolerant.'	

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			The advisors could not identify any plausible biological or clinical rationale for why the FIDELIO-DKD data would not be applicable to these patients. The expert group would recommend Kerendia for adult patients with significant albuminuria (uACR ≥30 mg/g) in the presence of stage 3 or 4 CKD (eGFR ≥25 to <60 ml/min/1.73 m^2) and T2D in patients who cannot tolerate or are unsuitable for SGLT2is. The expert group would also recommend Kerendia for adult patients with preserved eGFR (30–59 ml/min/1.73 m^2) and significant albuminuria (uACR ≥30 mg/g), a patient group with high unmet medical need. There is strong clinician support to ensure that Kerendia be made available for adult patients with CKD and T2D who are unsuitable for or intolerant to treatment with SGLT2is. **REFERENCES [CONSENSUS STATEMENT]** 1. Bayer HealthCare Pharmaceuticals Inc. Finerenone: prescribing information. 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/215341s000lbl.pdf. Accessed March 2022. 2. Bayer AG. Finerenone: Summary of product characteristics. 11 March 2022. https://www.ema.europa.eu/en/documents/product-information/kerendia-epar-product-information_en.pdf. Accessed March 2022. 3. FirstWord Pharma. Bayer receives MHRA authorisation in Great Britain for Kerendia (finerenone) as a new treatment for adult patients with chronic kidney disease associated with type 2 diabetes. 9 March 2022. https://old.firstwordpharma.com/node/1907382?tsid=17. Accessed March 2022. 4. Napp Pharmaceuticals Ltd. Canagliflozin: Summary of product characteristics. 2020. https://www.medicines.org.uk/emc/product/8855/smpc. Accessed March 2022. 5. AstraZeneca UK Ltd. Dapagliflozin: Summary of product characteristics. 2020. https://www.medicines.org.uk/emc/product/7607/smpc. Accessed March 2022. 6. UK Kidney Association. Clinical practice guideline: Sodium-glucose co-transporter-2 (SGLT-2) inhibition in adults with kidney disease. 28 September 2021. https://ukkidney.org/health-professionals/guidelines/ukka-clinical-practice-guideline-sodium-glucose-co-transporter-2. Accessed March 2022. 7. NICE guideline [NG28]. Type 2 diabetes in adults: management. 15 February 2022. https://www.nice.org.uk/guidance/ng28/chapter/Recommendations#chronic-kidney-disease. Accessed March	

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			2022. 8. Dashora U, et al. ABCD and Diabetes UK Joint position statement and recommendations for non-diabetes specialists on the use of sodium glucose co-transporter 2 inhibitors in people with type 2 diabetes (January 2021). *Clinical Medicine.* 2021;21(3):204–210. 9. Perkovic V, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med.* 2019;380:2295–2306. 10. Heerspink HJL, et al. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med.* 2020;383(15):1436–1446. 11. Bakris GL, et al. Design and baseline characteristics of the finerenone in reducing kidney failure and disease progression in diabetic kidney disease trial. *Am J Nephrol.* 2019;50:333–344. 12. Bakris GL, et al. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. *N Engl J Med.* 2020;383:2219–2229. 13. MHRA. SGLT2 inhibitors updated advice on the risk of diabetic ketoacidosis. 18 April 2016. https://www.gov.uk/drug-safety-update/sglt2-inhibitors-updated-advice-on-the-risk-of-diabetic-ketoacidosis. Accessed March 2022. 14. MHRA. SGLT2 inhibitors reports of Fournier's gangrene necrotising fasciitis of the genitalia or perineum. 18 February 2019. https://www.gov.uk/drug-safety-update/sglt2-inhibitors-reports-of-fournier-s-gangrene-necrotising-fasciitis-of-the-genitalia-or-perineum. Accessed March 2022. 15. MHRA. SGLT2 inhibitors updated advice on increased risk of lower limb amputation mainly toes. https://www.gov.uk/drug-safety-update/sglt2-inhibitors-updated-advice-on-increased-risk-of-lower-limb-amputation-mainly-toes. Accessed March 2022. 16. Brown P. How to use SGLT2 inhibitors safely and effectively. *Diabetes & Primary Care.* 2021;23:5–7. 17. Fadini GP, et al. Predictors of early discontinuation of dapagliflozin versus other glucose-lowering medications: a retrospective multicentre real-world study. *J Endocrinol Invest.* 2020;43:329–336. 18. Kim H, et al. Discontinuation rate and reason for discontinuation after sodium-glucose co-transporter 2 inhibitor prescription in real clinical practice. *J Clin Pharm Ther.* 2020;45:1271–1277.	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			19. Brenner BM, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med.* 2001;345:861–869. 20. Lewis EJ, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med.* 2001;345(12):851–860. 21. Kidokoro K, et al. Evaluation of glomerular hemodynamic function by empagliflozin in diabetic mice using in vivo imaging. *Circulation.* 2019:140;303–315. 22. Zelniker TA & Braunwald E. Cardiac and renal effects of sodium-glucose co-transporter 2 inhibitors in diabetes: JACC state-of-the-art review. *J Am Coll Cardiol.* 2018;72:1845–1855. 23. Heerspink HJ, et al. Sodium glucose cotransporter 2 inhibitors in the treatment of diabetes mellitus: cardiovascular and kidney effects, potential mechanisms, and clinical applications. *Circulation.* 2016;134:752–772. 24. Zelniker TA & Braunwald E. Mechanisms of cardiorenal effects of sodium-glucose cotransporter 2 inhibitors: JACC state-of-the-art review. *J Am Coll Cardiol.* 2020;75:422–434. 25. American Diabetes Association. 9. Pharmacologic approaches to glycaemic treatment: standards of medical care in diabetes 2020. *Diabetes Care.* 2020;43:S98–S110. 26. Agarwal R, et al. Steroidal and non-steroidal mineralocorticoid receptor antagonists in cardiorenal medicine. *Eur Heart J.* 2021;42:152–162. 27. Alicic RZ, et al. Diabetic kidney disease: challenges, progress, and possibilities. *Clin J Am Soc Nephrol.* 2017;12:2032–2045. 28. Mora-Fernández C, et al. Diabetic kidney disease: from physiology to therapeutics. *J Physiol.* 2014;18:3997–4102. 29. Bauersachs J, et al. Mineralocorticoid receptor activation and mineralocorticoid receptor antagonist treatment in cardiac and renal diseases. *Hypertension.* 2015;65:257–263. 30. Agarwal R, et al. Investigating new treatment opportunities for patients with chronic kidney disease in type 2 diabetes: the role of finerenone. *Nephrol Dial Transplant.* 2020;Dec 6:gfaa294. doi: 10.1093/ndt/gfaa294 31. Bakris GL, et al. Effect of finerenone on albuminuria in patients with diabetic nephropathy: a randomized	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			clinical trial. *JAMA.* 2015;314:884–894.	
11	Professional group	UK Kidney Association and Association of British Clinical Diabetologists – a joint response	The UK Kidney Association and the Association of British Clinical Diabetologists have significant concerns about the fact that NICE are unable to guide the healthcare community in relation to the use of Fineronone in preventing progression of diabetic kidney disease.	The recommendation in the FAD has been updated. Finerenone is recommended as an option for treating stage 3 and 4 chronic kidney disease (with albuminuria) associated with type 2 diabetes in adults. It is recommended only if it as an add-on to optimised standard care including ACE inhibitors or ARBs, and SGLT2 inhibitors, unless these are unsuitable See section 1.1 of the FAD.
12	Professional group	UK Kidney Association and Association of British Clinical Diabetologists – a joint response	The urgency of this matter cannot be overstated. We wish to highlight that there is a growing number of people with diabetic kidney disease being managed across the healthcare system that are at great risk of cardiovascular morbidity or reaching end-stage renal failure. NICE are well aware that this cohort of patients developed from the cohort of individuals with type 2 diabetes some 10 to 15 years ago and the number of people with type 2 diabetes has increased year-on-year since that time. Therefore, if we do not to take action the numbers with progressive CKD will grow significantly over the next 10 years. Furthermore, people are developing type 2 diabetes at younger ages and living longer with their type 2 diabetes because of better treatment of cardiovascular disease. We are therefore going to see much more kidney disease in this population and the current prevailing view that people who develop diabetic kidney disease are far more likely to die from cardiovascular disease than develop end-stage kidney failure will be altered over this period with many more people reaching end-stage kidney failure.	Comment noted. The recommendation in the FAD has been updated. Finerenone is recommended as an option for treating stage 3 and 4 chronic kidney disease (with albuminuria) associated with type 2 diabetes in adults. It is

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
				recommended only if it as an add-on to optimised standard care including ACE inhibitors or ARBs, and SGLT2 inhibitors, unless these are unsuitable See section 1.1 of the FAD. Additionally, the committee acknowledged that there is an unmet need for treatment options for chronic kidney disease associated with type 2 diabetes. See section 3.1 of the FAD.
13	Professional group	UK Kidney Association and Association of British Clinical Diabetologists – a joint response	Our current treatments include RAAS inhibition and now SGLT2 inhibitors. But even with maximum treatment there is still a very significant residual risk. Nephrologists around the country are regularly receiving referrals relating to people with type 2 diabetes, on appropriate dosage of RAAS inhibition and appropriate SGLT2 Inhibitor with significant residual albuminuria and impaired GFR and whose five year kidney failure risk is high. We need to be able to offer this cohort who may only be a small percentage of the total but who are significant in numbers for additional treatment. We also need to offer Fineronone for the few patients who are unable to tolerate or maintain SGLT2inhibitors.	Comment noted. The recommendation in the FAD has been updated. Finerenone is recommended as an option for treating stage 3 and 4 chronic kidney disease (with albuminuria) associated with type 2 diabetes in adults. It is recommended only if it as an add-on to optimised standard care including ACE inhibitors or ARBs,

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
				and SGLT2 inhibitors, unless these are unsuitable See section 1.1 of the FAD. Additionally, the committee acknowledged that finerenone could be recommended before or with SGLT2 inhibitors. See sections 3.3 and 3.4 of the FAD.
14	Professional group	UK Kidney Association and Association of British Clinical Diabetologists – a joint response	If we do not start actively managing these groups of individuals they will lose kidney function over the next few years while we prevaricate. The evidence from the FIDELIO is clear and is equivalent to the benefits seen in 2001 from the RENAAL and IDNT trials.	Comment noted. The recommendation in the FAD has been updated. Finerenone is recommended as an option for treating stage 3 and 4 chronic kidney disease (with albuminuria) associated with type 2 diabetes in adults. It is recommended only if it as an add-on to optimised standard care including ACE inhibitors or ARBs, and SGLT2 inhibitors, unless these are unsuitable See section 1.1 of the FAD.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
				Additionally, the committee acknowledged that evidence from FIDELIO-DKD is relevant. But it considered that additional clinical evidence from FIGARO-DKD and FIDELITY are also appropriate and took this in to its decision making. See sections 3.5, 3.6, 3.8 and 3.9 of the FAD.
15	Professional group	UK Kidney Association and Association of British Clinical Diabetologists – a joint response	It is for this reason that we urge NICE to recommend Fineronone for specialist care initiation where there is ongoing and significant risk of progression of diabetic kidney disease in the presence of current standard of care or where it needs to be added to RAAS inhibition because SGLT2 inhibitors are not able to be used.	Comment noted. The recommendation in the FAD has been updated. Finerenone is recommended as an option for treating stage 3 and 4 chronic kidney disease (with albuminuria) associated with type 2 diabetes in adults. It is recommended only if it as an add-on to optimised standard care including ACE inhibitors or ARBs, and SGLT2 inhibitors, unless these are unsuitable See section 1.1 of the FAD.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
				Additionally, the committee acknowledged that finerenone could be recommended before or with SGLT2 inhibitors. See sections 3.3 and 3.4 of the FAD.
16	Professional group	UK Kidney Association and Association of British Clinical Diabetologists – a joint response	Furthermore, as mentioned in our previous response, many of the reanalyses requested have already been carried out 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).	Comment noted. The recommendation in the FAD has been updated. Finerenone is recommended as an option for treating stage 3 and 4 chronic kidney disease (with albuminuria) associated with type 2 diabetes in adults. It is recommended only if it as an add-on to optimised standard care including ACE inhibitors or ARBs, and SGLT2 inhibitors, unless these are unsuitable See section 1.1 of the FAD. Additionally, the committee considered that additional clinical evidence from

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
				FIGARO-DKD and FIDELITY are also appropriate and took this in to its decision making. See sections 3.6 and 3.9 of the FAD.
17	Professional group	UK Kidney Association and Association of British Clinical Diabetologists – a joint response	As we stated before, 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 rationale for using the two agents together in DKD. Moreover, because of this difference in the mechanism of action between the two agents, finerenone may also be an option in those intolerant to SGLT2i.	Comment noted. The recommendation in the FAD has been updated. Finerenone is recommended as an option for treating stage 3 and 4 chronic kidney disease (with albuminuria) associated with type 2 diabetes in adults. It is recommended only if it as an add-on to optimised standard care including ACE inhibitors or ARBs, and SGLT2 inhibitors, unless these are unsuitable See section 1.1 of the FAD. Additionally, the committee acknowledged that finerenone could be recommended before or with SGLT2 inhibitors. See sections 3.3

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
				and 3.4 of the FAD.
18	Professional group	UK Kidney Association and Association of British Clinical Diabetologists – a joint response	May we also highlight that diabetic kidney disease is associated with a very incidence of CV events; incident heart failure in patients is a major cause of recurrent hospitalisations and poor quality of life. The FIDELITY study, mentioned above, demonstrated that Finerenone reduces composite CV outcomes including heart failure hospitalisation [vs placebo, hazard ratio (HR), 0.86; 95% confidence interval (CI), 0.78-0.95; P = 0.0018]	Comment noted. The committee considered that additional clinical evidence from FIGARO-DKD and FIDELITY are also appropriate and took this in to its decision making. See sections 3.6 and 3.9 of the FAD.

NICE National Institute for Health and Care Excellence

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

Consultation on the appraisal consultation document – deadline for comments 5pm on 06 June 2022. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Bayer plc

NICE National Institute for Health and Care Excellence

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

Consultation on the appraisal consultation document – deadline for comments 5pm on 06 June 2022. Please submit via NICE Docs.

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.
Name of commentator person completing form:	Lesley Gilmour

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	Bayer plc is disappointed that the NICE committee was minded not to recommend finerenone as an option for treating stage 3 and 4 chronic kidney disease with albuminuria associated with type 2 diabetes in adults. Despite standard of care therapy, and recent emerging therapies, overall, there remains a high residual risk of cardiorenal events in patients with chronic kidney disease (CKD) and type 2 diabetes (T2D). Therefore, as recognised by stakeholders to this appraisal, there is an unmet need for additional treatment options to further reduce cardiorenal morbidity and mortality in these patients. Current understanding of CKD and T2D suggests that three interrelated pathophysiological drivers promote CKD progression (1): • Metabolic factors (e.g. elevated blood sugar) • Haemodynamic factors (e.g. elevated blood pressure and/or intraglomerular pressure) • Inflammatory and fibrotic factors (e.g. pro-inflammatory cytokines and pro-fibrotic proteins) Metabolic and haemodynamic drivers of CKD in T2D are targeted by glucose-lowering agents and antihypertensive medications (e.g. angiotensin-converting enzyme inhibitors [ACEIs] and

	angiotensin receptor blockers [ARBs]). 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 (2, 3). However, despite existing therapies for CKD and T2D, there remains a residual risk of progression to more advanced CKD stages (4-7). Pathways that influence inflammation and fibrosis are complex, but pathological overactivation of the mineralocorticoid receptor (MR) remains a key driver of disease in the kidneys, heart, and vascular system (8-10). Finerenone is a non-steroidal, selective antagonist of the MR (11), addressing the third driver of disease progression. To optimise treatment outcomes, it is expected that all three drivers of disease progression should be addressed. Finerenone was demonstrated in the FIDELIO-DKD study (12), one of the largest contemporary studies to evaluate patients with CKD and T2D, to be efficacious in delaying the progression of kidney disease and reducing the risk of major CV events, on top of optimised background therapy, including a maximum tolerated labelled dose of either an ACEI or an ARB. Bayer presented a robust economic model which demonstrated that finerenone is a cost-effective use of NHS resources, compared to established NHS clinical practice with a base case ICER, using ERG preferred model assumptions of £13,626 (presented before the 1st committee meeting). Furthermore, there are aspects that have not been fully captured in the QALY calculation; 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 that were not fully captured in the economic model (13-15). In this response to the ACD, Bayer seeks to provide further information and analyses to the committee so that NICE reconsiders their draft decision and NHS clinicians are able to offer finerenone for appropriate patients with an unmet medical need. Specifically, the committee recommended that NICE request further clarification and analyses from Bayer, which should be made available for the second appraisal committee meeting, and should include: 1. a comparison of finerenone with sodium–glucose cotransporter-2 (SGLT2) inhibitors (see comment 3) 2. all data from the FIGARO-DKD and FIDELITY studies that are directly relevant to the decision problem in this appraisal (see comment 4) 3. updating the effectiveness data in the cost-effectiveness model with new point estimates from the additional clinical data (see comment 4) 4. cost-effectiveness scenario analyses of finerenone used at second line (compared with SGLT2 inhibitors in an SGLT2 inhibitor-naive population) and at third line (as an add-on to second-line SGLT2 inhibitors in an SGLT2 inhibitor-experienced population) (see comments 5 and 9) 5. comparisons of transition probabilities over time, and model predictions of time to events

	compared with empirical data from the trial (see comment 6) 6. base cases with both trial-based utilities and utilities from literature sources that are more recent and relevant than currently used in the model (see comment 2, 4, 5 and 7) 7. scenario analyses of alternative treatment waning effects for finerenone (see comment 7) 8. a valid probabilistic sensitivity analysis that includes accounting for parameter uncertainty in transition probabilities to reflect CKD progression (see comment 8) We take each of these points and address them in our response below.
2	Firstly, further to the 1st appraisal committee meeting, we have implemented the ERG/NICE preferred assumptions to the cost effectiveness model as follows: 1. Finerenone is discontinued if the eGFR falls below 15 ml/min/1.73 m^2, i.e. end stage renal disease, at the point where a patient requires renal replacement therapy (RRT) (this change was included in the updated CE model submitted before the 1st committee meeting), 2. The sources of the modelled utilities have been updated as a result of committee discussions. At the 1st committee meeting, two sets of utilities (based on FIDELIO-DKD and the literature) were discussed and compared with the utilities used in NICE TA775 (16). It was concluded that utilities for the CKD stages i.e., CKD 1/2, CKD 3, CKD 4 and CKD 5 without RRT obtained from FIDELIO-DKD were reliable taking into account the number of observations in the population most relevant for this submission. However, for disutilities applied for dialyses, kidney transplants, CV events and Other Health Events, it was considered that due to the low number of these events in the trial, their impact on quality of life could not have been robustly assessed based on FIDELIO-DKD. It was suggested at the committee meeting that the utilities for these events should be based on the most up to date literature. In line with that, Bayer includes the utilities from the recently published NICE guideline *Type 2 diabetes in adults: management* NG28 (17). The final sources of modelled utilities are set out below and summarized in Table 1: a. Utility for CKD 1 - CKD 5 without RRT based on the FIDELIO-DKD trial. Note that the ERG previously highlighted that the utility for CKD 1 / 2 did not exhibit clear face validity when compared to that obtained for CKD 3. To address this, the utility value for CKD 1/2 was assumed to be the same as for CKD 3. The value for CKD 3 has been selected as it was estimated based on a larger cohort from the FIDELIO-DKD trial. b. Utility for dialysis and kidney transplant based on the recently published NICE guideline *Type 2 diabetes in adults: management* NG28 (17), c. Utility for CV events based on NG28 (17), d. Utility for Other Health Events based on a systematic literature review as presented during the appraisal process (except for a sustained decrease in eGFR of 40% or more from baseline, which is sourced from FIDELIO-DKD, as no

alternative sources were identified in the literature).

Table 1. Utilities included in the CE model - summary

	Value	Source
Utility		
CKD1/2	[redacted]	FIDELIO-DKD trial (assumed as for CKD 3)
CKD3	[redacted]	FIDELIO-DKD trial
CKD4	[redacted]	FIDELIO-DKD trial
CKD 5 w/o RRT	[redacted]	FIDELIO-DKD trial
Dialysis (acute)	0.595	NG28 (17)
Dialysis (post-acute)	0.595	NG28 (17)
Kidney Transplant (acute)	0.748	NG28 (17)
Kidney Transplant (post-acute)	0.748	NG28 (17)
Utility decrements associated with first CV event, acute		
MI	-0.060	NG28 (17)
Stroke	-0.160	NG28 (17)
Hospitalization for HF	-0.110	NG28 (17)
Utility decrements associated with first CV event, post-acute		
MI	-0.032	NG28 (17), incurred only by patient with no CV history at baseline (45.9% of patients had CV history in the FIDELIO-DKD)
Stroke	-0.087	NG28 (17), incurred only by patient with no CV history at baseline (45.9% of patients had CV history in the FIDELIO-DKD)
Hospitalization for HF	-0.060	NG28 (17), incurred only by patient with no CV history at baseline (45.9% of patients had CV history in the FIDELIO-DKD)
Utility decrements associated with Other Health Events		
Hyperkalaemia, leading to hospitalisation	-0.030	Palaka 2020 (18)
Sustained decrease in eGFR ≥ 40% from baseline (over at least 4 weeks)	[redacted]	FIDELIO-DKD trial
New onset of atrial fibrillation / atrial flutter	-0.014	Rinciog 2019 (19)
Hyperkalaemia, not leading to hospitalisation	-0.030	Palaka 2020 (18)

3. A different method for modelling transition probabilities has been introduced into the model.

   The ERG was concerned that the transition probabilities in the model were not subjected to any form of sensitivity analysis. In order to address this concern, Bayer had to change the approach for handling transition probabilities. Transition probabilities for background therapy (BT) remain unchanged (See Table 43 in the main submission), however were sampled in the PSA from the Dirichlet distribution.

