NICE National Institute for Health and Care Excellence

NICE guidance

# Finerenone for treating chronic kidney disease in type 2 diabetes

Technology appraisal guidance
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# Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

# Contents

# 1 Recommendations

1.1 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 is an add-on to optimised standard care; this should include, unless they are unsuitable, the highest tolerated licensed doses of:
  - angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs) and
  - sodium–glucose cotransporter-2 (SGLT2) inhibitors and
- the person has an estimated glomerular filtration rate (eGFR) of 25 ml/min/1.73 $m^2$ or more.

1.2 This recommendation is not intended to affect treatment with finerenone that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

**Why the committee made these recommendations**

Standard care for chronic kidney disease in people with type 2 diabetes includes ACE inhibitors and ARBs, with SGLT2 inhibitors being added if needed. Finerenone would be added to ACE inhibitors and ARBs if they are not working well enough. It could be offered before, after, or with SGLT2 inhibitors.

The clinical evidence suggests that finerenone improves kidney function and helps to slow the worsening of the disease compared with placebo (both plus standard care, with and without SGLT2 inhibitors). There are no direct comparisons of finerenone against SGLT2 inhibitors when used as an add-on to standard care (without SGLT2 inhibitors).

The cost-effectiveness estimates are uncertain, but they are all within the range that NICE considers an acceptable use of NHS resources. Because finerenone has not been

compared directly with SGLT2 inhibitors as an add-on to standard care (without SGLT2 inhibitors), it cannot be recommended instead of them. So, finerenone is recommended as an add-on to standard care, when standard care includes SGLT2 inhibitors.

# 2 Information about finerenone

## Marketing authorisation indication

2.1 Finerenone (Kerendia, Bayer) is indicated 'for the treatment of chronic kidney disease (stage 3 and 4 with albuminuria) associated with type 2 diabetes in adults'.

## Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for finerenone.

## Price

2.3 The list price of finerenone is £36.68 for 28 tablets, for both the 10-mg and 20-mg doses. The daily cost of treatment is £1.31 (BNF online, accessed January 2023). Costs may vary in different settings because of negotiated procurement discounts.

# 3 Committee discussion

The appraisal committee considered evidence submitted by Bayer, a review of this submission by the evidence review group (ERG), and responses from stakeholders. See the committee papers for full details of the evidence.

## The condition

### There is an unmet need for treatment options for chronic kidney disease associated with type 2 diabetes

3.1 Chronic kidney disease (CKD) is a long-term condition involving abnormal kidney function or structure. It is affected by comorbidities, particularly type 2 diabetes. The excess glucose in type 2 diabetes can further affect kidney function and accelerate CKD progression. In severe cases, people can sometimes need dialysis or transplant. It is estimated that around 3 million people have type 2 diabetes in the UK and around 20% of these will need kidney disease treatment. The clinical experts commented that people with CKD and type 2 diabetes have significant additional risk of morbidity (including end-stage renal disease) and premature mortality compared with people with CKD alone. This is particularly because they are at higher risk of cardiovascular disease. The clinical experts added that the aim of treatment is to slow progression of disease. They described current treatments, which focus on lifestyle changes, using angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs), as well as increasing use of sodium–glucose cotransporter-2 (SGLT2) inhibitors because of the recent recommendations in the NICE guideline on the management of type 2 diabetes in adults (NG28) and NICE technology appraisal guidance on dapagliflozin for treating chronic kidney disease (TA775). The clinical experts emphasised the need for additional therapies for people with CKD and type 2 diabetes because of the residual risk of progressive deterioration in kidney function, despite current therapies. They also highlighted the need for managing complications such as foot ulcers and amputations caused by peripheral vascular disease. There is

an increased risk of developing peripheral vascular disease in diabetes, which is further exacerbated by CKD, in addition to needing dialysis or transplants. The clinical experts explained that comorbidities can prevent people from having dialysis. The patient expert submission highlighted the limited treatment options in this disease area, especially when SGLT2 inhibitors are not suitable, and that new options would be welcomed. The committee also acknowledged that younger people and people from certain family backgrounds were at increased risk of disease progression. The committee concluded that there is an unmet need for additional therapies for CKD associated with type 2 diabetes.