   - Transition probabilities from the FIN + BT arm were obtained relative to the BT transitions, as they were for CV events and Other Health Events, by applying HRs from the FIDELIO-DKD study. Three HRs reflecting the impact of finerenone on CKD progression were available in the trial. These HRs correspond to the transitions to CKD 5 without dialysis, to acute dialysis and kidney transplant. However, no impact of treatment on transplantation was assumed due to the limited number of transplants in the trial. It was also confirmed by clinical experts that kidney transplant is dependent on other aspects including donor availability, rather than any kind of treatment. The HRs applied are presented in the table below.

Table 2. HRs for Renal Events for FIN + BT arm, FIDELIO-DKD label population

Description	HR: FIN + BT vs BT [95%CI]
Onset of eGFR decrease < 15 mL/min/1.73m^2 sustained over at least 4 weeks	[redacted]
Progression to dialysis	[redacted]
Progression to kidney transplant	[redacted]

*Assumed no differences based on the clinical validation

HRs were applied to the BT transition probabilities by using the following formula:

$$P_{Finerenone+BT} = 1 - (1 - P_{BT})^{HR}$$

Following the inclusion of HRs, the transitions were adjusted to sum to 1. This was performed by weighting, with weights being the transitions as in the BT matrix (Table 43 in the main submission).

The transition probabilities for FIN + BT arm are presented in the table below.

Table 3. Transition probabilities for FIN + BT, FIDELIO-DKD label population

From \ To	CKD1/2	CKD3	CKD4	CKD5 w/o 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 w/o 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]

This approach enabled a robust PSA to be conducted, with inclusion of the variability of applied HRs and sampling the BT probabilities from the Dirichlet distribution. The transition probability matrix contains multinomial data divided into several categories, with the single transition always in range between 0 and 1, and the sum of transitions from each category equal to 1. In line with that, according to standard approaches (20), the Dirichlet distribution (multivariate generalization of the beta distribution) has been chosen for transiting among model health states.

To test the impact of the new approach to the transition probabilities on the model estimates, the results of the modified model were compared with the last version of the model Bayer submitted to NICE.

The impact on the ICER, and number of different events has been presented in the table below (Table 4). The results of the new approach to the transition probabilities are consistent with the original approach and somewhat conservative.

Table 4. Model validation for different transition probabilities options

	Transition probabilities directly from FIDELIO-DKD trial	Transition probabilities for FIN + BT by applying relevant HRs to the BT transitions
Incremental costs, discounted	£1,796	£1,687
Incremental LYs, discounted	0.134	0.127
Incremental QALYs, discounted	0.132	0.127
ICER, discounted	£13,626	£14,049
Average number of CV events, undiscounted	-0.073	-0.075
Average number of CV deaths, undiscounted	-0.002	-0.002
Average number of LYs with no CV event	0.327	0.322
Average number of LYs without RRT	0.331	0.335

4. Applying the revised NHS list price of finerenone of £1.31/ day

The impact of the changes on the ICER, and step-by-step results are presented in the table below.

Table 5. Deterministic results

Preferred assumption	Cumulative ICER, £/QALY
Base case (as for the company model at the 1st committee meeting)	£13,626
#1 ERG/AC preferred assumption Finerenone is discontinued if the eGFR falls below 15 ml/min/1.73 m^2, that is end stage renal disease (RRT)	£13,626 (already accounted for)
#2 Transition probabilities based of HRs	£14,049
#3 ERG/AC preferred assumption Source of utility	£15,190
#4 Finerenone price (£1.31)	£5,464

By taking account of these preferred ERG/ NICE committee assumptions and applying the recently agreed NHS list price, Bayer considers this ICER i.e. £5,464 to be the revised base case. We address the requests for further clarification and analyses in the following comments and these are indeed informative, but we maintain, due to the limitations of this additional analysis that the base case ICER of £5,464 is the most robust to inform committee decision making

The base case deterministic results are supported with robust PSA presented further in comment 8.

3

Bayer acknowledge the request from the appraisal committee to conduct a comparison to SGLT2i for this appraisal. However, Bayer retain the position that we have held throughout the process that SGLT2i are not an appropriate comparator in this appraisal and will not be presenting this analysis.

We refer to the 2013 NICE Methods Guide in place at the time of making our submission (21) which states in section 6.2.2. that the committee must consider several factors, when selecting the most appropriate comparator(s) one of which is “established NHS practice in England”. Additionally, section 6.2.3. states that the factors are not considered equally; rather, the committee will normally be guided by established practice in the NHS.

Whilst Bayer accepts the comments made by experts at the committee meeting that SGLT2i use will inevitably increase as a result of recent guidelines and technology appraisal guidance, experts also stated that these drugs are not yet standard of care in clinical practice. Clinicians also commented during the meeting that it took 10 years after the landmark ACEI / ARB trials for them to become established in clinical practice in CKD.

The ACD confirms the Committee’s conclusion that SGLT2 inhibitors are not currently established NHS practice:” The committee recognised that SGLT2 inhibitors were not established NHS treatment for CKD during the FIDELIO-DKD and FIGARO-DKD trials but could still be ***considered a relevant comparator in the future****.”* In addition, *“*The committee agreed that SGLT2 inhibitor use ***will*** increase and ***become*** incorporated into standard practice*.”* Whether such products may become established treatments in the future is not of course the

	relevant test under NICE's Methods Guide and we respectfully submit that as it is accepted they are not currently established treatments, they cannot properly be considered as comparators for the purposes of this appraisal. The NICE website currently states that *"a comparator technology is one that is currently used in the NHS and could be replaced by the intervention, if recommended."(22)* An expert view stated at the appraisal committee meeting was that a choice would generally not be made i.e. that finerenone would not *replace* SGLT2i, and that with time, SGLT2i will form part of background therapy, with finerenone being used in combination with SGLT2i or in those unsuitable for SGLT2i. Finally, Bayer would like to point out that the delay in the NICE appraisal of finerenone introduced by NICE, lead to the appraisal committee for finerenone being held after, instead of before, the appraisal committee for dapagliflozin. If the original timelines been followed, then finerenone would have been appraised at committee prior to the decision being taken by NICE regarding dapagliflozin.
4	The Committee have expressed an interest in reviewing the overlapping data of the FIGARO-DKD study (23) with the FIDELIO-DKD study (12), matching the licensed population i.e. adults with chronic kidney disease (stage 3 and 4 with albuminuria*), * eGFR ≥25ml/min/1.73m^2. Bayer would like to address the comments made in the ACD regarding the results from FIDELIO-DKD being underpowered for the population matching the marketing authorisation. The FIDELIO-DKD label population represents approximately 90% of the entire FIDELIO-DKD population, resulting in a marginal loss of power. FIDELIO-DKD was powered at 90% and the results of the label population are very close to the results of the full FIDELIO-DKD population. This consequently highlights that the FIDELIO-DKD label population provides a solid basis for decision making by NICE. Bayer also presented the full analysis set (FAS) from FIDELIO-DKD in the submission and in scenario analysis this was shown to be cost-effective compared to standard of care, with a revised ICER after technical engagement of £11,976 (and corresponding ICER of £6,047 in line with the updated model presented in comment 2). Bayer's position is that decision making should be based on the FIDELIO-DKD label dataset as this is reflective of the data on which the marketing authorisation was granted. Indeed, there are challenges in providing the overlapping FIDELIO-DKD and FIGARO-DKD data which generate concerns about its validity for decision making, which we set out below: • The combined analysis of FIDELIO-DKD and FIGARO-DKD limited to the indication ("FIDELIO-label population") was not pre-specified • Such analysis is combining a subgroup of FIDELIO-DKD with a subgroup from FIGARO-DKD and this is questionable from a statistical point of view Despite these limitations, Bayer have updated the cost effectiveness model with the data from the FIDELITY analysis for the label population. The FIDELITY analysis (full analysis set) has been published (24) and represents the pre-specified pooled analysis of the FIDELIO-DKD and FIGARO-DKD trials. Bayer sourced data from our global statistical team for the FIDELITY data that matched the population in the marketing authorisation, the "label population" so that this

could be applied in the updated cost-effectiveness model.

The inputs from the FIDELITY- label population are presented in Table 6.

The updated inputs include all clinical data available for finerenone, in the population of patients with CKD 3 and CKD 4 patients with albuminuria (i.e., eGFR ≥ 25 to <60ml/min/1.73m^2 at baseline) and type 2 diabetes.

Table 6. CE model inputs, FIDELITY- label population

Description	Value
Settings	
Mean age [years]	[redacted]
Proportion of males	[redacted]
Cumulative risk of premature discontinuation at 4 years, finerenone	[redacted]
Proportion of patients with CKD1/2 at baseline	[redacted]
Proportion of patients with CKD3 at baseline	[redacted]
Proportion of patients with CKD4 at baseline	[redacted]
Proportion of patients with CKD 5 w/o RRT at baseline	[redacted]
Proportion of patients with Dialysis at baseline	[redacted]
Proportion of patients with Kidney Transplant at baseline	[redacted]
BT Main Events rates	
Four-month risk of first modelled CV event, CKD1/2	[redacted]
Four-month risk of first modelled CV event, CKD3	[redacted]
Four-month risk of first modelled CV event, CKD4	[redacted]
Four-month risk of first modelled CV event, CKD 5 w/o RRT	[redacted]
Four-month risk of first modelled CV event, Dialysis (acute)	[redacted]
Four-month risk of first modelled CV event, Dialysis (post-acute)	[redacted]
Four-month risk of first modelled CV event, Kidney Transplant (acute)	[redacted]
Four-month risk of first modelled CV event, Kidney Transplant (post-acute)	[redacted]
BT other events rates	
Four-month risk of hyperkalaemia leading to hospitalisation, no modelled CV event	[redacted]
Four-month risk of new onset of atrial fibrillation / atrial flutter, no modelled CV event	[redacted]
Four-month risk of hyperkalaemia not leading to hospitalisation, no modelled CV event	[redacted]
Four-month risk of subsequent CV event, post-CV event	[redacted]
Four-month risk of hyperkalaemia leading to hospitalisation, post-CV event	[redacted]
Four-month risk of new onset of atrial fibrillation / atrial flutter, post-CV event	[redacted]
Four-month risk of hyperkalaemia not leading to hospitalisation, post-CV event	[redacted]

BT mortality rates	
Four-month CV mortality risk, CKD1/2	[redacted]
Four-month CV mortality risk, CKD3	[redacted]
Four-month CV mortality risk, CKD4	[redacted]
Four-month CV mortality risk, CKD5 w/o RRT	[redacted]
Four-month CV mortality risk, Dialysis (acute)	[redacted]
Four-month CV mortality risk, Dialysis (post-acute)	[redacted]
Four-month CV mortality risk, Kidney Transplant (acute)	[redacted]
Four-month CV mortality risk, Kidney Transplant (post-acute)	[redacted]
Four-month renal mortality risk, CKD5 w/o RRT	[redacted]
HR finerenone	
HR: Onset of eGFR decrease < 15 mL/min, FIN+BT vs BT	[redacted]
HR: Progression to dialysis, FIN + BT vs BT	[redacted]
HR: CV death, FIN + BT vs BT	[redacted]
HR: Renal death, CKD 5 w/o RRT, FIN + BT vs BT	[redacted]
HR: First modelled CV event, FIN + BT vs BT	[redacted]
HR: Subsequent CV event, FIN + BT vs BT	[redacted]
HR: Hyperkalaemia leading to hospitalisation, FIN + BT vs BT	[redacted]
HR: Hyperkalaemia not leading to hospitalisation, FIN + BT vs BT	[redacted]
HR: New onset of atrial fibrillation / atrial flutter, FIN + BT vs BT	[redacted]
CV events distribution	
Proportion of first modelled CV events that are MI	[redacted]
Proportion of first modelled CV events that are IS stroke	[redacted]
Proportion of first modelled CV events that are ICH stroke	[redacted]
Proportion of first modelled CV events that are Hospitalisations for HF	[redacted]

[1]Assumed as weighted average across the FIDELITY-label population, not differentiated by CKD stage, as suggested by ERG (point 6.2.1 of the ERG report)

* The discontinuation has been recalibrated as suggested by the ERG (point 6.1 of the ERG report), to ensure the modelled proportion of patients on treatment at 4 years aligned with the proportion observed in the FIDELIO-DKD study.

The transition probabilities used in the updated model are presented below. The matrix for BT is taken directly from the FIDELITY-label population. For the FIN + BT arm the transition probabilities are obtained as in the new company base case i.e. based on the BT matrix by applying HRs from the FIDELITY-DKD trial. The HRs are presented in the table above (Table 6. CE model inputs, FIDELITY- label population).

The transition matrices are presented below (Table 7, Table 8).

Table 7. Transition probabilities for BT, FIDELITY label

To / From	CKD1/2	CKD3	CKD4	CKD5 w/o 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 w/o 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]

Table 8. Transition probabilities for FIN + BT, FIDELITY label

To / From	CKD1/2	CKD3	CKD4	CKD5 w/o 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 w/o 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]

The population-specific inputs have been included in line with the FIDELITY- label population as presented in Table 6, Table 7, and Table 8. All other inputs and assumptions, as they are not population-dependent, remain unchanged (as for the updated FIDELIO-DKD label base case in comment 2).

The deterministic results are presented in the table below (Table 9). The results are based on the updated model as presented in comment 2 (Table 5).

	Table 9. Deterministic results, FIDELITY- label population **Incremental costs, undiscounted** | **Incremental costs, discounted** | **Incremental QALYs, undiscounted** | **Incremental QALYs, discounted** | **ICER, undiscounted** | **ICER, discounted** £1,102 | £1,016 | 0.12 | 0.08 | £9,167 | £12,710
5	As explained in comment 3 above, Bayer is not presenting a cost-effectiveness scenario analysis of finerenone used at second line (compared with SGLT2 inhibitors in an SGLT2 inhibitor-naive population). We have been advised by clinicians that they would like finerenone to be made available as an option for add-on to standard of care with ACEI/ARB in line with the marketing authorisation. Indeed, clinical experts stated during the meeting, as reflected in the ACD that "*a range of therapies are needed to target different causes of kidney damage, and that all of these treatments will likely work together for better renal protection than any of them alone*". We have been advised by experts however that finerenone will primarily be initiated in patients who are unsuitable for SGLT2i or as add-on to SGLT2i in those with high residual risk of adverse outcomes, in line with the marketing authorisation. Further, clinicians have advised us that it is possible to define the patients who are unsuitable for, or who become intolerant of, SGLT2i. Whilst Bayer maintain the position that these drugs are not yet standard of care, we have been advised that for patients who cannot take SGLT2i, then finerenone addresses a "substantial unmet medical need" as the alternative for these patients is standard of care with ACEI/ ARB alone. Please see more detail regarding this group and the expert consensus statement leading to this definition in comments 9 and 10. To address the request in the ACD (data for add-on to SGLT2 inhibitors), we set out below the supportive evidence for combined use of finerenone in addition to standard of care with ACEI/ARB plus SGLT2i with associated cost-effectiveness analysis. **Supportive evidence for combined use of finerenone and SGLT2i** **Analysis of FIDELIO-DKD data and FIDELITY data** In the FIDELIO-DKD sub analysis considering baseline use of SGLT2i, the benefits of finerenone on kidney and CV outcomes in patients with CKD and T2D appeared consistent in the absence or presence of SGLT-2i use at baseline (interaction p-value 0.21 and 0.46, respectively), or at any time during the trial (25). Regarding safety, this was balanced with or without SGLT-2i use at baseline, with fewer hyperkalaemia events with finerenone in the SGLT-2i group (8.1% vs. 18.7% without) (25). An analysis of the relationship between finerenone exposure in the FIDELIO-DKD study and the time to reach the key composite kidney endpoint, including prognostic factor (PF) such as baseline use of SGLT-2is or non-use was conducted. The Kaplan-Meier (KM) curves indicated a time-to-event (TTE) approach when a Weibull hazard model was used to investigate the exposure/response (ER). Co-medications with SGLT-2is decrease the hazard for the primary endpoint by [redacted] % (95% CI: [redacted] %) indicating an additive effect on top of finerenone; SGLT2i use did not significantly modify the drug effect (26).

The pre-specified FIDELITY analysis can provide more information on combination use of finerenone with SGLT2i. In this analysis set, 6.7% of patients were receiving SGLT2i at baseline and in the finerenone group, 11.8% of patients initiated SGLT2i after start of study drug (24). The benefits of finerenone on kidney and CV outcomes in patients with CKD and T2D in the FIDELITY analysis appeared consistent in the absence or presence of SGLT-2i use at baseline (interaction p-value [redacted] and [redacted], respectively), with the HRs [redacted] combined use of SGLT2i and finerenone.

UACR

Due to the low number of subjects with events in the FIDELIO-DKD trial, interpretability of subgroup data is limited, and UACR, a key predictor for CKD progression as strongly correlated with ESRD and a marker of CV risk, is perceived as the most applicable parameter to show efficacy (27).

A similar reduction in UACR from baseline to month 4 in the FIDELIO-DKD study was observed after treatment with finerenone in those who received an SGLT-2i at baseline and those who did not, with a 25% and a 31% reduction versus placebo, respectively (ratio of least-squares means = 0.75, 95% CI = 0.62–0.90 with an SGLT-2i and 0.69, 95% CI = 0.66–0.71 without an SGLT-2i, $P_{interaction}$ = 0.31). The lower mean UACR observed with finerenone compared with placebo at month 4 was maintained for the duration of the study with no apparent effect of SGLT-2i treatment at baseline (25). The data reveal that finerenone improved UACR reduction in patients who were already receiving an SGLT-2i, i.e. a drug known to reduce UACR (25).

Figure 1: Line plot for least square means for ratio to baseline of UACR values by visit and by SGLT-2 inhibitor use at baseline = YES (FAS)(27)

BAY 94 – 8862 = Finerenone

In 2018, a workshop led by the National Kidney Foundation, in collaboration with the FDA and EMA, evaluated whether changes in albuminuria or eGFR could be surrogate end points for kidney disease progression in clinical trials, and it was concluded that a UACR reduction of 21% to 27% is predictive of a benefit in clinical outcome in patients with UACR ≥30mg/g (28). As

described above, finerenone was found in the FIDELIO-DKD study to reduce UACR by an additional 25% in those patients receiving SGLT2i at baseline.

To further explore the benefit of finerenone added to SGLT-2i use over time, SGLT-2i use was applied as a time dependent covariate. Cox proportional hazards models including SGLT-2i intake as time-dependent covariate with and without variable selection for the primary renal endpoint demonstrated the [redacted] (27).

In addition, SGLT-2i use was tested (*posthoc*) for its potential to modify the treatment effect of finerenone in popPK analyses along with exposure versus time-to-event evaluations for the primary kidney composite endpoint based on FIDELIO-DKD data. [redacted] (27).

A population pharmacokinetic/pharmacodynamics (popPKPD) model was developed to assess the finerenone dose-exposure-response relationship for urine albumin-to creatinine ratio (UACR) and eGFR and the impact of combined SGLT2i-finerenone use using patient level data from the FIDELIO-DKD trial. The popPKPD model adequately described effects of finerenone exposure in reducing UACR and slowing eGFR decline over time. The reduction in UACR achieved with finerenone during the first year predicted its subsequent effect in slowing progressive eGFR decline. SGLT2i use did not modify finerenone efficacy and indicated with 97.5% confidence that finerenone was at least 94.1% as efficacious in reducing UACR in patients using SGLT2i compared with patients not using an SGLT2i. The results demonstrate independent and additive effects of SGLT2i on top of finerenone (29, 30).

A post hoc analysis of the CREDENCE trial reported that each 30% decrease in UACR over the first 26 weeks of canagliflozin treatment was independently associated with a lower hazard of cardiorenal events. It was also observed that there was a strong association between residual UACR at week 26 with cardiorenal outcomes; and residual albuminuria at week 26 of canagliflozin therapy was associated with similar cardiorenal risk as patients who received placebo (31). These findings underscore the likelihood that any therapies that confer further lowering of UACR on top of that from SGLT-2is, as is the case with finerenone, are likely to provide additional kidney and cardiovascular benefits beyond those of SGLT-2is alone (25). Indeed, clinical experts at the committee meeting advised that proteinuria is a “red flag” to be treated.