# Treatment pathway

## Finerenone is likely to be prescribed in secondary care to begin with, but will eventually be prescribed in primary care

3.2 The clinical experts expected that people with type 2 diabetes and proteinuria (which is elevated protein in the urine, indicating that the kidneys may be damaged) would be seen by nephrologists in secondary care. They stated that new treatments are usually prescribed in secondary care initially, and, as familiarity with the treatment increases, they eventually transition to primary care. But they noted that people who may be eligible for finerenone treatment may not always be receiving care in secondary care settings. The committee noted that the setting in which finerenone is prescribed is important when considering the confidential discounts of treatments used in standard care, and therefore the cost-effectiveness estimates. This is because some confidential discounts may not be available in primary care. The committee concluded that finerenone may initially be prescribed in secondary care, but will likely be prescribed in primary care once experience grows.

## Finerenone would be offered as an add-on after ACE inhibitors and ARBs, but its positioning relative to SGLT2 inhibitors is unclear

3.3 Finerenone is indicated for stage 3 and 4 CKD with albuminuria (with

albuminuria defined in the marketing authorisation as a minimum urine albumin to creatinine ratio of 3 mg/mmol). People with stage 3 or stage 4 CKD with albuminuria usually receive ACE inhibitors or ARBs, at the maximum tolerated licensed dose, as first-line therapy. Second-line SGLT2 inhibitors can be added, in line with NG28 and TA775. The company explained that it did not expect finerenone to replace existing therapies, because it has a different mode of action. Rather, it expands on current treatment options. The company also did not view SGLT2 inhibitors as established treatments in the NHS. So, the company submission focused on finerenone as a second-line treatment which would be added to first-line ACE inhibitors and ARBs. The clinical experts stated that although SGLT2 inhibitors were only recently recommended by NICE, their use is expected to increase, although this could take time. They also noted that a range of therapies is 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. The committee agreed that finerenone and SGLT2 inhibitors would be used after the maximum tolerated dose of ACE inhibitors and ARBs, but noted that which treatment would be chosen first was unclear. The clinical experts agreed that finerenone and SGLT2 inhibitors would be positioned sequentially in the treatment pathway, with the second treatment (after first-line ACE inhibitors and ARBs) depending on tolerance and proteinuria incidence. They agreed that which treatment would be chosen first is unclear, because both are new. But they would not both be started at the same time. The clinical experts described instances in which SGLT2 inhibitors may be preferred, for example in hyperkalaemia, and instances in which finerenone may be preferred, for example if there was a risk of diabetic ketoacidosis and foot disease. During consultation, the company highlighted clinical expert advice it had received suggesting that finerenone would not replace SGLT2 inhibitors. The advice suggested that SGLT2 inhibitors would form part of standard care; that is, finerenone would be used in combination with SGLT2 inhibitors, or offered to people for whom SGLT2 inhibitors are unsuitable. The committee concluded that in practice, finerenone could be given before or with SGLT2 inhibitors, depending on people's individual circumstances. But clinical and cost-effectiveness analyses comparing finerenone with SGLT2 inhibitors would further inform this decision (see section 3.4).