Summary

In summary, it can be concluded that co-administration of finerenone and SGLT-2i results in an independent and additive benefit on clinical outcomes. The additive effect is most evident from the additional UACR reduction of 25% in subjects already treated with an SGLT-2i at baseline, a treatment that is known to reduce albuminuria, and [redacted]. UACR is considered the most appropriate marker to show renal efficacy in smaller subgroups providing sufficient power due to its strong correlation to kidney failure. Complementary to the clinical data, [redacted] (27).

Cost-effectiveness analysis of combined use of finerenone and SGLT2i

Use of SGLT2 inhibitors as part of background therapy (BT) impacts the baseline risk of CKD progression and CV events among patients with CKD and T2D. To address this issue, an SGLT2is adjustment has been incorporated into the CE model, in order not to overestimate the absolute QALY gain with finerenone.

It has been assumed that the impact of SGLT2 inhibitors on modelled events is reflected by the HRs for CKD progression, CV death, and risk of first CV event according to the results of the DAPA-CKD study (32) (Table 10). Dapagliflozin has been selected as the SGLT2i for this analysis due to the recent publication of a NICE technology appraisal (16).

Table 10. HRs – dapagliflozin adjustment based on DAPA-CKD trial

Description	HR: Dapagliflozin + BT vs BT [95%CI]
Onset of eGFR decrease < 15 mL/min/1.73m2 sustained over at least 4 weeks (days)	0.73 [0.52;1.03]
Progression to dialysis	0.68 [0.47;0.98]
Progression to kidney transplant	1.00 [1.00;1.00]
First CV event (endpoint from DAPA-CKD study: CV death or hospital admission for HF)	0.70 [0.53;0.92]

The HRs, as presented in Table 10, were first used to calculate probabilities for non-SGLT2 inhibitors users and SGLT2 inhibitors users based on BT data from FIDELIO-DKD, in which 6.2% of patients used SGLT2 inhibitors. The probabilities were then weighted by the proportion of SGLT2 inhibitors users considered in the model (assumed 100%). This is further explained below.

The transition probabilities from FIDELIO-DKD for BT (for all patients i.e., SGLT2 inhibitors users and those who do not use SGLT2 inhibitors) were adjusted with the use of HRs from Table 10

- CKD progression: two publicly available HRs for SGLT2 inhibitors were used:
    - time to a sustained decrease in eGFR to <15mL/min/1.73 m^2
    - time to dialysis,
- CV events: HRs for time to CV death or hospital admission for HF.

The following formula is used to calculate the probability for all patients in the FIDELIO-DKD trial:

$$P_{ALL} = \%\ SGLT2 * (1 - (1 - P_{nonSGLT2})^{HR}) + (1 - \%\ SGLT2) * P_{nonSGLT2}$$

P_{ALL} – probability for all patients in FIDELIO-DKD, % SGLT2 – percentage of SGLT2 inhibitors users in FIDELIO-DKD, HR – based on the clinical results for SGLT2 inhibitors (e.g., DAPA-CKD), $P_{nonSGLT2}$ – probability for patients who do not use SGLT2 inhibitors in FIDELIO-DKD.

Thus, a specific probability for patients who do not use SGLT2 inhibitors in FIDELIO-DKD is calculated. Based on this, and the HRs for SGLT2 inhibitors, the model calculates the weighted

probability with the assumption that 100% of patients use SGLT2 inhibitors as part of BT.

The results from the model for the scenario that 100% of patients use SGLT2is as part of BT are presented in Table 11 below.

Table 11. Deterministic results, FIDELIO-DKD label – add-on to SGLT2I

Incremental costs, undiscounted	Incremental costs, discounted	Incremental QALYs, undiscounted	Incremental QALYs, discounted	ICER, undiscounted	ICER, discounted
£1,344	£1,216	0.14	0.09	£9,771	£12,984

As discussed in comment 2, Bayer considers that the FIDELIO-DKD data presented in our submission provides a solid basis for decision making, with the FIDELITY analysis subject to limitations when considering the label population. However, we present the same analysis below for the FIDELITY-label population.

Table 12. Deterministic results, FIDELITY- label – add-on to SGLT2I

Incremental costs, undiscounted	Incremental costs, discounted	Incremental QALYs, undiscounted	Incremental QALYs, discounted	ICER, undiscounted	ICER, discounted
£1,737	£1,528	0.10	0.07	£17,476	£23,432

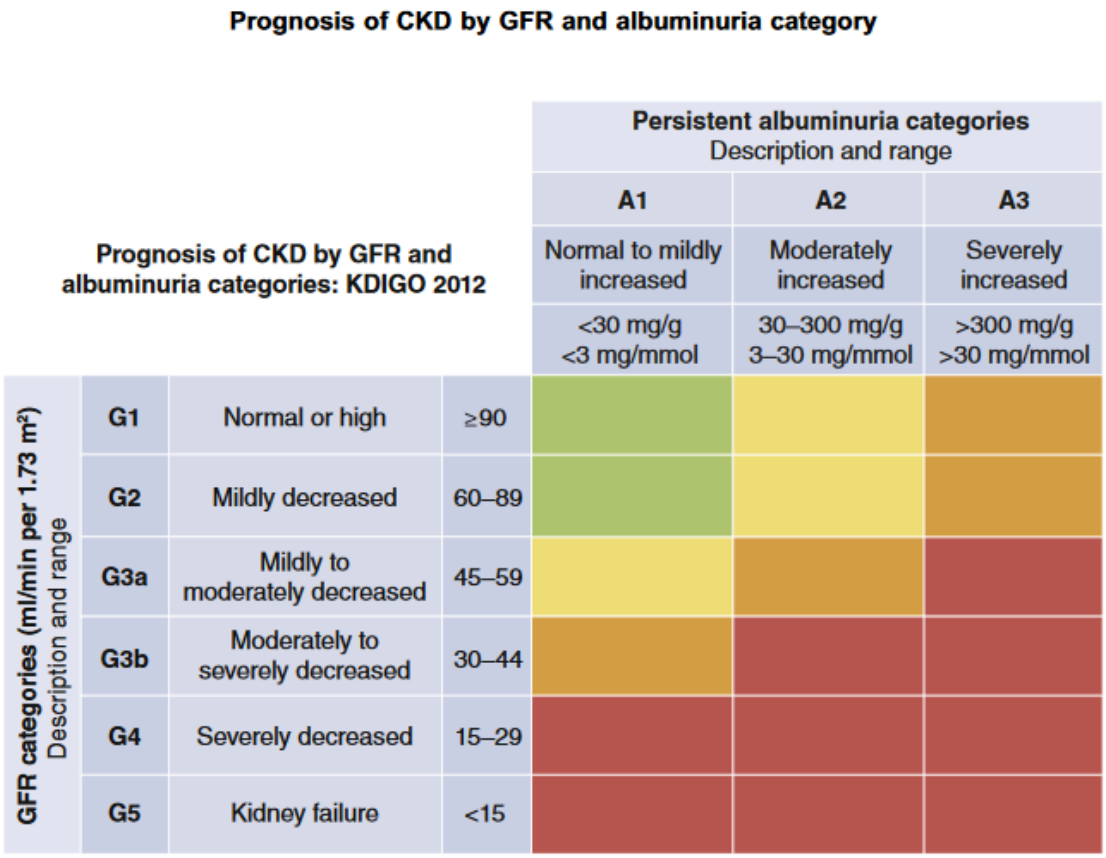
Discussions with clinical experts indicate that finerenone would initially be added to an SGLT2i (and ACEI/ARB) in those patients at highest risk of adverse outcomes. Such a group would be those with persistent albuminuria.

A review paper considering the role of albuminuria in detecting cardio-renal risk and outcome in diabetes, reports that increased albuminuria promotes higher tubular albumin reabsorption, with consequent intra-renal trafficking, which in turn activates the release of several inflammatory and pro-fibrotic mediators accelerating renal damage. The review goes on to state that these mechanisms explain why albuminuria is now considered the principal risk factor predicting the faster progression of renal disease towards end-stage renal disease (ESRD) (33). Indeed, albuminuria is a strong predictor of the risk of adverse outcomes in CKD (28) and a higher ACR has been found to be significantly associated with mortality and ESRD in these patients (34).

In a paper that reports the results of an individual patient-level Bayesian meta-analysis of treatment comparisons from RCTs, it was found that across all studies, with a meta-regression slope of 0·89 (95% Bayesian credible interval [BCI] 0·13–1·70), each 30% decrease in geometric mean albuminuria by the treatment relative to the control was associated with an average 27% lower hazard for the clinical endpoint (composite of treated end-stage kidney disease, eGFR < 15ml/ min/ 1.73m^2, or doubling of serum creatinine), (95% BCI 5–45%; median R^2 0·47, 95% BCI 0·02–0·96). The association strengthened after restricting analyses to patients with baseline albuminuria of more than 30 mg/g (i.e. 3·4 mg/mmol; R^2 0·72, 0·05–0·99]) (35).

Patients with CKD who fall within the eGFR category of G3a – G4 and have albuminuria levels that place them in the category A3 are all at very high risk of adverse outcomes according to the KDIGO classification (see figure below)(36).

Figure 2: Prognosis of CKD by GFR and albuminuria category (KDIGO)



Green, low risk (if no other markers of kidney disease, no CKD); yellow, moderately increased risk; orange, high risk; red, very high risk.

In an as yet unpublished CPRD analysis of patients with T2D and CKD, [redacted] (37).

In addition to expert opinion, there is therefore biological plausibility that patients with high levels of albuminuria could be a priority group for further optimisation of therapy to reduce the risk of adverse renal and CV outcomes.

As described above, data from FIDELIO-DKD reveal that finerenone improved UACR reduction by 25% in patients who were already receiving an SGLT-2i, i.e. a drug known to reduce UACR (25)

Bayer have explored the cost-effectiveness of add-on therapy (to ACEI/ARB and SGLT2i), in a particularly high-risk subgroup, should NICE consider that finerenone cannot be recommended in a wider population. This subgroup defined by eGFR and UACR is as follows;

Patients from the label population from FIDELITY in the A3 category of albuminuria i.e. eGFR ≥ 25 – < 60 + A3 (i.e., albuminuria >= 300mg/g).

In line with the inclusion/exclusion criteria for the FIGARO-DKD and FIDELIO-DKD trials, this population comes exclusively from the FIDELIO-DKD trial.

The results are presented in the table below, Table 13

Table 13. Deterministic results, FIDELITY- label + A3 – add-on to SGLT2I

Incremental costs, undiscounted	Incremental costs, discounted	Incremental QALYs, undiscounted	Incremental QALYs, discounted	ICER, undiscounted	ICER, discounted
£748	£768	0.12	0.08	£6,249	£9,554

6

An external validation was conducted to test the credibility of the cost-effectiveness model. The objective of the external validation step was to ensure that the model results are in line with the FIDELIO-DKD outcomes. The incidence of first CV events and CV deaths, as well as, the number of patients undergoing dialysis were compared with the model predictions. For each of the above-mentioned outcomes, a Kaplan–Meier curve for the observed cumulative event-free survival data from the trial was plotted against the cumulative event-free survival curve predicted by the model.

In order to test the null hypothesis of no difference between observed and predicted survival curves, Guyot's algorithm was used to produce patient level data from survival probabilities given by the model. The following statistical tests were then performed to assess whether the modelled survival coincided with that observed in the study:

- Log-rank test (using tests from survival and coin packages in R),
- Gehan-Breslow test.

The following assumptions were applied in the model for the purposes of this validation:

- A 48-month time horizon was considered (in line with FIDELIO-DKD follow-up period).
- Background mortality was not included.
- The increased mortality risk due to CKD stage as well as after the first CV event was not included.
- Half-cycle correction was not considered.
- For the number of patients undergoing dialysis, no dialysis was initiated in the model in the first three cycles (to reflect the FIDELIO-DKD data)
- No discontinuation was applied for the FIN+BT.

The model was validated on the overall population (ITT population) based on patient level data from FIDELIO-DKD.

The model results reflect the incidence of the first CV event observed in the FIDELIO-DKD trial. The model estimations for BT (Figure 3) are within the range of the FIDELIO-DKD confidence intervals (CIs).

The use of the HR in the model for the time to first CV event (0.87 in range [0.74;1.02]) for finerenone + BT vs. BT reflects the study results well (Figure 4).

The confidence intervals, determined by using lower and higher bounds of the HR from FIDELIO-

DKD in the model, also coincide with the confidence intervals directly from FIDELIO-DKD (Figure 5).

The results of the statistical tests indicate no reason to reject the null hypothesis of no difference between observed and modelled curves. The estimated p-values are presented in the table below.

Table 14. P-values for statistical tests comparing first CV event-free survival curves

Test	**Log rank** (survival package)	**Log rank** (coin package)	**Gehan-Breslow**
BT	0.900	0.916	0.784
FIN+BT	0.800	0.831	0.782

Figure 3 Time to first CV event for BT: model vs. FIDELIO-DKD results

Figure 4. Time to first CV event for finerenone + BT: model vs. FIDELIO-DKD results

Figure 5. Time to first CV event for finerenone + BT with CIs for HR: model vs. FIDELIO-DKD results

The validation demonstrates that the model reflects the CV mortality from FIDELIO-DKD. The estimates generated for BT indicate that the model predictions are within the range of the CIs directly observed in FIDELIO-DKD (Figure 6).

The use of the HR for the time to CV death (0.86 in range [0.68;1.08]) for finerenone + BT vs. BT in the model upfront to BT risks, also reflects the study results well (Figure 7).

The confidence intervals, determined by applying the lower and higher bounds of the HR from FIDELIO-DKD (0.68 and 1.08) to the model, also coincide with the CIs directly from FIDELIO-DKD (Figure 8)

Moreover, the results of the statistical tests indicate that there is no reason to reject the null hypothesis of no difference between observed and modelled curves. The estimated p-values are presented in the table below.

Table 15. P-values for statistical tests comparing CV death-free survival curves

Test	**Log rank** (survival package)	**Log rank** (coin package)	**Gehan-Breslow**
BT	0.700	0.711	0.756
FIN + BT	0.600	0.650	0.851

Figure 6. Time to CV death for BT: model vs. FIDELIO-DKD results

Figure 7. Time to CV death for finerenone + BT: model vs. FIDELIO-DKD results

Figure 8. Time to CV death for finerenone + BT with CIs for HR: model vs. FIDELIO-DKD results

It should be noted that, at the beginning of the FIDELIO-DKD trial, very few patients were observed starting dialysis. In the model, the rate of dialysis per cycle was calculated as an average across the entire follow-up of FIDELIO-DKD. Therefore, visual inspection of validation results showed that the model slightly overestimated the incidence of dialysis when the average rate of dialysis was used in the first few cycles. However, at the end of the FIDELIO-DKD duration (four years), the incidence of dialysis observed in the trial was consistent with model predictions.

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. Validation results presented below were generated assuming no dialysis in the model in the first three cycles.

With this assumption, the incidence of dialysis predicted by the model coincides with that observed in FIDELIO-DKD. The estimates generated for BT indicate that the model predictions fall within the range of CIs directly observed in FIDELIO-DKD (Figure 9).

The estimates generated for finerenone + BT arm also reflect the study results well (Figure 10)

Moreover, the result of statistical testing indicates that there are no reasons to reject the null hypothesis of no difference between observed and modelled curves. The estimated p-values are presented in the table below.

Table 16. P-values for statistical tests comparing dialysis-free survival curves

Test	**Log rank** (survival package)	**Log rank** (coin package)	**Gehan-Breslow**
BT	0.700	0.709	0.590
FIN+BT	1.000	0.956	0.945

Figure 9. Time to dialysis for BT: model vs. FIDELIO-DKD results

Figure 10. Time to dialysis for finerenone + BT: model vs. FIDELIO-DKD results

The validation has been also conducted based on the FIDELITY-DKD data. The same approach has been undertaken, and the results are presented in the graphs below.

The model estimations for BT (Figure 11) are within the range of the FIDELITY confidence intervals (CIs).

The use of the HR in the model for the time to first CV event (0.88 in range [0.76; 1.03]) for finerenone + BT vs. BT reflects the study results well (Figure 12)

The confidence intervals, determined by using lower and higher bounds of the HR from FIDELITY in the model, also coincide with the CIs directly from the study (Figure 13)

The results of the statistical tests indicate no reason to reject the null hypothesis of no difference between observed and modelled curves. The estimated p-values are presented in the table below (Table 17).

Table 17. P-values for statistical tests comparing first CV event-free survival curves.

Test	**Log rank** (survival package)	**Log rank** (coin package)	**Gehan-Breslow**
BT	0.600	0.651	0.857
BT + finerenone	0.500	0.550	0.911

Figure 11 Time to first modelled CV event for BT: model vs. FIDELITY results

Figure12. Time to first modelled CV event for finerenone + BT: model vs. FIDELITY results

Figure 13. Time to first modelled CV event for finerenone + BT with CIs for HR: model vs. FIDELITY results

CV death

The validation demonstrates that the model reflects the CV mortality from FIDELITY. The estimates generated for BT indicate that the model predictions are within the range of the CIs directly observed in the FIDELITY study (Figure 14).

The estimated modelled number of cardiovascular deaths based on the HR for the time to CV death (0.88 in range [0.76; 1.02]) for finerenone + BT vs. BT, also reflect the study results (Figure15).

The confidence intervals, determined by applying the lower and higher bounds of the HR from FIDELITY to the model, also coincide with the CIs directly from the trial (Figure 16).

Moreover, the results of the statistical tests indicate that there is no reason to reject the null hypothesis of no difference between observed and modelled curves. The estimated p-values are presented in the table below (Table 18).

Table 18. P-values for statistical tests comparing CV death-free survival curves.

Test	**Log rank** (survival package)	**Log rank** (coin package)	**Gehan-Breslow**
BT	0.600	0.636	0.597
BT + finerenone	0.600	0.636	0.795

Figure 14. Time to CV death for BT: model vs. FIDELITY results

Figure 15. Time to CV death for finerenone + BT: model vs. FIDELITY results

Figure 16. Time to CV death for finerenone + BT with CIs for HR: model vs. FIDELITY results

Number of patients undergoing dialysis

The incidence of dialysis predicted by the Bayer model coincides with that observed in FIDELITY. The estimates generated for BT (Figure 17) indicate that the model predictions are mostly within the range of the FIDELITY confidence intervals (CIs).

The immediate application of the HR for the time to dialysis (0.82 in range [0.65; 1.03]) for finerenone + BT vs. BT in the model reflects the study results well (Figure 18).

The confidence intervals, determined by applying the lower and higher bounds of the HR from FIDELITY to the model, are also consistent with the CIs directly from the FIDELITY analysis (Figure 19).

Moreover, the results of the statistical tests indicate that there are no reasons to reject the null hypothesis of no difference between observed and modelled curves. The estimated p-values are presented in the table below (Table 19).

Table 19. P-values for statistical tests comparing dialysis-free survival curves.

Test	**Log rank** (survival package)	**Log rank** (coin package)	**Gehan-Breslow**

BT	0.100	0.124	0.199
BT + finerenone	0.500	0.492	0.686

Figure 17. Time to dialysis for BT: model vs. FIDELITY results

Figure18. Time to dialysis for finerenone + BT: model vs. FIDELITY results

Figure 19. Time to dialysis for finerenone + BT with CIs for HR: model vs. FIDELITY results

Furthemore, in order to further validate the model estimates, a comparison of patients' distribution across the modelled health states with the trial data has been performed, as requested in the ACD.

The comparison has been made between:

- The percentage of patients in each CKD stage, at the end of each 4-month period, based on the trial data for FIDELIO-DKD - label population (separately for BT, and FIN+BT arm)
- The percentage of patients in each CKD stage, at the end of each 4-month cycle in the CE model for finerenone

The model includes all assumptions as for the external validation (presented at the beginning of this section). Results of the performed comparison are presented in the tables below (Table 20, Table 21).

Table 20. Percentage of patients in each CKD stage, at the end of each 4-month period, BT arm

Months	0	4	8	12	16	20	24	28	32	36	40	44	48
FIDELIO-label													
CKD 1/2	0%	5%	5%	5%	4%	4%	3%	3%	3%	3%	2%	3%	4%
CKD 3	88%	80%	75%	73%	69%	67%	63%	59%	56%	54%	53%	49%	49%
CKD 4	12%	15%	18%	20%	24%	26%	29%	30%	31%	33%	34%	36%	34%
CKD 5	0%	0%	0%	1%	1%	2%	3%	4%	5%	4%	5%	5%	5%
Dialysis	0%	0%	0%	0%	1%	1%	2%	3%	3%	4%	4%	6%	8%
Transplant	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
CE model													
CKD 1/2	0%	2%	3%	4%	4%	4%	4%	4%	4%	4%	3%	3%	3%
CKD 3	88%	79%	73%	69%	65%	63%	61%	59%	58%	57%	55%	54%	53%
CKD 4	12%	18%	22%	25%	27%	29%	29%	30%	30%	30%	30%	30%	30%
CKD 5	0%	1%	1%	2%	3%	3%	4%	4%	4%	4%	4%	4%	5%
Dialysis	0%	0%	0%	0%	1%	1%	2%	3%	4%	5%	6%	7%	8%
Transplant	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%

Table 21. Percentage of patients in each CKD stage, at the end of each 4-month period, Finerenone+BT arm

Months	0	4	8	12	16	20	24	28	32	36	40	44	48
FIDELIO-label													
CKD 1/2	0%	3%	3%	2%	2%	2%	2%	2%	3%	2%	2%	2%	2%
CKD 3	89%	77%	74%	72%	69%	66%	64%	60%	59%	58%	56%	55%	58%
CKD 4	11%	19%	22%	25%	27%	28%	29%	31%	30%	31%	32%	32%	30%
CKD 5	0%	0%	0%	0%	1%	1%	2%	3%	4%	4%	4%	4%	5%
Dialysis	0%	0%	0%	0%	1%	1%	2%	2%	3%	4%	5%	6%	5%
Transplant	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
CE model													
CKD 1/2	0%	2%	3%	4%	4%	4%	4%	4%	4%	3%	3%	3%	3%
CKD 3	88%	79%	72%	68%	64%	61%	59%	57%	56%	55%	53%	52%	51%
CKD 4	12%	18%	22%	25%	27%	28%	29%	29%	30%	30%	29%	29%	29%
CKD 5	0%	0%	1%	2%	2%	3%	3%	3%	4%	4%	4%	4%	4%
Dialysis	0%	0%	0%	0%	1%	1%	2%	2%	3%	4%	5%	6%	6%

Transplant	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%

Please find below the graphs corresponding tothe results in Table 20 and Table 21.

Figure 20. Percentage of patients in each CKD stage, at the end of each 4-month period, BT arm

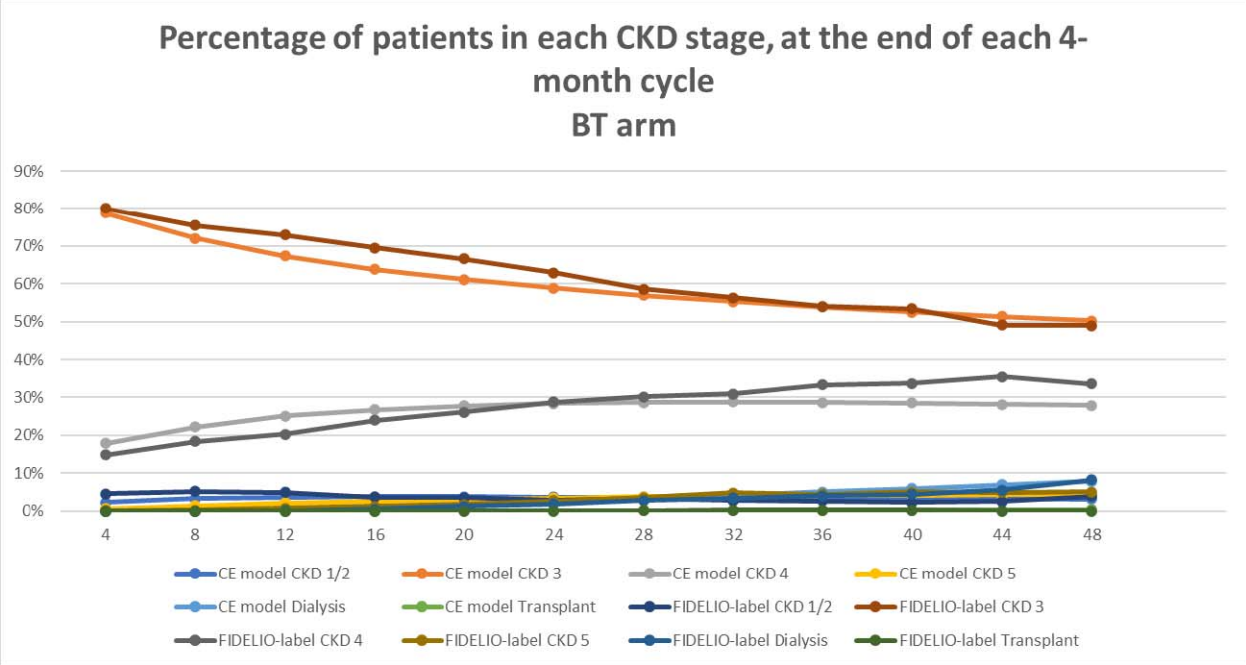
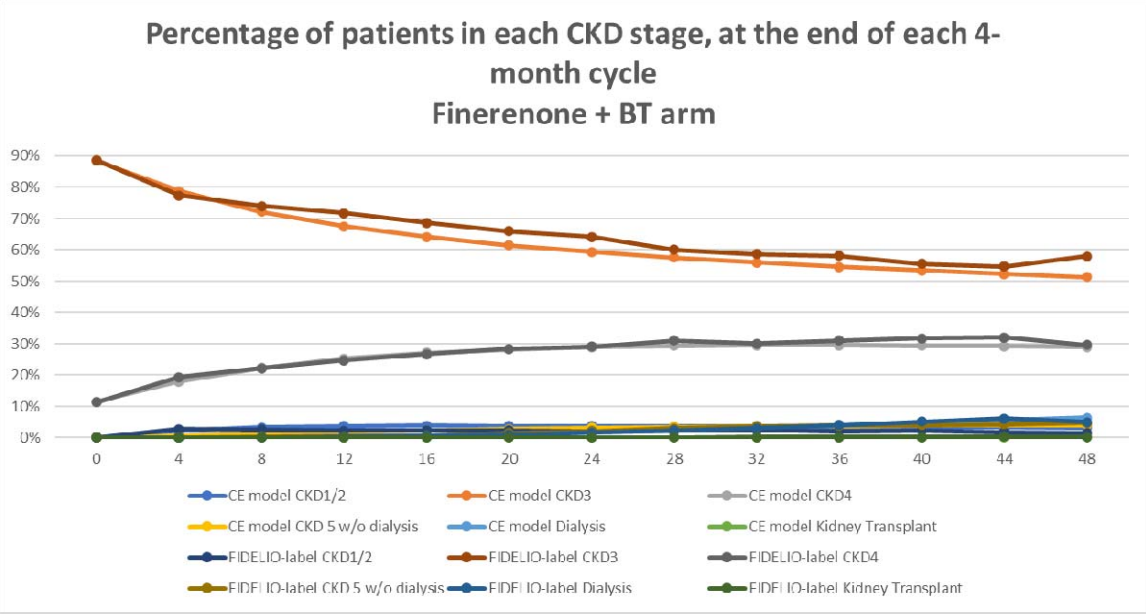


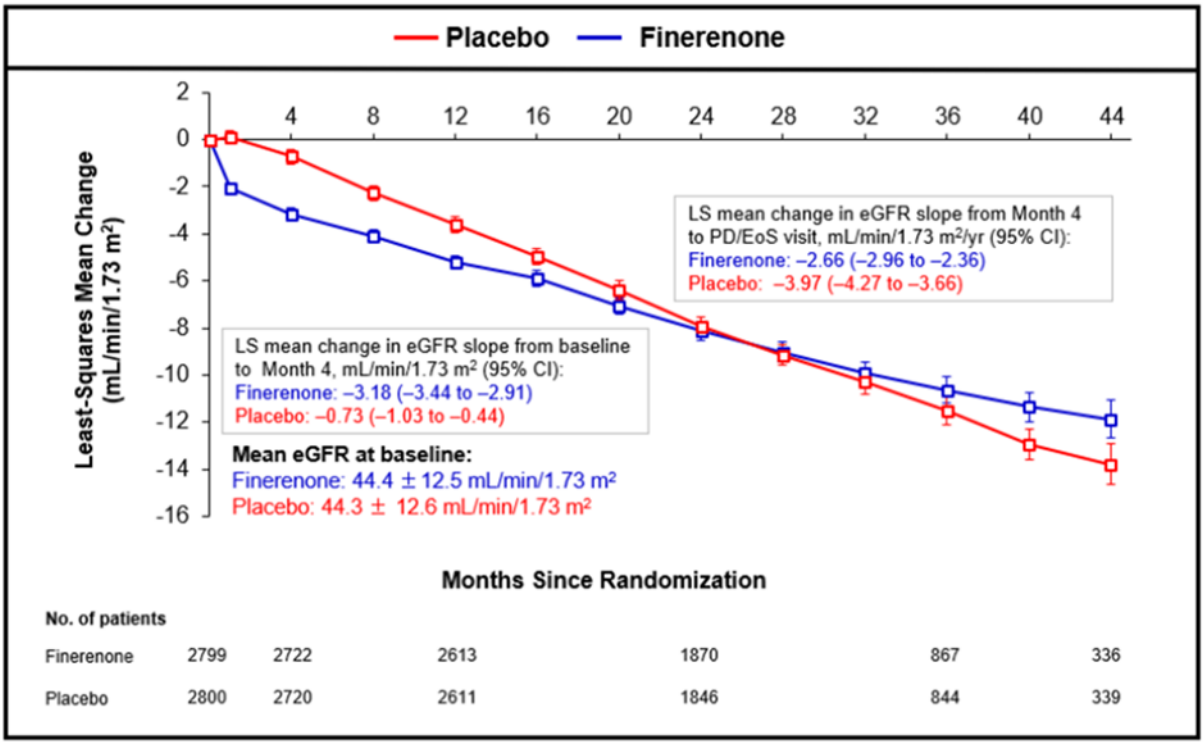
Figure 21. Percentage of patients in each CKD stage, at the end of each 4-month period, BT arm



7	Bayer are asked to explore the potential for a waning of effect for finerenone. Bayer do not consider this to be appropriate for the reasons as set out below. With continued use, the effect of finerenone treatment is persistent and the FIDELIO-DKD data supports the treatment effect of finerenone during a median follow-up of 2.6 years. Bayer provided as an appendix to the main submission (Appendix L) the proportional hazard assumption justification i.e. demonstrating that there is no evidence that the proportional hazard assumption was not met. In summary, the plausibility of the proportional hazard's assumption can be assessed by visually examining: - the plot of the log of the negative log of Kaplan-Meier estimates of the survival function versus the log of time for evidence of non-parallelism; - the smoothed plot of the scaled Schoenfeld residuals to directly visualise the log hazard ratio; - by including a time-treatment interaction term in the Cox model (time log transformed). The significance of the interaction was tested at the 5% type I error level. If the interaction is significant and there is strong evidence of non-proportionality from the plots, time-dependent hazard ratios should be estimated within the model that includes the interaction term. Two outcomes from FIDELIO-DKD were considered: - Time to onset of kidney failure, a sustained decrease of eGFR 40% or renal death (days) (primary outcome from FIDELIO-DKD); - Time to first occurrence of non-fatal CV event (days) (component of key secondary outcome from FIDELIO-DKD). It was determined that there was no evidence against the proportional hazards assumption. Further analysis was also presented by Bayer in response to ERG clarification question A8. When the potential for waning of treatment effect was discussed at committee, the clinical expert opinion was that biologically there is no reason why finerenone benefits would decline over time. There was a suggestion that patients would have better results the longer that they are on treatment and therefore the relative benefit may increase over time. Indeed, in the FIDELIO-DKD study, a more pronounced effect of finerenone on the key composite kidney outcome has been shown in the on-treatment population (all events whilst on treatment and ≤30 days after the last dose of study medication following permanent discontinuation) compared with the ITT population (HR: 0.78 (95% CI: 0.68-0.89) vs HR: 0.82 (95% CI: 0.73–0.93, respectively). A similar effect has been confirmed for the key composite cardiovascular outcome (HR: 0.78 (95% CI: 0.66–0.92) vs HR: 0.86 (95% CI: 0.75–0.99) for the on-treatment analysis and ITT analysis, respectively)(12). A constant treatment effect was observed for finerenone based on the least-squares mean change from the baseline in the eGFR slope in the FIDELIO-DKD study. Aside from the initial decrease in eGFR in the first month, which was more pronounced, treatment with finerenone was associated with a consistently slower decrease in eGFR compared with placebo over the

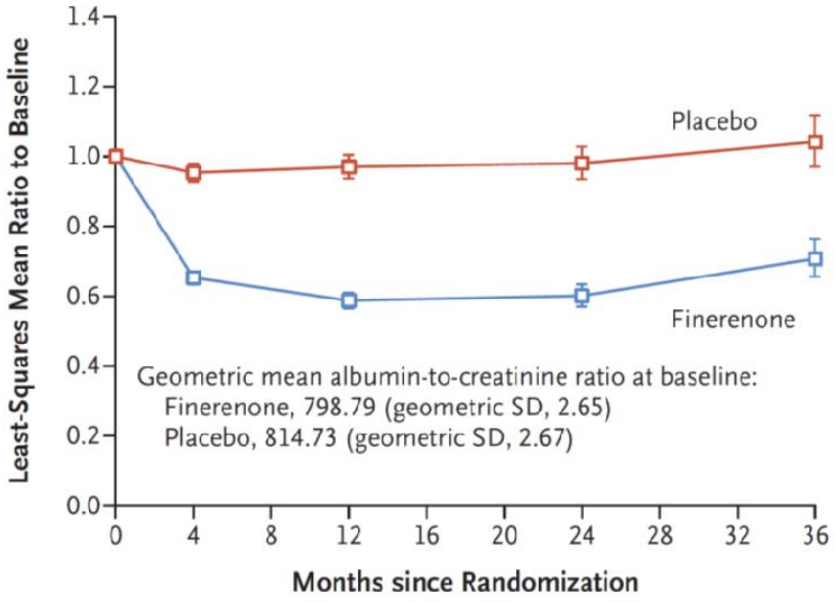
whole study follow-up (up to 44 months). This may imply that the trajectory would continue in a linear fashion.

Figure 22: Effect of finerenone and placebo on eGFR; FIDELIO-DKD study



Further support for a persistence of effect comes from the analysis of change in UACR during the FIDELIO-DKD study. 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 (see figure 23 below).

Figure 23: Urinary albumin-to-creatinine ratio (FAS) (12)



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

In the pre-specified CSR analyses for FIDELIO-DKD, Bayer tested for a potential time-dependent treatment effect on all primary and secondary time-to-event endpoints, but none of the corresponding tests indicated that this was the case. If the p-value for the interaction of time and treatment is found to be small this would indicate that the treatment effect isn't constant over time; this has not been found. Please see below for the analysis for the primary endpoint which does not indicate a waning of treatment effect over the course of the study:

[redacted]

Despite not agreeing that a waning effect should be applied, Bayer have conducted scenario analyses as set out below.

The key HRs which have a major impact on the cost-effectiveness results (as presented in the DSA results, presented in comment 8 below) were selected to provide the scenario of treatment waning. These are as follows:

- Onset of eGFR decrease < 15 mL/min/1.73m^2 sustained over at least 4 weeks,
- Progression to dialysis,
- CV death,
- First CV event.

The scenario assumes treatment effect waning as presented in the table below:

Table 22. Treatment effect waning – FIDELIO-DKD label – assumptions applied

Time in model [years]	Onset of eGFR decrease < 15 mL/min/1.73m2 sustained over at least 4 weeks		Progression to dialysis		CV death		First CV event	
	HR	Source/ Assumption	HR	Source/ Assumption	HR	Source/ Assumption	HR	Source/ Assumption
0-4	0.85	FIDELIO-DKD	0.85	FIDELIO-DKD	0.93	FIDELIO-DKD	0.87	FIDELIO-DKD
4-8	0.89	25% reduction	0.88	25% reduction	0.94	25% reduction	0.90	25% reduction
8-12	0.92	50% reduction	0.92	50% reduction	0.96	50% reduction	0.93	50% reduction
12-16	0.96	75% reduction	0.96	75% reduction	0.98	75% reduction	0.96	75% reduction
16+	1.00	100% reduction	1.00	100% reduction	1.00	100% reduction	1.00	100% reduction

The results of the base case in the model with assumed waning of the treatment effect are presented below (Table 23).

Table 23. Treatment waning – FIDELIO-label – deterministic results

Incremental costs, undiscounted	Incremental costs, discounted	Incremental QALYs, undiscounted	Incremental QALYs, discounted	ICER, undiscounted	ICER, discounted
£991	£891	0.13	0.09	£7,461	£9,471

Finerenone remains a cost-effective treatment despite inclusion of a waning of treatment effect.

8

Bayer has updated the sensitivity analyses (both DSA and PSA) in order to address the limitations raised by ERG/NICE.

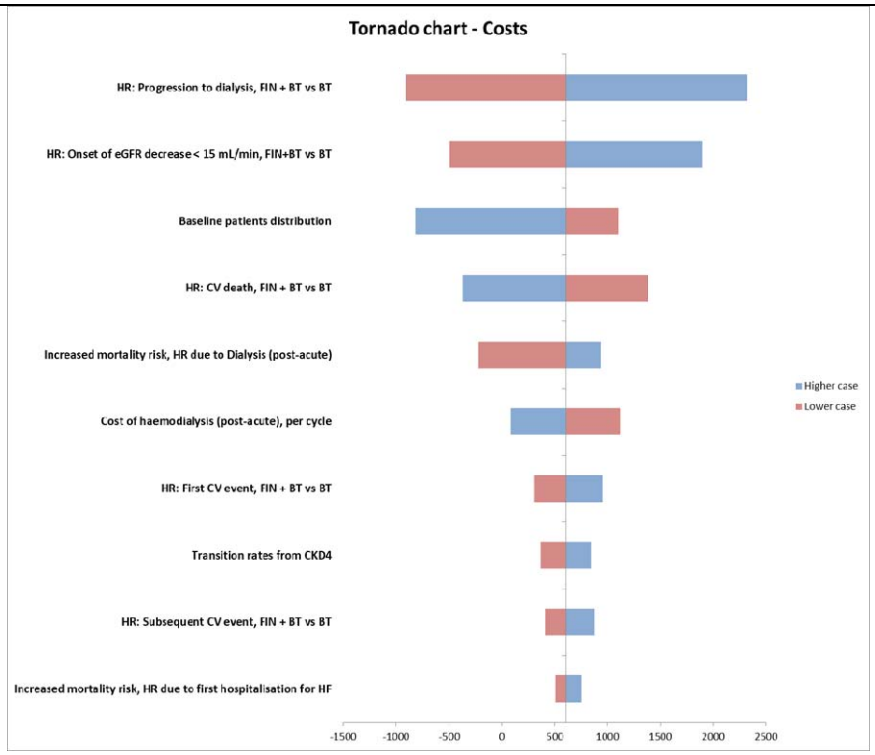
The ERG was concerned that the transition probabilities in the model were not subjected to any form of sensitivity analysis. To address this issue, Bayer changed the approach for handling transition probabilities (this has been described in the comment 2). This approach enabled a robust PSA to be conducted, with inclusion of the variability of applied HRs and sampling the BT probabilities from the Dirichlet distribution.

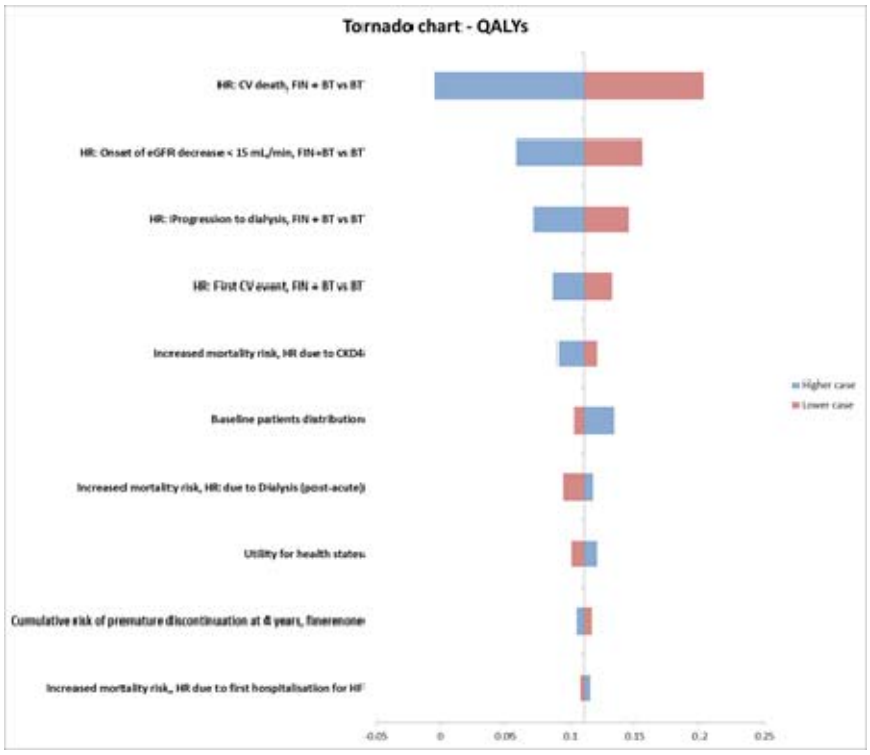
The list of inputs which have been added to the DSA and PSA are presented in the table below (**Table 24**)

Table 24. List of inputs and variables of the cost-effectiveness analysis included in the DSA and PSA

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)
Transition rates from CKD1/2	As presented in Table 43 of the main submission	Dirichlet [redacted]
Transition rates from CKD3		Dirichlet [redacted]
Transition rates from CKD4		Dirichlet [redacted]
Transition rates from CKD5		Dirichlet [redacted]
Transition rates from Dialysis (acute)		Dirichlet [redacted]
Transition rates from Dialysis (post-acute)		Dirichlet [redacted]
Transition rates from Transplant (acute)		Dirichlet [redacted]
Transition rates from Transplant (post-acute)		Dirichlet [redacted]
HR: Onset of eGFR decrease < 15 mL/min, FIN+BT vs BT	[redacted]	CI ([redacted]) LogNormalY (μ,σ)
HR: Progression to dialysis, FIN + BT vs BT	[redacted]	[redacted]
CKD1/2 utility		
CKD3 utility		
CKD4 utility		
CKD 5 w/o RRT utility		
Dialysis (acute) utility	0.595	CI(0.536;0.653) Beta (μ,σ)
Dialysis (post-acute) utility	0.595	CI(0.536;0.653) Beta (μ,σ)
Kidney Transplant (acute) utility	0.748	CI(0.673;0.816) Beta (μ,σ)
Kidney Transplant (post-acute) utility	0.748	CI(0.673;0.816) Beta (μ,σ)
Utility decrement associated with first MI (acute)	-0.060	CI(-0.055;-0.065) Beta (μ,σ)
Utility decrement associated with first MI (post-acute)	-0.032	CI(-0.029;-0.037) Beta (μ,σ)
Utility decrement associated with first stroke (acute)	-0.160	CI(-0.145;-0.176) Beta (μ,σ)
Utility decrement associated with first stroke (post-acute)	-0.087	CI(-0.079;-0.095) Beta (μ,σ)
Utility decrement associated with first hospitalisation for HF (acute)	-0.110	CI(-0.099;-0.122) Beta (μ,σ)
Utility decrement associated with first hospitalisation for HF (post-acute)	-0.060	CI(-0.055;-0.065) Beta (μ,σ)
Utility decrement associated with hyperkalaemia leading to hospitalisation	-0.030	CI(-0.026;-0.034) Beta (μ,σ)
Utility decrement associated with hyperkalaemia not leading to hospitalisation	-0.030	CI(-0.026;-0.034) Beta (μ,σ)
Utility decrement associated with sustained decrease in eGFR >=40% from baseline	[redacted]	[redacted]
Utility decrement associated with new onset of atrial fibrillation / atrial flutter	-0.014	CI(-0.014;-0.014) Beta (μ,σ)

The results of the DSA, for the base case as described in comment 2, are presented below in the form of two tornado charts. Total incremental costs and the number of QALYs gained are displayed in separate tornado charts (please see graphs below).