## SGLT2 inhibitors are a relevant comparator

3.4 The company did not include SGLT2 inhibitors as a comparator in its decision problem, because it did not view SGLT2 inhibitors as established NHS practice. The company referenced a low percentage market share by volume of SGLT2 inhibitors compared with oral or parenteral hypoglycaemics, and uncertainty about the proportions that are used for CKD associated with type 2 diabetes. The committee noted that in the FIGARO-DKD study, the proportion of people taking SGLT2 inhibitors was higher than in the FIDELIO-DKD study, which was completed a year earlier (see section 3.5), suggesting increased use of SGLT2 inhibitors. But the company and clinical experts noted that in this case, the SGLT2 inhibitors were used for lowering glucose. 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. It noted that the recent NICE recommendations will likely increase uptake at a faster rate. The clinical experts agreed that SGLT2 inhibitor use is likely to increase, and that finerenone and SGLT2 inhibitors would be used in combination, sequentially, unless either drug is not tolerated (see section 3.3). The ERG suggested that, because of the multiple potential places of finerenone in the pathway, multiple approaches could be used to compare finerenone with SGLT2 inhibitors. This could include an indirect treatment comparison, with finerenone as an alternative to SGLT2 inhibitors, or a comparison involving adding finerenone to standard care including SGLT2 inhibitors using trial data (although the sample sizes would be small). The ERG noted that the trial and model were not informative enough to allow such comparisons as they were. Spironolactone, a steroidal mineralocorticoid receptor antagonist, was also discussed, but the committee did not consider it relevant for CKD associated with type 2 diabetes. This was because there was a lack of comparative trial evidence and the clinical experts agreed that finerenone and spironolactone are different and are used in different contexts. During consultation, the company highlighted that it primarily expects finerenone to be offered to people for whom SGLT2 inhibitors are unsuitable, or as an add-on to SGLT2 inhibitors in people who remain at high risk of deteriorating kidney function. So, it considered that a comparison of finerenone with SGLT2 inhibitors in an SGLT2 inhibitor-

naive population was not appropriate. Instead, it compared finerenone plus standard care (including SGLT2 inhibitors) with standard care alone (including SGLT2 inhibitors) in scenario analyses (see section 3.10). The committee agreed that SGLT2 inhibitor use will increase and become incorporated into standard practice. It recalled that, in practice, finerenone could be given before or with SGLT2 inhibitors in the treatment pathway (see section 3.3). The committee concluded that SGLT2 inhibitors are a relevant comparator. But 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 when these are unsuitable.

# Clinical evidence

## Clinical evidence from FIDELIO-DKD is relevant

3.5 The clinical effectiveness evidence for finerenone was from the FIDELIO-DKD trial. This was a phase 3, randomised, double-blind, multicentre, placebo-controlled trial that enrolled over 5,000 adults with CKD and type 2 diabetes in the full analysis set. The inclusion criteria included:

- an albumin to creatinine ratio of 3.4 mg/mmol to less than 33.9 mg/mmol, an estimated glomerular filtration rate (eGFR) of 25 ml/min/1.73 $m^2$ to less than 60 ml/min/1.73 $m^2$, and diabetic retinopathy, or

- an albumin to creatinine ratio of 33.9 mg/mmol to 565 mg/mmol, and an eGFR of 25 ml/min/1.73 $m^2$ to less than 75 ml/min/1.73 $m^2$.

People took 10 mg or the target 20-mg dose of finerenone once daily in addition to standard care. In the full analysis set, 14 people (0.25%) were not receiving any ACE inhibitors or ARBs at baseline. Follow up was every 4 months including after discontinuation, with the final follow up being 4 weeks and 5 days after the last dose of the study drug. The primary outcome was the time to the first event of a composite end point consisting of: onset of kidney failure, a sustained decrease of eGFR of 40% or more from baseline over at least 4 weeks, or renal death. The results from the population covered by the marketing authorisation (approximately 90% of the study population) were presented to the committee. But the committee noted that the trial was powered for the full analysis set rather than the marketing authorisation population. The clinical experts were satisfied that the baseline characteristics reflected the population that would be seen in the NHS, in particular noting a good balance of family backgrounds including a significant number of people from Asian family backgrounds. In the full analysis set, the proportions of ACE inhibitors and ARBs at baseline were in line with the marketing authorisation population. So, the committee agreed that the company's proposed positioning of finerenone was in line with the marketing authorisation population (see section 3.3). There was a relatively low proportion of people using SGLT2 inhibitors at baseline, which the clinical experts suggested was because, at the time of study, SGLT2 inhibitors were used for glycaemic control only, and, at the beginning of the trial, were contraindicated for people with an eGFR of less than 60 ml/min/1.73 $m^2$ (this restriction no longer exists in NHS practice). So, SGLT2 inhibitors would have been actively discouraged for the marketing authorisation population because it included people with an eGFR of less than 60 ml/min/1.73 $m^2$. The committee concluded that the clinical evidence from FIDELIO-DKD was relevant.

## Additional clinical evidence from FIGARO-DKD and FIDELITY is also appropriate

3.6 The committee was aware of the FIGARO-DKD phase 3 trial, which the company excluded from its evidence base because the full data was not available at the time of the submission. The primary outcome in FIGARO-DKD was a composite cardiovascular end point, and the key

secondary end point matched the primary end point in FIDELIO-DKD. There were some differences in the inclusion criteria between the trials, with more early-stage CKD allowed in FIGARO-DKD. The clinical experts agreed that, although the trial populations were different, there was significant overlap, so that some patients could have entered either study. A meta-analysis called FIDELITY pooled results from FIDELIO-DKD and FIGARO-DKD. The committee thought that a similar analysis would provide additional insight into the marketing authorisation population. A clinical expert commented that they would feel confident using data from FIDELIO-DKD if this was the only trial available, but the committee felt that not all the potentially relevant evidence had been presented. This was because the results from FIDELIO-DKD were underpowered for the marketing authorisation population, and evidence from additional trials could give further supportive evidence and reduce uncertainty (see section 3.8). In response to consultation, the company highlighted that the marketing authorisation population represents approximately 90% of the FIDELIO-DKD population. It suggested that combining FIDELIO-DKD and FIGARO-DKD data for the marketing authorisation population was not prespecified and was questionable from a statistical point of view. But the company did provide scenario analyses using additional evidence from FIDELITY. The committee concluded that, although FIDELIO-DKD, the key clinical trial, was relevant, further clinical evidence from FIGARO-DKD and FIDELITY were also relevant and appropriate for decision making.

## The eGFR ranges in the marketing authorisation are appropriate

3.7 The marketing authorisation population submitted by the company included patients with stage 3 and stage 4 CKD with an eGFR of 25 ml/min/1.73 $m^2$ or greater. This is narrower than the definition of stage 3 and stage 4 CKD used by the NHS, which is an eGFR of 15 ml/min/1.73 $m^2$ to less than 60 ml/min/1.73 $m^2$. The clinical experts explained that in practice, each decline in eGFR is looked at individually, rather than as CKD stages. In addition, the clinical experts reported that from a patient perspective, the percentage of kidney function is the main concern. They were therefore satisfied with the CKD stages defined in the marketing authorisation. The ERG noted a lack of clarity about finerenone use when the eGFR is between 15 ml/min/1.73 $m^2$ and 25 ml/min/1.73 $m^2$ because

people in this category have CKD stage 4, and the company's submission did not include an analysis of this population. The company explained that the trial only enrolled people with an eGFR of 25 ml/min/1.73 $m^2$ and above, and although 2.4% of people in the trial had an eGFR below this, their eGFR had deteriorated in the time between screening and randomisation. The ERG was satisfied with the analyses presented at technical engagement. The committee noted that the marketing authorisation does not recommend starting finerenone with an eGFR of less than 25 ml/min/1.73 $m^2$, but:

- it allows continuation if the eGFR drops below this
- if the eGFR is 15 ml/min/1.73 $m^2$ or more, finerenone use can continue with dose adjustment according to serum potassium
- if the eGFR falls below 15 ml/min/1.73 $m^2$, that is end-stage CKD, and finerenone should be stopped because of limited data.