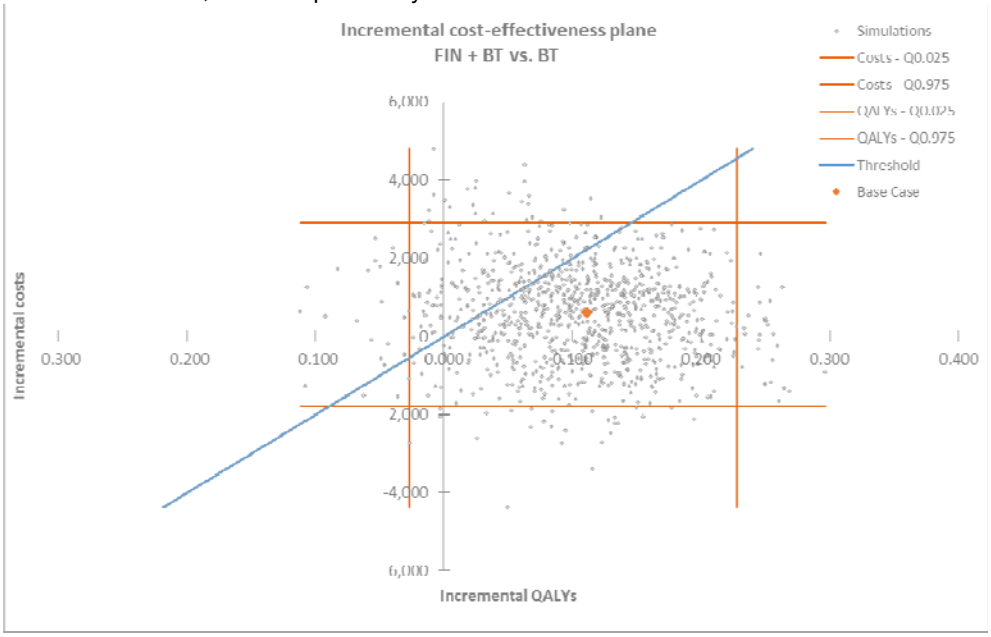


It is visible that the two HRs included in the transition probabilities (i.e., HR of onset of eGFR decline <15 and HR for progression to dialysis) as well as the HR for CV death have the biggest impact on the incremental costs and incremental QALYs.

The results of the PSA, for the base case as described in comment 2 are presented below.

	Inc. costs	Inc. QALYs	ICER
Base Case	**607**	**0.111**	**5,464**
Mean	573	0.103	5,557
Std Deviation	1,216	0.066	188,822
Median	637	0.106	5,284
Min	-4,368	-0.112	-850,073
Q 0.025	-1,811	-0.027	-88,728
Q 0.975	2,907	0.228	116,420
Max	4,802	0.297	5,056,355
Proba. CE Threshold			80.0%
Proba. Dominant			28.9%
Proba. Dominated			4.9%

Inc. - incremental; Proba. – probability



The mean ICER of the PSA is very close to the deterministic result. The inclusion of the variability in the transition probabilities did not cause the results to deviate from the base case.

9	Bayer would also like to highlight to the committee that there is a patient group with a particular unmet need, which will become apparent as more patients are considered for an SGLT2i. This group are those patients who are unsuitable for SGLT2i or who permanently discontinue SGLT2i e.g. for intolerance. Indeed, this group was highlighted by both the clinical experts during the committee and the patient expert submission. To help define this patient group, the unmet need, and the applicability of the FIDELIO-DKD data to this population, Bayer convened a multidisciplinary panel of UK experts. The description of the methodology and the outputs – "The Consensus Statement" can be found as Appendix A. (Comment 10). The group discussed the characteristics and factors that could result in a patient with CKD progression associated with T2D being unsuitable for SGLT2i, those in whom SGLT2is may be used with caution, and in identifying those who are intolerant to treatment with SGLT2is. Although each advisor had specific clinical reasons why they would consider not treating a patient with SGLT2is or using them with caution, only factors where there was consensus were recorded. The outputs of the discussion were both reviewed and agreed by the participants at the conclusion of the working group meeting and in reviewing the final report. The group also reported on the unmet need for such patients whose standard of care is ACEI/ARBs, which is associated with a significant residual risk of CKD progression. Finally, the group considered that finerenone would be suitable for patients who were SGLT2i unsuitable/ intolerant and set out their rationale. Importantly, the advisors could not identify any plausible biological or clinical rationale for why the FIDELIO-DKD data would not be applicable to these patients. A conclusion of the consensus statement is set out below: *"There is strong clinician support to ensure that Kerendia be made available for adult patients with CKD and T2D who are unsuitable for or intolerant to treatment with SGLT2is."* Utilising the consensus statement as a framework, Bayer has conducted a thorough evaluation of the size of the SGLT2i unsuitable population. Extensive desk research has been supplemented with expert opinion where insufficient information was available in the literature. Expert opinion was also utilised to estimate the degree of overlap both within and between categories of patients. For example, a single patient may have two or more risk factors that invoke ineligibility for SGLT2i prescription. In the same manner, a single patient may have two or more risk factors that cause caution to be expressed about the initial prescription of an SGLT2i. Likewise, there will exist some degree of overlap between those in whom caution is expressed and those who are ultimately prescribed and discontinue or do not adhere to SGLT2i. For the latter situation, an assumption has been made about degree of overlap. Finally, there will also exist a proportion of ineligible patients with one or more caution characteristics in their medical history. Utilising the same approach, a degree of overlap in medical history has been accounted for when estimating patient numbers. Bayer therefore estimate that the number of patients in England who are likely to be unsuitable, intolerant or where caution may be exercised in the prescription of SGLT2i is approximately 20k in 2023. This represents approximately 20% of the eligible population that Bayer presented in the budget impact assessment for the full label population.

10 – Appendix A	**Establishing the potential of Kerendia (finerenone) to delay chronic kidney disease progression associated with type 2 diabetes in adult patients who are unsuitable for, or intolerant to, treatment with SGLT2 inhibitors.** **INTRODUCTION** Kerendia (finerenone) is a novel, non-steroidal, selective mineralocorticoid receptor antagonist (MRA) that has been extensively investigated in adult patients with chronic kidney disease (CKD) associated with type 2 diabetes (T2D). Kerendia was approved in the US (September 2021)[1] and in Europe for the treatment of CKD progression associated with T2D (February 2022).[2] Subsequent to the date of this expert group meeting (22 February 2022), Kerendia has received MHRA authorisation in the UK with the following indication (March 2022):[3] ● Kerendia is indicated for the treatment of chronic kidney disease (stage 3 and 4 with albuminuria) associated with type 2 diabetes in adults.[2,3] In the last 2 years, the sodium-glucose co-transporter 2 inhibitors (SGLT2is), canagliflozin and dapagliflozin,[4,5] have been authorised for the treatment of CKD progression associated with T2D (and dapagliflozin for CKD progression not associated with T2D) and are now increasingly being considered an integral part of the current standard of care (SoC) in combination with angiotensin converting enzyme inhibitors (ACEis) or angiotensin receptor blockers (ARBs). Guidelines have recently been updated for T2D, CKD and heart failure which suggest the earlier use of SGLT2is to improve outcomes, regardless of glycaemic control, and concerns about prescribing SGLT2is are decreasing.[6-8] SGLT2is have been demonstrated to improve cardiovascular and renal outcomes for many patients with T2D; however, there are some people who may not benefit from SGLT2is because they are either contraindicated, or unable to tolerate SGLT2is due to other patient-related factors or patient preferences. These patients remain at risk of CKD progression, and for these patients there is a need for an effective alternative treatment. Kerendia could meet the needs of these patients. Bayer convened an expert working group of specialists working in CKD and T2D to build consensus on the potential use of Kerendia to delay CKD progression associated with T2D in adult patients who are unsuitable for or intolerant to treatment with SGLT2is. This included defining the particular patient population who are unsuitable for or intolerant to treatment with SGLT2is and understanding whether currently available data are applicable to this patient population.

Authors and working group participants:

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METHODOLOGY

Selection – The selection of advisors was based on specialty knowledge and expertise, differing skills, practice types representing secondary and primary care centres and geography (ensuring that as much regional representation as possible was secured).

Research – Each advisor considered their patient population and current clinical practice. The advisors reviewed the literature for RCTs of SGLT2is and Kerendia (CREDENCE, DAPA-CKD, and FIDELIO-DKD),[9-12] SPCs[4,5] and MHRA Drug Safety Updates,[13-15] clinical practice guidelines,[6-8] and papers on the safe and effective use of SGLT2is,[16] and discontinuation rates

and reasons for discontinuation with SGLT2is from real word evidence.[17,18]

Discussion and consensus – The group discussed the characteristics and factors that could result in a patient with CKD progression associated with T2D being unsuitable for or intolerant to treatment with SGLT2is. Although each advisor had specific clinical reasons why they would consider not treating a patient with SGLT2is or using them with caution, only factors where there was consensus have been recorded and the results below were both reviewed and agreed at the conclusion of the working group meeting and in reviewing the final report.

RESULTS

The group concluded that while differences in clinical practice exist across the country, a consensus could be reached that defined the clinical factors determining if a patient with CKD associated with T2D would be unsuitable for SGLT2is, those in whom SGLT2is may be used with caution, and in identifying those who are intolerant to SGLT2is.

Discussions included knowledge of recent guidelines[6-8] and other clinical pathways not necessarily available in formal guidelines.

The recommendations below highlight the criteria which either would lead to a clear and absolute decision that SGLT2is would be unsuitable, or where clinical judgement combined with guideline recommendations could lead to a clinical decision that SGLT2is may be unsuitable for a particular patient.

Consensus on criteria for patient unsuitability for SGLT2is

1. Patients who should not receive SGLT2is

- History of unprovoked diabetic ketoacidosis (DKA)
- In patients where there has been a very rapid progression to insulin (within 12 months of diagnosis of T2D)
- In patients during an acute (and dehydrating) illness, though they may be considered for an SGLT2i at a later date
- History of recurrent mycotic genital infections, especially those with poorly controlled glycaemia
- Urinary sepsis resulting in recurrent hospital admissions
- Pancreatic disease
- History of Fournier's gangrene
- Women of reproductive age who are not using reliable contraception and there is pregnancy potential

2. Patients with whom to exercise caution with initial prescribing of SGLT2is (but still offer an SGLT2i)

- Complex stone disease (including staghorn calculus)
- Overactive bladder, prostatitis, and recurrent urinary tract infections
- Previous lower limb amputation
- Active peripheral vascular disease (ulceration, or intermittent claudication)
- Potential drug interactions
- Very high HbA1c levels (>86 mmol/mol or 10%)
- Low body weight (BMI <23)
- Significant frailty
- History of fragility fractures or osteoporosis
- People with dietary restrictions, e.g., those who fast/on a ketogenic diet/very low-calorie diet

3. Patients who choose not to take an SGLT2i

- People may choose not to take an SGLT2i due to concern about certain known side effects with SGLT2is, such as Fournier's gangrene

Patients who should not continue on SGLT2is

1. Patients who develop intolerance after an initial trial of an SGLT2i (5–10% of patients)

- Recurrent genital infections (men are less likely to tolerate recurrent infections than women)
- Patients who suffer symptomatic hypotension on an SGLT2i
- Urinary symptoms – frequency and recurrent infections
- Idiosyncratic adverse events

2. Patients who do not adhere to treatment with SGLT2is

- Patients who start and discontinue SGLT2i treatment for any reason (10–20% of patients)
    - For example, real world evidence shows discontinuation of dapagliflozin within 3 months in approximately 10% of patients (N=149/1663)[18]
        - One-quarter of those patients discontinued due to elevated HbA1c, increased body weight or increased appetite

- Half of those patients discontinued due to adverse events (two major side effects were genital and urinary tract infections).

Identified unmet need

The advisors identified the unmet need for the 'SGLT2i unsuitable or intolerant' patient population as follows:

- The current optimal SoC (ABCD) provides insufficient protection
  - A – ACEi/ARB at maximal doses
  - B – Blood pressure targeting
  - C – Cardiovascular risk factor reduction
  - D – Diabetes, glycaemic control - utilising agents that have cardio-renal benefit preferentially
- In the placebo arm of the SGLT2i studies and FIDELIO-DKD trial, patients were on optimal SoC but there was still progression of CKD
- For SGLT2i ineligible patients, the current SoC is ACEi/ARBs and there is significant residual risk of CKD progression for T2D patients on ACEi/ARBs
  - In studies of ARBs in patients with T2D and proteinuria, the relative risk reduction was only 16–20% (RENAAL and IDNT studies)[19,20]

Rationale for Kerendia as an alternative to SGLT2is

The advisors considered that Kerendia would be suitable to use in an 'SGLT2i unsuitable or intolerant' patient population for the following reasons:

- FIDELIO-DKD, DAPA-CKD and CREDENCE studies included broadly the same patient population; the baseline characteristics between the clinical trials are comparable[9-11]
- Although SGLT2i intolerant patients were not specifically recruited to studies of Kerendia, Kerendia may be expected to provide similar kidney protection irrespective of whether the patient is SGLT2i tolerant or not as none of the reasons for SGLT2i intolerance would be expected to interfere with Kerendia's mechanism of action
- Kerendia has a different mechanism of action to the SGLT2is:
  - SGLT2is primarily target haemodynamic (elevated blood pressure and/or intraglomerular pressure) and metabolic factors (poor glycaemic control)[21-25]
  - Kerendia targets the mineralocorticoid receptor (MR); there is a growing body of evidence that MR overactivation leads to inflammation and fibrosis and is a key driver of CKD progression[26-30]

- In clinical studies, Kerendia was associated with reduced albuminuria versus placebo, despite only modest reductions in blood pressure and no effect on glycaemic control in patients with CKD and T2D.[12,30,31] Albuminuria is a significant risk factor for rapid decline in kidney function[6]

- An SGLT2i-excluded cohort would have similar characteristics as those patients recruited for FIDELIO-DKD
- Patients are SGLT2i intolerant predominantly for metabolic reasons, or due to complications either from insulinopenia or septic complications of glycosuria
- A higher proportion of SGLT2i intolerant patients may be insulinopenic and more type 1 diabetes-like; however, there is no biological reason to suggest that these patients would not respond to Kerendia. These patients would usually be prescribed an ACEi/ARB
- The FIDELIO-DKD, DAPA-CKD and CREDENCE studies resulted in similar renal outcomes (decline in eGFR or doubling of serum creatinine) for similar patient populations
    - Hard outcomes for example, end-stage kidney failure and renal death are most important for HTA bodies; however, the numbers of patients who go into kidney failure in the studies has been small due to the medium term follow up duration
- Patients with lesser degrees of albuminuria need to be monitored carefully and may be considered for Kerendia in the future if there is evidence of deteriorating albuminuria and progressive diabetic kidney disease.

CONCLUSIONS

The expert group was able to reach consensus in defining the clinical factors that would result in an adult patient with T2D and CKD being unsuitable for SGLT2is, those in whom SGLT2is may be used with caution, and in identifying those who are intolerant to SGLT2is.

The group advised that a substantial unmet medical need to reduce the risk of CKD progression remains for people who are 'SGLT2i unsuitable or intolerant.'

The advisors could not identify any plausible biological or clinical rationale for why the FIDELIO-DKD data would not be applicable to these patients.

The expert group would recommend Kerendia for adult patients with significant albuminuria

(uACR ≥ 30 mg/g) in the presence of stage 3 or 4 CKD (eGFR ≥ 25 to <60 ml/min/1.73 m^2) and T2D in patients who cannot tolerate or are unsuitable for SGLT2is.

The expert group would also recommend Kerendia for adult patients with preserved eGFR (30–59 ml/min/1.73 m^2) and significant albuminuria (uACR ≥ 30 mg/g), a patient group with high unmet medical need.

There is strong clinician support to ensure that Kerendia be made available for adult patients with CKD and T2D who are unsuitable for or intolerant to treatment with SGLT2is.

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

Consultation on the appraisal consultation document – deadline for comments 5pm on 06 June 2022. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**UK Kidney Association and Association of British Clinical Diabetologists – a joint response**]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**None**]
Name of commentator person completing form:	[**Prof Indranil Dasgupta, Prof Debasish Banerjee, Dr Andrew Frankel**]

Comment number	**Comments** Insert each comment in a new row.

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NICE National Institute for Health and Care Excellence

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

Consultation on the appraisal consultation document – deadline for comments 5pm on 06 June 2022. Please submit via NICE Docs.

	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	The UK Kidney Association and the Association of British Clinical Diabetologists have significant concerns about the fact that NICE are unable to guide the healthcare community in relation to the use of Fineronone in preventing progression of diabetic kidney disease.
2	The urgency of this matter cannot be overstated. We wish to highlight that there is a growing number of people with diabetic kidney disease being managed across the healthcare system that are at great risk of cardiovascular morbidity or reaching end-stage renal failure. NICE are well aware that this cohort of patients developed from the cohort of individuals with type 2 diabetes some 10 to 15 years ago and the number of people with type 2 diabetes has increased year-on-year since that time. Therefore, if we do not to take action the numbers with progressive CKD will grow significantly over the next 10 years. Furthermore, people are developing type 2 diabetes at younger ages and living longer with their type 2 diabetes because of better treatment of cardiovascular disease. We are therefore going to see much more kidney disease in this population and the current prevailing view that people who develop diabetic kidney disease are far more likely to die from cardiovascular disease than develop end-stage kidney failure will be altered over this period with many more people reaching end-stage kidney failure.
3	Our current treatments include RAAS inhibition and now SGLT2 inhibitors. But even with maximum treatment there is still a very significant residual risk. Nephrologists around the country are regularly receiving referrals relating to people with type 2 diabetes, on appropriate dosage of RAAS inhibition and appropriate SGLT2 Inhibitor with significant residual albuminuria and impaired GFR and whose five year kidney failure risk is high. We need to be able to offer this cohort who may only be a small percentage of the total but who are significant in numbers for additional treatment. We also need to offer Fineronone for the few patients who are unable to tolerate or maintain SGLT2inhibitors.
4	If we do not start actively managing these groups of individuals they will lose kidney function over the next few years while we prevaricate. The evidence from the FIDELIO is clear and is equivalent to the benefits seen in 2001 from the RENAAL and IDNT trials.
5	It is for this reason that we urge NICE to recommend Fineronone for specialist care initiation where there is ongoing and significant risk of progression of diabetic kidney disease in the presence of current standard of care or where it needs to be added to RAAS inhibition because SGLT2 inhibitors are not able to be used.
6	Furthermore, as mentioned in our previous response, many of the reanalyses requested have already been carried out 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).
7	As we stated before, 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 rationale for using the two agents together in DKD. Moreover, because of this difference in the mechanism of action between the two agents, finerenone may also be an option in those intolerant to SGLT2i.
8	May we also highlight that diabetic kidney disease is associated with a very incidence of CV events; incident heart failure in patients is a major cause of recurrent hospitalisations and poor quality of life. The FIDELITY study, mentioned above, demonstrated that Finerenone reduces composite CV outcomes including heart failure hospitalisation [vs placebo, hazard ratio (HR), 0.86; 95% confidence interval (CI), 0.78-0.95; P = 0.0018]

Insert extra rows as needed

Checklist for submitting comments

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NICE National Institute for Health and Care Excellence

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

Consultation on the appraisal consultation document – deadline for comments 5pm on 06 June 2022. Please submit via NICE Docs.