The clinical experts did not expect the eGFR ranges in which SGLT2 inhibitors would be used would influence the treatment pathway, because they expected SGLT2 inhibitors to be used widely because of their many indications. The finerenone marketing authorisation specifies that people must have albuminuria, which the company defined as at least 3 mg/mmol urine albumin, because this was the cut-off used in FIDELIO-DKD. But the degree of albuminuria does not affect finerenone use. The clinical experts commented that the greater the degree of albuminuria, the more potential benefit a person will have from additional therapies. The committee concluded that, although the marketing authorisation population submitted by the company did not cover all of the stage 3 and stage 4 CKD as defined by the NHS, the eGFR ranges specified by the company were appropriate for likely finerenone use.

## The primary composite outcome is appropriate, but further evidence from FIGARO-DKD would help supplement the data

3.8 The components of the primary composite outcome of FIDELIO-DKD (see section 3.5) were kidney failure (and its subcomponents: end-stage renal disease and a sustained decrease in eGFR of less than 15 ml/min/1.73 $m^2$), a sustained decrease in eGFR of 40% or more from baseline, and death from renal causes. The committee noted that of these

components, only 1 result was statistically significant. But the company emphasised that the study was not powered for the components of the primary composite outcome – it was only powered for the primary composite outcome for the full analysis set. The ERG accepted that the primary composite outcome was clinically relevant. At technical engagement, the company did statistical analyses to assess heterogeneity (that is, the interaction between components of the composite end point), and did not identify any heterogeneity. But the ERG stated that the company's test for heterogeneity would also be underpowered if the trial itself was underpowered for individual components. So, the committee acknowledged that all outcomes presented were underpowered because the marketing authorisation is based on a subset of the population, and the trial was only powered for the full population. Despite this, the clinical experts and committee acknowledged that numerically, if not always statistically, the components of the composite outcome were consistent in favouring finerenone. The clinical experts explained that the trial would have to be a lot longer for all the components to be individually powered. They further clarified that death from renal causes is a rare outcome in clinical trials because it only occurs in people who do not have dialysis. The committee understood that the composite outcome components are not mutually exclusive, so each component is a smaller subset of the same people. It also understood that wider confidence intervals are expected for rarer events. The clinical experts agreed that the primary composite outcome was clinically relevant. The committee agreed that renal outcomes from FIGARO-DKD (see section 3.5) would have been useful, but acknowledged that some of the FIGARO-DKD population was not relevant in this disease area. The committee noted that the Kaplan–Meier curves had a lot of censoring and not many events, and that the company had not provided confidence intervals. This emphasised the importance of using additional data from FIGARO-DKD for a better powered analysis. The committee concluded that the primary composite outcome of FIDELIO-DKD is clinically relevant, but further evidence from FIGARO-DKD would help supplement the data.

## Additional evidence from FIGARO-DKD supports the results of the primary composite outcome, but has limitations

3.9 During consultation, the company provided a scenario analysis, in which clinical evidence from FIDELITY, matching the population in the marketing authorisation for finerenone, was used to update the cost-effectiveness analysis. The company highlighted that the population in FIGARO-DKD included some people with less marked albuminuria (even at the same level of eGFR) than in FIDELITY. So, it said that including these people would dilute the effect seen in FIDELIO-DKD. But the committee noted that people in both trials had some degree of albuminuria, in line with finerenone's marketing authorisation. At the second committee meeting, the clinical experts emphasised that, in NHS practice, prescribers would want to offer finerenone to people who met either definition of albuminuria. So the committee considered that the best evidence to estimate the effectiveness of finerenone in practice would be the pooled data from people in FIDELIO-DKD and FIGARO-DKD who met the criteria in the marketing authorisation. The ERG noted that the presentation of data from FIDELITY was limited and lacking in transparency, preventing a clear assessment of the scenario analysis results. It agreed with the company's view that this scenario analysis was subject to limitations (see section 3.6). But it could not rule out using additional evidence from FIGARO-DKD to inform the model instead of relying solely on the more optimistic evidence from FIDELIO-DKD. The committee concluded that additional evidence from FIGARO-DKD supports the results of the primary analysis from FIDELIO-DKD, but has limitations.

## Results from modelling standard care including SGLT2 inhibitors with and without finerenone are uncertain

3.10 During consultation, the company provided scenario analyses to estimate the cost effectiveness of finerenone as an add-on to standard care including SGLT2 inhibitors. It used evidence on the effectiveness of an SGLT2 inhibitor (dapagliflozin) in delaying transitions for time to end-stage renal disease, time to dialysis and time to a cardiovascular event. It calculated how these outcomes would be affected in FIDELIO-DKD and FIGARO-DKD for the proportion of people taking SGLT2 inhibitors. This

allowed estimation of outcomes in a population in which 100% of people take SGLT2 inhibitors and finerenone. The company assumed that the effects of finerenone and SGLT2 inhibitors are independent and additive. This was based on evidence from FIDELIO-DKD, which suggested that background SGLT2 inhibitors use did not reduce the benefit of finerenone. The ERG highlighted that the company had provided insufficient details to allow an informed critique of the approach, and noted that it was uncertain whether the effects of finerenone and SGLT2 inhibitors would actually be additive. It explained that, although there is some evidence that combining finerenone and SGLT2 inhibitors may provide more benefit than SGLT2 inhibitors alone (an 'additional' effect), this is not necessarily the same as the combined benefit being the sum of both independent benefits (an 'additive' effect). The committee concluded that the company's attempt to model standard care including SGLT2 inhibitors with and without finerenone was uncertain. Because it could not know whether the effects were truly additive, the committee considered that the analyses provided a useful upper bound to the likely cost effectiveness of finerenone in that setting.

## Hyperkalaemia is the main adverse event associated with finerenone, but overall the adverse events are not concerning

3.11 The main adverse event in FIDELIO-DKD associated with finerenone was hyperkalaemia. But the committee acknowledged that it seemed to be mild in most cases. The clinical experts agreed that the adverse events were not unexpected and noted that in the FIDELIO-DKD protocol, finerenone and placebo were withheld when serum potassium levels were greater than 5.5 mmol/litre. But they agreed that in clinical practice, the level would be allowed to go slightly above this in some circumstances. Hospitalisation rates were around 1% higher in the finerenone arm than in the placebo arm, but the clinical experts did not see this as being a significant concern if these hospitalisations were for short durations. The committee concluded that hyperkalaemia is an important adverse event to consider, but overall, the adverse events results from FIDELIO-DKD were not particularly concerning.

# Cost effectiveness

## The structure of the company's model is appropriate for decision making

3.12 The company presented a cohort-level, state-transition Markov model to estimate the cost effectiveness of finerenone plus standard care compared with placebo plus standard care. A representative treatment from each relevant class of therapy in standard care was used in the model, at its maximum dose. The ERG agreed with this approach. The clinical experts agreed that the treatments used were typical of NHS practice, but also agreed with stakeholder comments that some of the doses were lower than expected. But if the average or most common dose was assumed, then they were not unreasonable. The committee acknowledged that any inaccuracies were likely to have a minor impact on results because they applied to both arms of the model. The health states used were CKD stage 1 or 2, CKD stage 3, CKD stage 4, CKD stage 5 without dialysis, dialysis, transplant, and death. These health states were all duplicated into 2 sub-models for before and after a cardiovascular event. The model had a cycle length of 4 months, in line with data collection in the trial, and a lifetime time horizon of 34.2 years. Originally, the utilities used in the model were 5-level EQ-5D (EQ-5D-5L) values from the trial mapped onto the EQ-5D-3L. But after technical engagement, the company updated these to utilities from the literature (see section 3.18). No treatment waning effects were included in the model (see section 3.15). The committee noted that the model showed possible large jumps in progression, for example from CKD stage 3 to CKD stage 5, and from CKD stage 3 to dialysis or transplant. The clinical experts considered this to be plausible because in clinical practice, people with CKD associated with type 2 diabetes can move between health states, rather progress linearly. The committee noted that a shorter cycle length may have showed more intermediate states. Overall, the committee concluded that structurally, the company's model was suitable for decision making.