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

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

A Single Technology Appraisal

ERG Response to ACD Submissions

October, 2022

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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1. INTRODUCTION

The purpose of this document is to provide the Evidence Review Group's (ERG's) critique of the company's response to the Appraisal Consultation Document (ACD) report produced by the National Institute for Health and Care Excellence (NICE) for the appraisal of finerenone (ID3773).

In response to technical engagement, the company have sought clinical consultation, presented a series of new analyses, and have updated their economic model to incorporate new clinical efficacy inputs as well as a revised list price for finerenone. The company responded only to key issues raised by the ERG; no additional key issues were raised by the company.

The ERG has reviewed the additional evidence presented by the company to address key uncertainties raised in the ACD. A response to each of the issues raised by the company is presented in the sections below.

The ERG response includes Section 2: ERG response to the company's submission at technical engagement; and Section 3: ERG response to updates in the company's base case.

The ERG was unable to produce a new base case using the company's resubmitted model. This was due to irregularities in the way the company resubmitted the model. These issues are detailed in Section 3.

2. ERG CRITIQUE OF COMPANY'S ACD RESPONSE

2.1. Summary of the company's position

The company's response to the ACD addresses issues in both clinical effectiveness and cost effectiveness. From a clinical effectiveness perspective, the company insisted in its response that a direct comparison between finerenone and SGLT2 inhibitors (SGLT2is) was inappropriate, thereby refusing to estimate the comparative effectiveness of these two drugs. As a result, the company's position includes an additional analysis with SGLT2is as background therapy (BT). The company makes reference to additional data from the FIDELITY pooled analysis, but does not systematically present the results of these analyses, and provides an additional clinical consultation claiming to demonstrate a group of patients for whom SGLT2is are unsuitable exists, thus justifying an analysis without a direct comparison to SGLT2is.

From a cost effectiveness perspective, the company also pursued a number of changes to their model, resulting in a new base case. The revised base-case analysis presented by the company is provided in Table 1. The revised base-case ICER presented (£5,464) was based on the following edits to the company's preferred settings and assumptions:

- Alignment with ERG/committee preferred assumptions
- Alternative approach to elicit transition probabilities
- Change to preferred utility values
- Change to price of finerenone

Table 1: Summary of base-case analyses

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained
Company original base-case analysis					
Finerenone + BT	[redacted]	6.11	-	-	-
BT	[redacted]	6.01	[redacted]	0.10	£17,552
ERG report base-case analysis					
Finerenone + BT	[redacted]	6.06	-	-	-
BT	[redacted]	5.98	[redacted]	0.08	£23,706
Company revised base-case analysis					

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained
Finerenone + BT	[redacted]	6.03*	-	-	-
BT	[redacted]	5.92*	[redacted]	0.11	£5,464

Key: BT, background therapy; ERG, Evidence Review Group; QALYs, quality adjusted life years.

Note: *Not reported, values identify by ERG.

The ERG highlights that the company's model provided in response to the ACD removes all functionality introduced as part of the ERG's original critique, including all switches implemented by the ERG to investigate alternative settings and assumptions. As such, the ERG cannot re-produce all of its previous analyses, and the ERG is limited in terms of how feasible it is for it to check all of its preferred settings have been implemented correctly. Most notably, the ERG highlights an error on the 'Results' sheet which introduces an error in the estimation of the total costs for the finerenone + BT arm (affected cell ranges: E28, I28, and G28). The final ICER is unchanged, but the total costs presented in the company's model are incorrect for the finerenone + BT arm.

2.2. Changes to preferred settings and assumptions (company comment 2)

The company has implemented three changes to its preferred settings and assumptions:

- Finerenone discontinued once patients require renal replacement therapy (RRT)
- Revised list price of finerenone (previously £[redacted] per day, now £1.31 per day)
- Change to some utility values

The ERG accepts the first two changes and has no further comments. For the third comment (change to utility values), the ERG has prepared a comparison of the previous utility values preferred by the company and the ERG, compared with the revised utility values preferred by the company (Table 2).

Table 2: Comparison of utility values

State or condition	CS	ERG report	Company revised
Utility			
CKD 1/2	[redacted]	0.800	[redacted]

State or condition	CS	ERG report	Company revised
CKD 3	[redacted]	[redacted]	[redacted]
CKD 4	[redacted]	[redacted]	[redacted]
CKD 5 w/o RRT	[redacted]	[redacted]	[redacted]
Dialysis (acute)	[redacted]	[redacted]	0.595
Dialysis (post-acute)	[redacted]	[redacted]	0.595
Kidney Transplant (acute)	[redacted]	[redacted]	0.748
Kidney Transplant (post-acute)	[redacted]	[redacted]	0.748
Utility decrements associated with first CV event, acute			
MI	[redacted]	[redacted]	-0.060
Stroke	[redacted]	[redacted]	-0.160
Hospitalisation for HF	[redacted]	[redacted]	-0.110
Utility decrements associated with first CV event, post-acute			
MI	[redacted]	[redacted]	-0.032
Stroke	[redacted]	[redacted]	-0.087
Hospitalisation for HF	[redacted]	[redacted]	-0.060
Utility decrements associated with Other Health Events			
Hyperkalaemia, leading to hospitalisation	[redacted]	[redacted]	-0.030
Sustained decrease in eGFR ≥ 40% from baseline (over at least 4 weeks)	[redacted]	[redacted]	[redacted]
New onset of atrial fibrillation / atrial flutter	0.000	0.000	-0.014
Hyperkalaemia, not leading to hospitalisation	[redacted]	[redacted]	-0.030

Key: CKD, chronic kidney disease; CS, company submission; CV, cardiovascular; ERG, Evidence Review Group; HF, heart failure; MI, myocardial infarction; RRT, renal replacement therapy; w/o, without.

The ERG has no major concerns with the changes made to the utility values, but raises the following comments:

- The utility values for dialysis are noticeably lower than those previously used (taken from NG28), which the ERG expects provide a more realistic representation of the health-related quality of life experienced by patients on dialysis
- Utility after transplant is now assumed to remain as per the utility prior to transplant, in line with NG28, which the ERG considers somewhat conservative (as patients may experience a utility benefit after transplant), but acceptable

- Utility decrements for cardiovascular events are notably larger (and by extension, better aligned with expectation), and are also based on NG28
- Utility decrements for other health events have also been updated:
    - For hyperkalaemia, this has increased from [redacted] to -0.030; however, as this parameter has a very small impact on model results the ERG accepts this change and does not provide further comment
    - New onset of atrial fibrillation / atrial flutter previously had no impact based on analysis of data from FIDELIO-DKD, but now is included. As above, this has a small impact on results, and so is not discussed further

2.3. Change in approach to estimate transition probabilities and impact on sensitivity analyses (company comments 2 & 8)

The company has replaced its original approach to estimating transition probabilities with a new approach. In summary, the new approach works as follows:

- Point estimates for the transitions for the BT arm remain the same as the original approach. However, in the probabilistic sensitivity analysis (PSA), samples are drawn from a Dirichlet distribution to account for parameter uncertainty
- Transition probabilities for the finerenone + BT arm are estimated via applying a hazard ratio (HR) to the BT arm transition probabilities
    - HR of [redacted] was applied to transitions to CKD 5 without dialysis
    - HR of [redacted] was applied to transitions from CKD 5 without dialysis to dialysis

Due to limited detail provided in the company's ACD response, the ERG is unclear precisely how the Dirichlet distributions were parameterised, but the PSA outputs illustrate that these parameters are now varied across each of the PSA iterations. However, the ERG notes that zero-yet-plausible transitions (i.e., those with a base value of 0% but could theoretically occur) are still assumed to be fixed at 0% within the PSA. For example, no patients were recorded as progressing from [redacted] to [redacted], and so this parameter is fixed at 0% across all PSA iterations, even though at least one patient progressed from [redacted] to [redacted]. Overall, the ERG considers the implementation of the parameter sampling to be an improvement on the

original approach, but cannot verify that this has been implemented correctly due to limited reporting, and is concerned about how zero transitions have been handled.

For the finerenone + BT arm, the company's revised approach now means that no direct effect of finerenone is reflected on transitions in the earlier stages of CKD, but instead transitions associated with CKD5 are amended (with 'knock-on' [indirect] effects for the other health states where applicable to ensure all transitions sum to 100%). Without a clear explanation having been provided in the company's ACD response, the ERG is unclear why this approach is now preferred since it removes any previously assumed benefit of finerenone in earlier CKD stages in terms of CKD progression. Plausibly, the company could have mirrored the edits made to the BT transitions within the finerenone + BT transitions, and maintained the original count method for deriving the base transitions for both arms. The ERG acknowledges, however, that by fixing some parameters to be equal between arms, some previously highlighted inconsistencies have been removed (e.g., that the introduction of finerenone potentially led to a reduction in the probability of patients moving from [redacted] to [redacted]).

In spite of the above, the ERG notes that the impact on the ICER is relatively small, and no major concerns were found with the updated transition probabilities used. However, both this approach and the original approach continue to rely on the assumption that transitions are time-invariant, as well as the effect of finerenone being time-invariant, which is not commented on within the company's ACD response in the context of these updated transitions (but is discussed separately in its response, and commented on in Section **Error! Reference source not found.** of the ERG's critique). Ultimately, the ERG's view that the transition probabilities are a key area of uncertainty underpinning the company's economic analysis remains unchanged in light of the company's ACD response.

2.4. Comparison to SGLT2is (company comments 3, 5, & 9)

As described in the summary of the company's position, ultimately, the company continues in its assertion that SGLT2is are not considered comparators to finerenone. The ERG considers the two main points made by the company to be centered on the following:

- Finerenone could be used with SGLT2is, and so it is not a comparator *per se*; rather, SGLT2is represent part of the pool of BT available. This is identical to the ERG's original position that finerenone could be considered a BT.

- Finerenone could be used in populations for whom SGLT2is are unsuitable. The company presents evidence from a clinical consultation in support of this point.

As a result of this evolution in position, the company now appears to be targeting two distinct positions/populations: those for whom SGLT2is are unsuitable, and those who have finerenone as an add-on to SGLT2i drugs (discussed mostly in company's ACD response comment number 5). Both of these populations are poorly characterised with respect to the FIDELIO-DKD trial. While the company has presented a consensus statement to describe the 'SGLT2i-unsuitable' population, the company have not established the generalisability of trial results to this 'real-world' population. This remains a critical area of uncertainty.

Related to this, the clinical evidence presented for the add-on position is vague and does not provide clear evidence of equivalent effectiveness, or indeed effectiveness at all, in this subgroup. In company's ACD response comment 5, a series of p-values from interaction tests in FIDELIO-DKD and FIDELITY of treatment effects with baseline SGLT2i use are shown to be non-significant ($p>0.05$). In addition, it is implied, though not explicitly stated, that co-treatment with SGLT2is is more effective than SGLT2is alone for the primary composite kidney endpoint, and numerically similar results for UACR reductions. However, the presentation of results is not dispositive, even though the company states that [redacted], both because populations are poorly characterised and because results are poorly presented.

In particular, the ERG raises issue with the following concluding remark included in the company's ACD response: *"In summary, it can be concluded that co-administration of finerenone and SGLT-2i results in an independent and additive benefit on clinical outcomes"* (Company's ACD response, p.15). It is the ERG's view that such a conclusion cannot be reached on the basis of the evidence presented. While there is evidence of additional benefit for patients receiving finerenone as well as SGLT2is beyond SGLT2is alone, this should not be conflated with an 'additive' treatment effect.

2.5. Scenario analysis including SGLT2is as part of background therapy (company comments 5 & 9)

The company presents a scenario analysis in which SGLT2is are included for all patients as part of BT. However, as no switch has been included, the ERG cannot reproduce the results presented in the company's ACD response, but for comparison purposes these are presented in Table 3 against the company's revised base-case results.

Table 3: Comparison of revised company base-case analysis and scenario with SGLT2i included as background therapy

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained
Company revised base-case analysis					
Finerenone + BT	[redacted]	6.03	-	-	-
BT	[redacted]	5.92	[redacted]	0.11	£5,464
Scenario with SGLT2is included as BT					
Finerenone + BT	NR*	NR*	-	-	-
BT	NR*	NR*	[redacted]	0.09	£12,984

Key: BT, background therapy; ERG, Evidence Review Group; NR, not reported; QALYs, quality adjusted life years.
Note: *Values could not be identified by ERG due to absence of a switch to re-produce this scenario.

To produce this comparison, the company edited transition probabilities for the BT arm via the following formula:

$$P_{All} = \%_{SGLT2} * (1 - (1 - P_{NonSGLT2})^{HR}) + (1 - \%_{SGLT2}) * P_{NonSGLT2}$$

To illustrate with an example, progression to dialysis is associated with an HR of 0.68. Therefore, if the probability of progressing to dialysis for BT patients not treated with an SGLT2i was 20%, but 100% of patients are assumed to receive SGLT2is, the revised probability would be calculated as follows:

$$P_{All} = \%_{SGLT2} * (1 - (1 - P_{NonSGLT2})^{HR}) + (1 - \%_{SGLT2}) * P_{NonSGLT2}$$

$$P_{All} = 100\% * (1 - (1 - 20\%)^{0.68}) + (1 - 100\%) * 20\%$$

$$P_{All} \approx 14.1\%$$

Beyond this formula, limited details are provided concerning the application of the revised probabilities within the economic model, and so the ERG cannot comment further on this analysis. However, the ERG highlights that the company's ACD response explains that the formula above is used to adjust probabilities for the BT arm. Therefore, the relative effect of finerenone is not adjusted by the inclusion of SGLT2is as a part of BT (or in other words, the effect of finerenone is assumed to be additive). The ERG considers the assumption of an additive effect of finerenone to be strong and based on limited evidence.

2.6. Scenario analysis using FIDELITY data in the model (company comment 4)

In its ACD response, the company states that it has *"updated the cost effectiveness model with the data from the FIDELITY analysis for the label population"* (ACD response, comment 4, p.9). The ERG clarifies that in this context, 'update' only applies within this scenario, as the company's revised base-case analysis is aligned with the FIDELIO-DKD study per its original base-case analysis and the ERG's base-case analysis per its report. The ERG was unable to verify this scenario analysis as the model provided does not contain a switch to change all the necessary input parameters. Therefore, the ERG's critique is limited to the presentation of the affected parameters and the impact on results (a comparison of which is provided in Table 4). Moreover, presentation of data from FIDELITY was limited and lacking in transparency, precluding a clear assessment as to the results and their rigour.

Table 4: Comparison of revised company base-case analysis and scenario using FIDELITY data

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained
Company revised base-case analysis					
Finerenone + BT	[redacted]	6.03	-	-	-
BT	[redacted]	5.92	[redacted]	0.11	£5,464
Scenario using FIDELITY data					
Finerenone + BT	NR*	NR*	-	-	-
BT	NR*	NR*	[redacted]	0.08	£12,710

Key: BT, background therapy; ERG, Evidence Review Group; NR, not reported; QALYs, quality adjusted life years.
Note: *Values could not be identified by ERG due to absence of a switch to re-produce this scenario.

Acknowledging the company's revised approach taken to implement the transition probabilities (see Section 2.3), the ERG expects that one of the main reasons behind the difference in ICER is that the FIDELITY scenario analysis includes broadly lower transition probabilities to CKD 5 without dialysis from CKD 3, CKD 4, or CKD 5 without dialysis. However, without a full breakdown of results, nor the ability to reproduce the results within the model, the ERG is unable to comment further on the potential reasons behind the differences in results.

The ERG agrees with the company's view that this scenario analysis is subject to limitations, especially when considering that it relies on subgroup analyses from two studies and was not pre-specified. However, without an adequate explanation behind the differences in results

having been presented (noting in particular that [redacted]), the ERG cannot rule out the possibility that the FIGARO-DKD study should be incorporated into the model so as to avoid relying solely on the more optimistic FIDELIO-DKD study data. A more transparent and appropriate presentation of results from FIDELITY would be required to reduce uncertainty arising from this issue.

2.7. External validation of model (company comment 6)

The company conducted a validation exercise to assess how accurately the model predicted the occurrences of cardiovascular events and initiation of dialysis. The ERG highlights that as the model uses input data from the same study data, this does not represent a true 'external' validation, but instead provides a means of assessing if the model structure is suitably flexible to provide an accurate reflection of the trial data used to derive input parameters. The ERG considers this an important distinction to make, since this validation exercise is therefore limited to demonstrating how accurately the model projects the events in the study over a limited ~4-year time horizon.

The analyses provided by the company support the expectation that cardiovascular events and onset of dialyses can be accurately reflected by the model over a ~4-year time horizon (also acknowledging the initial lack of dialysis events in the first ~12 months, which is accounted for in the company's model). Nevertheless, the ERG highlights that the model projects outcomes over a 34-year time horizon, and so the remaining 30 years, all probabilities are assumed fixed. This therefore remains a limitation of the model, and the impact on the true cost-effectiveness results is unclear.

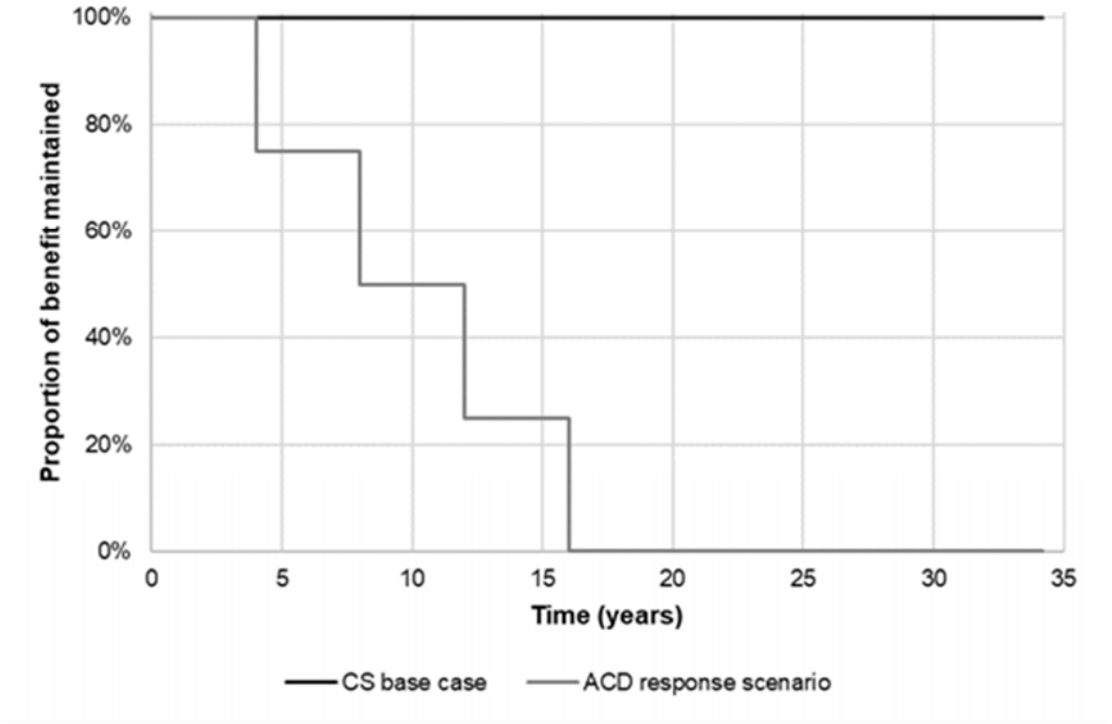
2.8. Potential waning effect of finerenone (company comment 7)

The company presented evidence of a treatment by time interaction in support of their view that treatment waning is not relevant for decision-making. The result, which generated a [redacted] for the interaction, is probative but not dispositive as this only relates to the trial time horizon. Indeed, the ERG notes that treatment waning effects are included often to address extrapolations beyond the time horizon of included trials.

While the company does not agree with the possibility of there being a waning effect of finerenone over time, it conducted an exploratory scenario analysis to quantify the potential impact of this on cost-effectiveness results. The treatment waning scenario as implemented

suggests the effect of finerenone may wane over a period of 16 years, decreasing by 25% every 4 years until it dissipates entirely by 16 years (demonstrated visually in Figure 1).

Figure 1: Graphical representation of treatment effect waning scenario



Key: ACD, appraisal consultation document; CS, company submission.

Noting that the company does not support any particular waning effect, no supporting evidence is presented in the company's ACD response for any particular relationship of benefit over time (including, for example, the relevance of 16 years as a time point after which any residual effect of finerenone is expected to wane entirely). The ERG, therefore, is unclear how relevant this scenario is for decision making. However, it is noted that the impact on the ICER is relatively large, causing the revised base-case ICER to increase from £5,464 to £9,471. Scenarios accounting for potential treatment effect waning may be of relevance to decision making, but are subject to substantial uncertainty in light of the lack of long-term data to quantify such an effect, and therefore rely on arbitrary assumptions.