## The modelled health state-transition probabilities are uncertain

3.13 The individual health states in the model were empirically based on FIDELIO-DKD and applied as a 4-month probability for the whole of the model. So, the probability of transitioning from 1 state to another was repeated for the duration of the model. The ERG was concerned that assuming constant transition probabilities over time may have been an over-simplification. It added that the large FIDELIO-DKD dataset could allow for more complex transitions in the model. The company agreed, but explained that its experts had advised against this approach. The company clarified that time-varying risks are accounted for (albeit in a simplified way) because cardiovascular risk over time varies by age. The company used this approach to minimise interference with trial data, and because its health economists and clinicians had advised that its method of validating progression was reasonable. It added that its model structure was common in modelling CKD progression, and clinical expert advice was that current eGFR level is the main predictor for progression, so the same rates of cardiovascular events were applied for all people with the same CKD state. Mortality was also accounted for separately because of competing risks. The ERG agreed that the model captured the additional risk linked with age. But overall CKD progression between health states did not vary with time, and the ERG determined that the model was oversimplified. To validate its approach, the company compared its model with the Study of Heart and Renal Protection (SHARP)-CKD-CVD Markov model. This validation compared the cumulative probabilities per 1,000 participants at 5 and 10 years, with 95% confidence intervals around the company model results, and ranges around the SHARP-CKD-CVD model. The company concluded that its model results were within the ranges shown by SHARP-CKD-CVD. But the ERG explained that although the company's model results may have been within the ranges of the SHARP-CKD-CVD model, these ranges were extremes rather than confidence intervals. So, they could be obtained from varying inputs. The ERG highlighted that it was important to consider how the results were obtained, for example how events accrued over time. It noted that the tight confidence intervals observed around the company's model results in the cross validation were because of the time-invariant transition probabilities used. The ERG noted that although the SHARP-CKD-CVD model could inform some parts of the

company's model, this was limited because it was built for a different purpose and the populations could not be exactly matched. For example, there were more renal replacement events in the SHARP-CKD-CVD model, but fewer people with relatively mild CKD, because the minimum CKD stage was 3b. The ERG explained that the effect of time-invariant transitions on the model output was uncertain. This was because it was not possible to assess CKD over time. The company also clarified that it had not compared transitions with the trial data. The ERG felt that validating the distribution of outputs over a time period would have been a better approach. The committee considered that the effects of using time-invariant transition probabilities were uncertain; a comparison of transitions over time with the trial data would be informative. In particular, the committee would have liked to see modelling predictions of time to various events, for example cardiovascular or renal replacement therapy events, compared with empirical Kaplan–Meier curves from the relevant populations in FIDELIO-DKD and FIGARO-DKD. The committee concluded that the modelled health state-transition probabilities were uncertain.

## The updated health state-transition probabilities are also uncertain

3.14 During consultation, the company updated its transition probabilities for the finerenone arm by applying hazard ratios to the standard care transition probabilities corresponding to the 'CKD5 without dialysis' and 'CKD5 without dialysis to dialysis' health states. The ERG and the committee noted that for the finerenone arm, no direct effect of finerenone was reflected on transitions in the earlier stages of CKD, but instead transitions associated with CKD5 were amended. The ERG highlighted that 2 possible sets of transitions were explicitly modelled to differ by arms through applying a simple hazard ratio, 1 of which was for a different outcome (that is, progression to CKD5 without dialysis rather than 'onset of eGFR decrease less than 15 ml/min sustained over at least 4 weeks'). Furthermore, the transitions and the effect of finerenone remained time-invariant. Also during consultation, the company did an external validation of the cost-effectiveness model to ensure that its results were in line with the FIDELIO-DKD outcomes. It compared incidence of first cardiovascular events, cardiovascular deaths and the