2.9. Outstanding issues

The ERG highlights that the most appropriate means of accounting for CV event history remains an area of uncertainty, and it is not clear how this has been factored into the company's revised

base-case analysis. This was discussed in the ACD (Section 3.13) which states: *"The committee concluded that the company's approach likely resulted in optimistic cost-effectiveness results, and restructuring the model into 3 sub-models would reduce uncertainty."*

3. ERG BASE-CASE ANALYSIS

As noted previously in Section **Error! Reference source not found.**, the ERG was unable to produce a preferred base-case analysis taking into consideration the company's changes to its model made in response to the ACD. This is because the company's changes were applied within a model file which does not contain any of the functionality the ERG implemented as part of its original review. The ERG was able to identify some evidence of changes made in the model file, but cannot reliably ascertain whether these changes represent the full extent of changes made.

The company's revised model includes a large number of edits (compared with its originally submitted model) but does not preserve any original functionality with switches. Therefore, the ERG cannot determine if implementation of these changes was accurate or appropriate. Moreover, the ERG cannot verify the new changes made to the model since there is no ability to switch the model settings back to those used to inform the results presented at the first appraisal committee meeting.

The ERG is able to reproduce its preferred base-case analysis from its original report (presented at the first appraisal committee) including the revised price for finerenone (Table 5). However, the ERG highlights that this does not represent the ERG's preferred analysis. Due to the lack of transparency, the ERG cannot determine which of the edits made by the company following the ACD it would incorporate within an ERG-preferred analysis.

Table 5: Original ERG base-case analysis with updated price for finerenone

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained
ERG report base-case analysis with revised price for finerenone					
Finerenone + BT	[redacted]	6.06	-	-	-
BT	[redacted]	5.98	[redacted]	0.08	£10,162

Key: BT, background therapy; ERG, Evidence Review Group; QALYs, quality adjusted life years.

Bayer plc response to ERG preferred model settings and assumptions request November 2022

Thank you for your request for us to provide a model with the functionality to allow the ERG preferred model settings and assumptions to be implemented.

We provide the model and also add brief comments for clarity by adding a further column in Table 1. We also summarise the scenarios and ICERs at the end of the file.

Table 1: ERG's preferred model assumptions

Model setting or assumption	Preferred by ERG (post ACD)	Bayer response
From ERG report		
ERG-corrected company's base-case	✓	To allow the ERG to explore this change, a switch has been added to the CE model (Scenario 9). This includes stopping the use of finerenone once RRT is initiated + calibration of the discontinuation of finerenone in line with ERG recommendations.
Set risk of CV events to be independent of CKD stage	✓	To allow the ERG to explore this change, a switch has been added to the CE model (Scenario 1)
Amend application of renal deaths	✓	To allow the ERG to explore this change, a switch has been added to the CE model (Scenario 3)
Set risk of CV death to be independent of CKD stage	✓	To allow the ERG to explore this change, a switch has been added to the CE model (Scenario 2)
Assume 45.9% of patients enter post-CV event sub-model	✓	To allow the ERG to explore this change, a switch has been added to the CE model (Scenario 4)
Remove all death costs	✓	To allow the ERG to explore this change, a switch has been added to the CE model (Scenario 5)
Edit BT cost to ERG's calculations	✓	To allow the ERG to explore this change, a switch has been added to the CE model (Scenario 6)
Include one additional pack of finerenone to reflect wastage	✓	To allow the ERG to explore this change, a switch has been added to the CE model (Scenario 7) Furthermore, as noted by the ERG, the inclusion of wastage of finerenone has been added only to the incremental costs. The way in which this option was implemented was intentional, as only incremental results were reported for this scenario.. The detailed costs (per arm) were not presented in the response to the ACD

Model setting or assumption	Preferred by ERG (post ACD)	Bayer response
		document. In line with that we would like to request an amendment of the wording used in the ERG report as there was no error in the model only a difference in reporting. Nevertheless, as pointed out by the ERG, wastage of finerenone can be implemented at the level of the per arm costs. In this version of the model, a modification has been made to reflect the ERG preference, (i.e., wastage of finerenone is accounted for in Cell E28 in the Results worksheet).
Assume utility for CKD1/2 is 0.80	**×** – utility values changed post ACD, which are accepted by ERG	To allow the ERG to explore this change, a switch has been added to the CE model (Scenario 0).
Assume post-acute disutility is half of acute disutility	**×** – utility values changed post ACD, which are accepted by ERG	
From company's ACD response		
Alignment with ERG/committee preferred assumptions *ERG expects these changes include the ERG's preferred assumptions above plus discontinuation of finerenone upon initiation of RRT.*	**?** – opaque application of edits to the company's model. ERG cannot verify that all ERG and/or committee preferred assumptions have been appropriately made in the revised model	Functionality has been added to the model to allow the ERG to explore these settings and assumptions and also allow the ERG to verify the implementation of Bayer's approach. All changes are presented in the *'Scenarios'* worksheet.
Alternative approach to elicit transition probabilities	**?** – transitions remain a key area of uncertainty. Alternative	To allow the ERG to explore this change, a switch has been added to the CE model (Scenario 8). Furthermore, Bayer would like to take this opportunity to address few outstanding areas of uncertainty:

Model setting or assumption	Preferred by ERG (post ACD)	Bayer response
	approach does not address all concerns previously raised with the original approach	**1) Transitions are time-invariant, as well as the effect of finerenone being time-invariant** The results of the SLR demonstrate that the model structure is well-aligned with previously published models, which also utilize time invariant transition matrices. Moreover, although the transition probabilities to health states post-first CV event in the model are not time variant in the way the ERG suggested, they do increase with time. The time horizon in the model can be divided into two parts. The first part is consistent with the study follow-up. In this follow-up, the constant probability of CV events is based on the trial results. In the second part (beyond the study follow-up), the probability of the first CV event increases-with patient's age (due to the application of a HR based on the literature[1]). Regarding CKD progression, the corresponding transition matrices are time invariant in the model and it is assumed that disease progression depends only on the current CKD stage. Nevertheless, as patients are changing CKD stages with every model cycle, the overall probability of CKD progression in the model is increasing with time. Based on the uncertainty raised by the ERG, we have looked into this again and found two publications which may be helpful. These papers *(see below in our response regarding waning of effect)*, indicate that it takes a median of approximately 7.5 years for patients with CKD to progress from stage 3a to stage 5, when RRT is required. This is consistent with the results of the finerenone model, which indicate that the average time without RRT is around 9 years in the model. The transition probability matrix we have used in the model accounts for the time variance in disease progression observed during the trial follow up i.e., for around 4 years. Considering the average time with RRT in the model, a sizeable proportion of the transitions are taking place within the trial period which is well reflected by the transition matrices used. Hence, the potential issue of using time invariant matrices concerns only part of the modelled cohort during 3.5-5 years of the modelled time horizon. Therefore, this potential issue is likely not significant from the perspective of model results. 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

[1] Wilson, P.W., et al., *An international model to predict recurrent cardiovascular disease.* Am J Med, 2012. **125**(7): p. 695-703.e1.

Model setting or assumption	Preferred by ERG (post ACD)	Bayer response
		to the existing predictive tools. It has been shown through model validation (validation with the SHARP CKD-CVD model), which we presented at technical engagement, that the finerenone model meets these requirements, while also being potentially conservative in its approach. Bayer considers 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. The ERG felt that validating the distribution of outputs over a time period would have been a better approach. Also, the committee concluded that a comparison of transitions over time to the trial data would be informative. Bayer would like to underline that this additional validation has been performed with positive results and provided to the ERG and NICE in our response to the ACD. **2) The ERG is unclear why the new approach is preferred (it removes any previously assumed benefit of finerenone in earlier CKD stages in terms of CKD progression)** Bayer apologise for not making this clearer in our response. The ERG was concerned that the transition probabilities in the model were not subjected to any form of sensitivity analysis. In order to address this concern, Bayer changed the approach for handling transition probabilities. Transition probabilities for background therapy (BT) remain unchanged, however they were sampled in the PSA from a Dirichlet distribution. Transition probabilities for the FIN + BT arm were obtained relative to the BT transitions, as they were for CV events and Other Health Events, by applying HRs from the FIDELIO-DKD study. Bayer introduced this approach to address the ERG concern in terms of the sensitivity analyses and this is the main reason why this approach was preferred in the model Bayer presented in response to the ACD. It should be noted that while this new approach allows assessment of the uncertainty around transition probabilities, it has only a small impact on the base case results. **3) ERG is unclear precisely how the Dirichlet distributions were parameterized** Bayer apologise for not making this clearer in our response. The transition probability matrix contains multinomial data divided into several categories, with the single transition always in range between 0 and 1, and

<table>
<tr><th>Model setting or assumption</th><th>Preferred by ERG (post ACD)</th><th>Bayer response</th></tr>
<tr><td></td><td></td><td>the sum of transitions from each category equal to 1. The Dirichlet distribution (multivariate generalization of the beta distribution) has been chosen for transiting among model health states.

The 95% CIs were calculated based on the number of patients in each state and the number of patients outside this state, assuming that the transition probabilities from each single state should add up to 100%. The number of patients were derived from the FIDELIO-DKD data. The details on the parametrization are presented below.

Table 2. Dirichlet distribution parameters
<table><tr><td>Transition rates from CKD1/2</td><td>Dirichlet[redacted]</td></tr><tr><td>Transition rates from CKD3</td><td>Dirichlet[redacted]</td></tr><tr><td>Transition rates from CKD4</td><td>Dirichlet[redacted]</td></tr><tr><td>Transition rates from CKD5</td><td>Dirichlet[redacted]</td></tr><tr><td>Transition rates from Dialysis (acute)</td><td>Dirichlet([redacted]</td></tr><tr><td>Transition rates from Dialysis (post-acute)</td><td>Dirichlet[redacted]</td></tr><tr><td>Transition rates from Transplant (acute)</td><td>Dirichlet[redacted]</td></tr><tr><td>Transition rates from Transplant (post-acute)</td><td>Dirichlet[redacted]</td></tr></table>
4) The ERG notes that zero-yet-plausible transitions (i.e., those with a base value of 0% but could theoretically occur) are still assumed to be fixed at 0% within the PSA

Indeed, this is true for all inputs which have 0 in the base case, they are not tested in the DSA nor the PSA. The transition probabilities reflect the results of the FIDELIO-DKD study, and lack of transitions indicate that they did not occur during the study duration (4 years). As such, there is no evidence base on which to implement a variation in the sensitivity analysis. Whilst theoretically plausible, as they have not been observed in a large RCT it is likely these would be minimal and therefore Bayer does not believe they would drive the cost-effectiveness findings.</td></tr>
<tr><td>Change to preferred utility values</td><td>✓ – utility values changed post ACD, which are accepted by ERG</td><td>To allow the ERG to explore this change, a switch has been added to the CE model (Scenario 0).</td></tr>
<tr><td>Change to price of finerenone</td><td>✓</td><td>To allow the ERG to explore this change, a switch has been added to the CE model (Scenario 6)</td></tr>
</table>

Model setting or assumption	Preferred by ERG (post ACD)	Bayer response
Other model settings or assumptions		
Potential treatment waning effect of finerenone	**?** – no data available either for or against a lifetime treatment effect (for patients that continue treatment). This remains an area of uncertainty	Bayer acknowledges the uncertainty raised by the ERG. Whilst Bayer cannot provide definitive evidence beyond the trial duration that establishes a persistence of effect of finerenone, we are able to provide several sources that indicate that this relationship is likely to exist. These include statistical analyses of the FIDELIO-DKD trial data and clinical expert opinion. In addition, the modelled duration of treatment reflects natural history data which indicates that for patients with CKD, controlled diabetes and uncontrolled proteinuria, the time to transition between CKD stage 3a and 5 is a median of approximately 7.5 years (see further discussion below). With continued use, the effect of finerenone treatment is persistent and the FIDELIO-DKD data supports the treatment effect of finerenone during study follow-up. Bayer provided as an appendix to the main submission (Appendix L) the proportional hazard assumption justification which indicates that there was no strong evidence against the proportional hazards assumption. Further, Bayer scientists have highlighted that UACR is a key marker and evidence for a persistence of effect can be demonstrated with the analysis of change in UACR during the study. By analysis of covariance test, finerenone was associated with a greater reduction in the UACR from baseline to month 4 than placebo ($p<0.0001$), and lower levels were maintained thereafter out to 36 months with the difference in curves appearing to be maintained/ grow over time. Along with this evidence, we also provided supporting evidence in our response to the ACD regarding “on-treatment analysis”, the eGFR slope and pre-specified analyses of “time-dependency of treatment effect”. Importantly, clinical opinion expressed at the appraisal committee meeting was that persistence of effect would be expected from a biological point of view. Indeed, there was a suggestion during the committee discussion that the relative benefit may increase over time. As such, Bayer maintain that treatment waning is not appropriate for any base case analysis. Whilst there is no clinical evidence to suggest a waning of effect of finerenone, Bayer provide a source of US observational real-world evidence that suggests, if a waning of effect were to exist, its impact on decision making would likely be minimal. This US observational cohort study[1] reports on estimates of typical time spent in each CKD stage, taking account of risk factors/ co-morbidities. Reading from the graphs in Figure 2 of the paper, indicates that a CKD patient with “controlled diabetes and uncontrolled proteinuria” would spend a median of approximately 3 years in stage 3a, 2 years in 3b and 2.5 years in stage 4 (total of 7.5 years). This time frame

<table>
<tr><th>Model setting or assumption</th><th>Preferred by ERG (post ACD)</th><th>Bayer response</th></tr>
<tr><td></td><td></td><td>
seems to be supported by a publication[2] relating to the CREDENCE study estimating delay in time to dialysis (Figure 1 in the paper).

Bayer would like to draw attention to the built-in option which exists in each version of the CE model – Finerenone is stopped after a specified period (Cell D64 in the Settings). This option affects treatment costs (equal to BT treatment costs) as well as efficacy (transitions and events probabilities are the same as for BT arm) after discontinuation of finerenone. Hence, it is possible to test hypothetical scenarios and the impact of shorter duration of treatment with finerenone on the model results.

Shorter treatment duration means lower uncertainty related to the extrapolation of the constant effect of finerenone beyond the trial period as this extrapolation is limited in time. Based on the publications set out above[1,2], it takes a median of approximately 7.5 years for patients with CKD to progress from stage 3a to stage 5, when RRT is required. This is consistent with the results of the finerenone model, which indicate that the average time without RRT is around 9 years in the model. As agreed by the Committee, ERG and Bayer, it is reasonable to assume that finerenone is stopped after initiation of RRT. Taking that into account, two additional scenarios have been tested in which it is assumed that finerenone is discontinued after 7 and 9 years. Results of these scenarios are consistent with the base case. This consistency in the obtained results should reduce the uncertainty around the lifetime effect of finerenone considered in the model.

Table 3. Finerenone is stopped after 7 years
<table>
<tr><th>Incremental costs, undiscounted</th><th>Incremental costs, discounted</th><th>Incremental QALYs, undiscounted</th><th>Incremental QALYs, discounted</th><th>ICER, undiscounted</th><th>ICER, discounted</th></tr>
<tr><td>£260</td><td>£359</td><td>0.13</td><td>0.09</td><td>£2,054</td><td>£3,943</td></tr>
</table>

Table 4. Finerenone is stopped after 9 years
<table>
<tr><th>Incremental costs, undiscounted</th><th>Incremental costs, discounted</th><th>Incremental QALYs, undiscounted</th><th>Incremental QALYs, discounted</th><th>ICER, undiscounted</th><th>ICER, discounted</th></tr>
<tr><td>£336</td><td>£423</td><td>0.14</td><td>0.10</td><td>£2,387</td><td>£4,235</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Model setting or assumption</th><th>Preferred by ERG (post ACD)</th><th>Bayer response</th></tr>
<tr><td>Appropriate handling of CV event history</td><td>? – unclear how CV event history has been factored into the company's revised base-case analysis, and so this remains an outstanding area of uncertainty</td><td>To allow the ERG to explore this change, a switch has been added to the CE model (Scenario 4).

Bayer has agreed with NICE that a proportion of the FIDELIO cohort has a recorded CV event history (i.e., 45.9%). Thus, these patients could have incurred post-acute costs and disutilities due to CV events before entering the model.

As such, Bayer has corrected this in the model, and does not account for these post-acute consequences again in the model. In line with the base case, the post-acute consequences of CV events to 45.6% of patients entering FIDELIO with a history of CV events are not accounted for.

In addition, following the discussion at the committee meeting, the effect of the history of CV events on patients' mortality was also considered and implemented in the model as an additional scenario (scenario 11). It has been implemented in the same way as for the utility and costs.

Bayer considers the applied method of accounting for the CV event history in the model as robust. Implementing these changes does not impact the conclusion of finerenone being cost-effective vs BT,

Table 5. Impact of CV history on mortality, costs and utilities
<table>
<tr><th>Incremental costs, undiscounted</th><th>Incremental costs, discounted</th><th>Incremental QALYs, undiscounted</th><th>Incremental QALYs, discounted</th><th>ICER, undiscounted</th><th>ICER, discounted</th></tr>
<tr><td>£728</td><td>£707</td><td>0.14</td><td>0.10</td><td>£5,217</td><td>£7,190</td></tr>
<tr><td>£721</td><td>£699</td><td>0.14</td><td>0.10</td><td>£5,164</td><td>£7,114*</td></tr>
</table>
* With wastage correction implemented</td></tr>
<tr><td>Role of the FIDELITY data</td><td>? –it is unclear if these data should be preferred over the FIDELIO-DKD data. In addition, there is limited description included within the reporting</td><td>Scenario analyses were provided in response to the ACD for the "FIDELITY-label" population as requested by committee. However, Bayer do not believe this data is appropriate for decision making and have not provided the functionality in the model for the ERG to further explore this data.

Bayer's view is that the FIDELIO-DKD data is the most appropriate source for decision making in this appraisal. We sourced "FIDELITY-label" data from our global statistical colleagues to address the request for further</td></tr>
</table>

Model setting or assumption	Preferred by ERG (post ACD)	Bayer response
	of this analysis, and no ability to revert transitions to the original method but using the FIDELITY data	exploration using all data that could be viewed as relevant to the decision problem. However, we set out in our response to the ACD our concerns about the use of this data for decision making: • The combined analysis of FIDELIO-DKD and FIGARO-DKD limited to the indication ("FIDELIO-label population") was not pre-specified • Such analysis is combining a subgroup of FIDELIO-DKD with a subgroup from FIGARO-DKD and this is questionable from a statistical point of view Regarding the observation that there was limited description within the reporting of this analysis, Bayer would like to highlight that the data requested was not pre-specified and as such, the data we presented in our response to the ACD was limited to that required for populating the economic model.

Abbreviations: ACD, appraisal consultation document; CKD, chronic kidney disease; CV, cardiovascular; ERG, Evidence Review Group; RRT, renal replacement therapy.

Table 6. Bayer ACD model with ERG preferences (scenarios 0-9)

	Incremental costs, undiscounted	Incremental costs, discounted	Incremental QALYs, undiscounted	Incremental QALYs, discounted	ICER, undiscounted	ICER, discounted
ACD model results (all ERG preferences included + model corrections) – without wastage correction	£623	£607	0.16	0.11	£3,870	£5,464
ACD model results (all ERG preferences included + model corrections) – with wastage correction implemented	£615	£599	0.16	0.11	£3,823	£5,397

Table 7. Step by step approach for the ACD model results (FIN price £1.31)

		Incremental costs, undiscounted	Incremental costs, discounted	Incremental QALYs, undiscounted	Incremental QALYs, discounted	ICER, undiscounted	ICER, discounted
Scenario 0	Use utility values from literature	£930	£827	0.16	0.11	£5,875	£7,518
Scenario 0-1	Set risk of CV event to be independent of CKD stage by taking the average value	£945	£842	0.16	0.11	£6,019	£7,710
Scenario 0-2	Set risk of CV death to be independent of CKD stage by	£644	£620	0.15	0.10	£4,332	£6,006

	taking the average value						
Scenario 0-3	Remove renal deaths from the model and re-include as part of background mortality	£647	£622	0.15	0.10	£4,364	£6,042
Scenario 0-4	Exclude costs and utility decrements associated with the first CV event for 45.9% of patients with a CV history at baseline	£771	£722	0.15	0.10	£5,201	£7,013
Scenario 0-5	Remove all death costs	£773	£725	0.15	0.10	£5,215	£7,039
Scenario 0-6	Switch background therapy cost to ERG's calculations	£760	£716	0.15	0.10	£5,123	£6,950
Scenario 0-7	Include half of additional pack of finerenone to reflect wastage – and performing correction as per row 8 in this table (FIN price £1.31 per tablet which needs to be changed in cell G14)	£778	£734	0.15	0.10	£5,246	£7,128
Scenario 0-8	Use HRs to calculate the CKD progression rates for FIN+BT arm	£691	£654	0.14	0.10	£5,056	£6,843

	based on the rates for BT arm						
Scenario 0-9	Discontinue finerenone after initiation of RRT & calibrate discontinuation rate	£615	£599	0.16	0.11	£3,823	£5,397

Exploratory analysis

Following the discussion at the committee meeting, an attempt has been made to explore the effect of the history of CV events on patients' mortality (scenario 11).

Table 8 – Effect of history of CV events on mortality in addition to ERG preferences (scenarios 0-9)

		Incremental costs, undiscounted	**Incremental costs, discounted**	**Incremental QALYs, undiscounted**	**Incremental QALYs, discounted**	**ICER, undiscounted**	**ICER, discounted**
Scenario 0-9 + 11	Take into account the impact of having a CV history at baseline on mortality & calibrate discontinuation rate	£721	£699	0.14	0.10	£5,164	£7,114

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

A Single Technology Appraisal

ERG Response to ACD Submissions 2

December, 2022

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 addendum is linked to ERG report	Crathorne L et al. Finerenone for treating chronic kidney disease in people with type 2 diabetes [ID3773]. Peninsula Technology Assessment Group (PenTAG), 2022.

1. INTRODUCTION

The purpose of this document is to provide the Evidence Review Group's (ERG's) critique of the company's further response to the Appraisal Consultation Document (ACD) 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 (ID3773). More specifically, this document is concerned with updates made to the company's model in response to the ACD, and per the ERG's previous addendum which contained a review of the additional evidence presented by the company to address key uncertainties raised in the ACD.

This ERG response includes the ERG's review of the company's model edits, and an overview of outstanding uncertainties. For specific reasons outlined in this response, the ERG was unable to produce a new base case using the company's resubmitted model.

2. ERG REVIEW OF COMPANY'S MODEL EDITS

2.1. Summary of changes made

The company has implemented a number of switches in its revised model so that it is possible to enable or disable various settings explored by the ERG (but re-implemented by the company). The company has implemented its switches using Visual Basic for Applications (VBA) code via a Worksheet_Change macro, whereas the ERG would typically prefer to include switches within the Excel file itself (so that cell range dependency can more easily be traced). However, the ERG can confirm that the following switches function as intended and are aligned with the approach taken by the ERG to implement these switches within its version of the model:

- ERG-corrected company's base-case
- Set risk of cardiovascular (CV) events to be independent of CKD stage
- Amend application of renal deaths
- Set risk of CV death to be independent of CKD stage
- Remove all death costs
- Edit background therapy (BT) cost to ERG's calculations
- Include one additional pack of finerenone to reflect wastage

In addition, the company has changed the price of finerenone, which affects the wastage scenario listed above, and the company has changed the utility values based on sources identified in the literature (accepted by the ERG in its previous response).

However, the ERG highlights that the company has not transferred over all functionality implemented by the ERG. This means that not all of the switches used to inform the ERG's base-case per its report are included in this version of the model, as well as a number of exploratory analyses. Most notably, the company's approach to incorporating a switch to determine the impact of CV event history on the model is not aligned with the ERG's approach used to inform its preferred base-case analysis (per the ERG's report).

2.2. Cardiovascular event history

The company's approach changes the costs and disutilities incurred by patients that experience a CV event by only applying these to a proportion of patients (i.e., disabling

these for a proportion equivalent to those that had at least one prior CV event before entering the FIDELIO-DKD study). Conversely, the ERG's approach was to make use of the post-CV event sub-model, and impose the assumption that 45.9% of patients (i.e., those with a CV event recorded prior to baseline), would enter the post-CV event sub-model.

As discussed in the ACD, the committee considered that neither the company's nor the ERG's approach was optimal, but both had valid reasons to be considered. In addition, the ACD states: *"The committee concluded that the company's approach likely resulted in optimistic cost-effectiveness results, and restructuring the model into 3 sub-models would reduce uncertainty."* To confirm, the company has not attempted to restructure the model into 3 sub-models, and so this remains an outstanding area of uncertainty.

There is no additional information contained within the latest company response, nor any previous documentation, that persuades the ERG that the company's approach to handling CV event history is optimal. As such, the ERG's preference for this aspect of the model remains unchanged from its original report, yet it cannot implement this within the latest version of the company's model since the functionality to do so has been removed.

The company also presents an additional analysis in which CV event history impacts mortality. In brief, this scenario applies a hazard ratio (consistent with the company's base-case analysis for when patients move to the 'post CV event' sub-model) to 45.9% of patients within the background mortality calculations, to account for the fact that these patients enter the model with history of at least one CV event. This scenario has a limited impact on results, though is arguably a more suitable setting to inform the base-case analysis since these patients would be expected to have a different life expectancy compared with patients with no CV event history. However, the application of this scenario is subject to similar limitations as per the company's approach to adjusting costs and disutilities (since all patients are combined within the 'no prior CV event' sub-model).

2.3. Transition probabilities

The ERG previously highlighted that the company's revised approach to estimating transition probabilities may have some advantages versus its original approach, but that these advantages were unclear based on the company's previous response. The company focuses on two broad points raised by the ERG, which are discussed in turn below.

2.3.1. *Transitions are time-invariant, with a new approach taken for the finerenone arm*

The ERG appreciates the efforts made by the company to identify further evidence of long-term outcomes and validate the outputs of the model with these. While the ERG considers these to be helpful, the long-term projections from the model remain (unavoidably) an area of uncertainty.

The ERG highlighted previously that the company changed its approach to handling parameter uncertainty for the transition probabilities, but in doing so changed the transitions themselves for the finerenone arm. The company has now confirmed that this change was made solely in the interest of addressing the issue of parameter uncertainty. However, the ERG is still unclear why this is preferred given that the company introduced parameter uncertainty for the background therapy (BT) arm without changing the base transitions, and so theoretically a similar approach could have been taken for the finerenone arm. The ERG suspects that sampling transitions independently by treatment arm may have yielded unusual results, but this is purely speculation since it is not possible within the company's model to sample transitions for the finerenone arm using the original transitions via a Dirichlet distribution.

Despite this, the company explains that the new approach to handling transitions has *"a small impact on the base case results"*. For context, the incremental costs reduced by approximately 15%, whereas the incremental QALYs reduced by approximately 8% when switching the approach taken to handling transitions. The ERG agrees that the impact on the ICER is relatively small (£5,464 versus £5,885 per the company's revised base-case analysis, with and without the change made to transitions, respectively). However, the ERG highlights that with other changes combined, this could have a larger impact on results.

2.3.2. *Unclear parameterisation and handling of 'zero-transitions'*

The company also provided additional information concerning how the parameter uncertainty was implemented, and how 'zero-transitions' were handled (that is, plausible but unobserved transitions). The ERG notes that the Dirichlet formulae have been implemented within custom VBA code, which while lacking transparency functions as expected. However, transitions that take a value of 0% are assumed to be impossible.

The ERG would normally expect to see a correction applied to account for the fact that unobserved but plausible values could occur – for example, in NICE HST10 an approach was taken where a Dirichlet distribution was used including a non-informative prior belief in which a probability of 1% was assigned to every possible transition (even if it did not occur).

The ERG accepts that the omission of a correction is perhaps unlikely to have a large impact on results but should nevertheless be included within the programming of the sensitivity analysis.

2.4. Potential waning of treatment effect for finerenone

The company reaffirmed its position with respect to the duration of treatment effect for finerenone and has presented available evidence concerning the effect of finerenone over time. The ERG agrees with the company that this is an area of uncertainty since there is no definitive evidence beyond the trial duration that establishes a persistence of effect of finerenone, and acknowledges that there is some evidence to support the expectation of a persistent treatment effect over time. However, alternative scenarios may be helpful to inform decision making, and the company has provided two scenarios in which finerenone is stopped after 7 and 9 years of treatment, respectively. The ERG considers the provision of these scenarios to be potentially informative for the committee, but ultimately is unable to comment further on the plausibility of a treatment effect for finerenone beyond the duration of follow-up provided by the available trial data.

2.5. FIDELITY data

The company has not provided a version of its model where FIDELITY data (i.e., data from both the FIDELIO-DKD and FIGARO-DKD studies) could be used to inform transitions. With respect to this, the ACD requested that the company: *"Present analyses that include relevant data from FIGARO-DKD to reduce the uncertainty in the results for the population in the marketing authorisation".* While in its previous response the company provided scenarios including these data, the company explains within its latest response that these data should not be used to inform decision-making and this scenario is therefore not included in the latest version of the model shared, citing two main reasons:

- The analysis was not pre-specified
- The analysis requires combining subgroups from both studies, which is *"questionable from a statistical point of view"*

The ERG highlights that should the committee wish to explore scenarios including data from FIGARO-DKD, this is currently only possible when all of the company's preferred base-case settings are enabled.

2.6. Inability to produce ERG-preferred base-case analysis

As noted previously, and as per the ERG's previous response, the ERG was unable to produce a preferred base-case analysis taking into consideration the company's changes to its model made in response to the ACD. This is because the company's changes were applied within a model file which does not contain the full range of functionality the ERG implemented as part of its original review, including critically the approach for handling CV event history. The ERG was, however, able to successfully re-produce the company's original base-case analysis, and so the ERG is satisfied that the company's changes are implemented as described within the company's response.

Response to ERG request December 2022

From: Daniel Davies <Daniel.Davies@nice.org.uk>
Sent: 14 December 2022 11:57
To: Julie Broughton <julie.broughton@bayer.com>
Cc: Lesley Gilmour <lesley.gilmour@bayer.com>
Subject: RE: Update model with ERG functionality: Finerenone for treating CKD in people with type 2 diabetes [ID3773]

Dear Julie and Lesley

Thank you for sharing an updated model with us. We can confirm that the model now opens without error, but unfortunately it still does not address the ERG's need to have one model version which can reflect all the analyses presented to date. It appears that, as the recent edits have been done in a different model version, the switches implemented by the ERG no longer exist (these were originally implemented so that you could revert the model back to your base-case analysis). Therefore, the ERG is still unable to implement its preferred assumptions in the model.

As a potential solution, the ERG has asked whether you could use your model file to prepare three different versions of the model: one saved with settings per your original base case, one saved with settings per your revised base case, and one saved with settings per the ERG's original base case; along with a clear description of which settings have been used to do this.

We appreciate the short turnaround, but please could you consider this request and provide a response along with the model files by 12pm 15 December.

Best regards

Daniel Davies

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Dear Daniel,

Please find attached the models. Three versions are prepared as requested:

- one saved with settings per company original base case – with *_company_orginal* at the end of the title,
- one saved with settings per company revised base case – with *_company_revised* at the end of the title,
- one saved with settings per the ERG's original base case – with *_ERG* at the end of the title

The first two models with company base cases are the same as the model recently shared with you with appropriate scenarios considered.

To replicate the ERG's original base case (from the ERG report) additional scenarios have been added to the third version of the model (scenarios: 12, 13 and 14) while some others have been disabled (scenarios: 0, 4, 8, 9, 10, 11). Also, scenario 7 has been slightly modified. We would like to add a few comments concerning the modified/added scenarios:

- Scenario 7: A wastage of a full pack of finerenone has been considered as in the ERG's original base case, despite it being agreed at the committee meeting that inclusion of half of a pack is more appropriate.
- Scenario 12: Equivalent to Scenario 9 in the company base case, which includes stopping the use of finerenone once RRT is initiated + calibration of the discontinuation of finerenone in line with ERG recommendations.
- Scenario 13: Assumed utility for CKD1/2 of 0.80 as in the ERG's original base case, despite utility values having changed post ACD and accepted by the ERG. This change of utilities was reflected in Scenario 0 in the company base case.
- Scenario 14: Post-acute disutility assumed to be half of acute disutility as in the ERG's original base case, despite utility values having changed post ACD and accepted by the ERG. This change of utilities was reflected in Scenario 0 in the company base case.

Furthermore, please find below the table which indicates the ERG's original base case starting from the company's original base case. **Please also note that the price of finerenone was changed to £1.31/ day effective June 2022 which is not reflected in the ICERs below (price at £1.84/day).**

Table 1: ERG's preferred model assumptions

Preferred assumption	**Scenario in the model**	**Cumulative ICER (£/QALY)**
Company's original base-case	-	17,552
ERG-corrected company's base-case	Scenario 12	17,882
Set risk of CV events to be independent of CKD stage	Scenario 1	18,309
Amend application of renal deaths	Scenario 3	18,357
Set risk of CV death to be independent of CKD stage	Scenario 2	17,413
Assume 45.9% of patients enter post-CV event sub-model	'Assume the percentage of patients with a CV history at baseline enter the post-CV event sub-model'	22,510

Preferred assumption	Scenario in the model	Cumulative ICER (£/QALY)
Remove all death costs	Scenario 5	22,528
Edit BT cost to ERG's calculations	Scenario 6	22,423
Include one additional pack of finerenone to reflect wastage	Scenario 7	23,066
Assume utility for CKD1/2 is 0.80	Scenario 13	23,587
Assume post-acute disutility is half of acute disutility	Scenario 14	23,706

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

A Single Technology Appraisal

ERG Response to ACD Submissions 3

January 2023

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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This addendum is linked to ERG report	Crathorne L et al. Finerenone for treating chronic kidney disease in people with type 2 diabetes [ID3773]. Peninsula Technology Assessment Group (PenTAG), 2022.

1. INTRODUCTION

The company's revised model (shared via NICE Docs on 5 Jan 2023) allows for successful reproduction of the company's original base-case ICER (£[redacted]), the ERG's original base-case ICER (£[redacted]), and the company's revised base-case ICER (£7,114). The ERG notes two points when considering these ICERs:

- In written materials from the company, the revised base-case analysis is erroneously referred to as being £5,464 (for example, see company's response to the ACD). The ERG assumes this is an error since the company's model includes a button labelled 'Set company revised base case' which produces an ICER of £7,114, which is also described as the revised base-case ICER in later written materials prepared by the company (for example, see Bayer plc response to ERG model request December 2022)

- The original base-case ICERs from both the company and the ERG are marked as commercial-in-confidence owing to the fact that these ICERs were estimated on the basis of a price for finerenone which was not the same as the published list price which is now available (£1.31). Consequently, neither the company's nor the ERG's original base-case ICERs constitute a reliable basis on which to inform decision making, but are provided for completeness.

Owing to the timeframe available for the ERG to review the company's revised model, the remainder of this document focuses on the revised settings and assumptions, their impact on results, and their suitability for decision making. The ERG was unable to perform a thorough quality control check of the company's updated model, but did not identify any immediate programming errors while reviewing the model.

The ERG highlights however that the company's revised modelling approach makes use of VBA code to calibrate a discontinuation rate, which is triggered upon changing specific drop-down menus within the company's model. This is not ideal for transparency purposes, but the ERG acknowledges that the intention behind including this functionality is most likely to ensure that any combination of switches can yield results that mean the discontinuation rate is appropriately calibrated.

2. CHANGES ACCEPTED

The ERG accepts the following changes made to the company's original base-case analysis, and/or the ERG's original base-case analysis:

- Scenario 0: Use utility values from literature
- Scenario 1: Set risk of CV event to be independent of CKD stage
- Scenario 2: Set risk of CV death to be independent of CKD stage
- Scenario 3: Remove renal deaths from the model and re-include as part of background mortality
- Scenario 5: Remove all death costs
- Scenario 6: Switch background therapy cost to ERG's calculations
- Scenario 7: Reflect wastage of finerenone
- Scenario 9: Discontinue finerenone after initiation of RRT & calibrate discontinuation rate
- Scenario 10: Update finerenone price to £1.31

As such, no further commentary is provided related to these settings in this document.

3. CHANGES REQUIRING FURTHER INVESTIGATION

The following settings and assumptions are subjected to further investigation which the ERG believes is important in order to understand how influential these settings and assumptions are in terms of their impact on model results:

- Scenario 4: Exclude costs and utility decrements associated with the first CV event for the percentage of patients with a CV history at baseline
- Scenario 8: Use HRs to calculate the CKD progression rates for FIN+BT arm based on the rates for BT arm
- Scenario 11: Take into account the impact of having a CV history at baseline on mortality & calibrate discontinuation rate

Ultimately, these four scenario settings are related to how the model handles transition probabilities for the FIN+BT arm, how finerenone is discontinued over time, and how the model considers CV event history. Combined, these settings can have a large impact on model results.

Scenario 4 refers to how CV event history may influence the estimation of costs and utility decrements. The ERG highlights that this approach is only necessary to consider if some patients with CV event history (i.e., an event before the start of the FIDELIO-DKD trial) are incorporated within the 'no prior CV event' sub-model. The ERG acknowledges that CV event history is a challenging aspect of this disease area, since patients can be considered to have CV event history with respect to both their own individual history (preceding the trial), and CV event history with respect to study entry.

As previously noted in the ACD, the committee considered that neither the company's nor the ERG's approach to handling CV event history is ideal, which the ERG agrees with. However, the ERG does not accept the company's view that its preferred application of CV event history is correct, and the ERG's application of CV event history is incorrect. **The ERG considers scenarios including how CV event history affects costs and utilities to be relevant for inclusion only if using the company's preferred approach to handling CV event history. However, the ERG considers scenarios using both the company's and the ERG's approach to handling CV event history to be relevant for decision making.**

The ERG notes that a third approach using three sub-models was discussed within the ACD. The company has attempted to introduce such an approach within its revised model, though this approach allows three types of patients to be run through the model independently.

While the ERG appreciates the efforts made to consider this alterative approach to modelling CV event history, this does not fully align with the request of the committee – that is, to track over time patients in each of the three groupings: (i) no CV event history, (ii) CV event history on model entry, (iii) CV event after model entry. Instead, the company's approach models three distinct populations over time: (i) no CV event history (but disables the ability for these patients to experience a CV event in the future), (ii) CV event history on model entry, (iii) CV event after model entry (assuming none of these patients had CV event history at baseline). **The ERG does not consider the company's alternative approach to handling three sub-models relevant to decision making**. Thus, this alternative approach is not discussed further, and remains an outstanding area of uncertainty.

Scenario 8 is concerned with the use of hazard ratios (HRs) to determine transitions for the FIN+BT arm relative to the BT only arm, instead of the company's original approach in which transition probabilities were estimated for each arm independently, using data from both arms of the FIDELO-DKD study. The company's alternative approach was introduced based on a request from the ERG for the company to include parameter uncertainty within the estimation of the transition probabilities, such that these vary when undertaking probabilistic sensitivity analysis. The ERG highlights that changing the fundamental approach to estimating transitions for the FIN+BT arm means that the base-case deterministic results will differ (though totals for the BT only arm will be the same), and the company made several assumptions through switching the approach taken to estimating transition probabilities. These can be summarised as follows:

- Transitions to CKD5 w/o dialysis estimated based on application of an HR of 0.85 for the outcome: 'Onset of eGFR decrease < 15 mL/min sustained over at least 4 weeks'
- Transitions to Dialysis (acute) estimated based on application of an HR of 0.85 for the outcome: 'Progression to dialysis'
- All other transitions left either unchanged (i.e., same as BT only arm), or adjusted to ensure transitions all sum to 100%

The ERG acknowledges the attempt made by the company to incorporate parameter uncertainty, but is concerned with the assumptions made to allow this approach to be undertaken – namely, that only two possible sets of transitions were explicitly modelled to differ by arms through application of a simple HR, one of which is for a different outcome (i.e., progression to CKD5 w/o dialysis is not 'Onset of eGFR decrease < 15 mL/min sustained over at least 4 weeks'). **The ERG considers scenarios that use both the company's original approach to estimating transition probabilities and the company's**

revised approach to estimating transition probabilities may be useful for committee decision making. However, only the company's revised approach allows for consideration of parameter uncertainty for the transition probabilities.

Scenario 11 refers to how background mortality is adjusted to account for CV event history prior to initiation of treatment within the company's model. As per the ERG's commentary related to adjustment of costs and utilities, this approach is required only if there are some patients included within the 'no prior CV event' sub-model that actually have CV event history (here, this refers to an event that happened prior to model entry). If using the company's approach to handling CV event history, this approach is suitable to account for the impact on mortality within the model. **The ERG considers scenarios including how CV event history affects costs and utilities to be relevant for inclusion only if using the company's preferred approach to handling CV event history**. The ERG considers scenarios using both the company's and the ERG's approach to handling CV event history to be relevant for decision making.

4. SCENARIOS FOR DECISION-MAKING

The ERG presents four scenarios for decision-making, based on the acceptance or rejection of the company's revised approaches to handle transitions and/or CV event history. These are summarised in Table 1.

Table 1: Scenario analyses related to company's revised approaches for transitions and CV history

#	Accept new transitions?	Accept new CV event history?	Incremental costs	Incremental QALYs	ICER
1	× No	× No	£712	0.10	£7,246
2	✓ Yes	× No	£572	0.09	£6,370
3	× No	✓ Yes	£831	0.11	£7,753
4*	✓ Yes	✓ Yes	£700	0.10	£7,118

Note: *Scenario 4 is the same as the company's revised base-case analysis.

Based on the results included within Table 1, the ERG's preferred base-case ICER falls within the range of £6,370 to £7,246, depending on whether or not the company's revised approaches to handling CV event history and/or transitions are accepted. As the ERG remains unconvinced that switching these approaches to the company's revised applications represent a definitive improvement on the previous approach, the ERG's tentatively preferred base-case analysis is aligned with Scenario 1 in Table 1 (£7,246). The ERG notes that this ICER is very similar to the company's preferred base-case, shown as Scenario 4 in Table 1 (£7,118).