number of people having dialysis with the model predictions. The model results reflected the incidence of the first cardiovascular event, cardiovascular mortality and incidence of dialysis observed in the FIDELIO-DKD trial. The ERG noted that because the validation used input data from the same study, it did not represent a true 'external' validation. The ERG highlighted that the analyses supported the expectation that cardiovascular events and onset of dialysis could be accurately reflected by the model over a 4-year time horizon. But the model projected outcomes over a 34-year time horizon, and so for the remaining 30 years, all probabilities were assumed fixed. The committee acknowledged that the company addressed its request to provide analyses comparing model outputs with empirical data from the trial. For both outcomes considered (time to dialysis and time to a cardiovascular event), the model outputs closely approximated the observed data. The committee was reassured that the model provided a reasonable representation of expected outcomes and, in particular, that using time-invariant transitions did not compromise the model's validity, at least over the 4 years for which empirical data was available. The committee noted that the ERG's scenario analyses that used both the company's original approach and revised approach to estimating transition probabilities were useful for decision making. But only the latter allowed for consideration of parameter uncertainty in the probabilistic sensitivity analyses. The committee concluded that the updated transition probabilities were also uncertain.

## Treatment effects beyond 4 years are uncertain

3.15 In the model, the company assumed that people would stop taking finerenone at the rate observed in FIDELIO-DKD. After this, people accrued the costs and effectiveness of standard care. The company did not explore treatment effect waning because it claimed that in the trial, the relative effect of finerenone was almost constant over 4 years. The company also assumed that in clinical practice, finerenone would be stopped (see section 3.16) if there was no treatment effect. The clinical experts thought that finerenone benefit is likely to be maintained over time. They added that at more advanced CKD stages, it takes fewer events to progress to dialysis, with a large impact on quality of life. So there may be a greater absolute benefit of finerenone in more advanced

CKD. During consultation, the company provided scenario analyses assuming the effect of finerenone waning over a period of 16 years, that is, decreasing by 25% every 4 years until it dissipated entirely by 16 years. It provided 2 further scenario analyses in which finerenone was stopped before the point at which finerenone's constant effect was extrapolated to end after the trial period. These assumed finerenone would be stopped after 7 years, based on a median of 7.5 years spent in stages 3 and 4 CKD (Wilson et al. 2012), and 9 years, based on the average time without renal replacement therapy in the economic model. Although the ERG considered the 16-year waning scenario an arbitrary assumption, it highlighted that the finerenone discontinuation scenarios (7 years and 9 years) were potentially informative. The committee acknowledged that uncertainty around the treatment waning effect was inherent beyond the trial period. It concluded that extrapolating relative treatment effects beyond the 4 years seen in the trial was uncertain, but that the company had made a reasonable attempt to explore this.

## Finerenone is stopped after renal replacement therapy starts

3.16 In the company's model, finerenone was stopped after starting renal replacement therapy. The ERG did not have a preference about whether finerenone should be stopped or continued after renal replacement therapy is started. The clinical experts stated that finerenone would be stopped if a person's eGFR dropped below 15 ml/min/1.73 $m^2$ (see section 3.7), which would occur before renal replacement therapy was started. The stopping rule decreased the incremental cost-effectiveness ratio (ICER) in a scenario analysis. The committee concluded that finerenone would be stopped after renal replacement therapy is started.

## Modelling of previous cardiovascular disease remains an outstanding area of uncertainty

3.17 The ERG explained that some people in FIDELIO-DKD would have had at least 1 previous cardiovascular event. This is because, although people were excluded if they experienced cardiovascular events in the 30 days before the screening visit, the exclusion criterion did not cover cardiovascular events that happened before this. The ERG and company agreed that 45.9% of people entered the model with a history of

cardiovascular disease. The company preferred to model this proportion of people from the point of entering FIDELIO-DKD (that is, to use the simplifying assumption that no patients had experienced a cardiovascular event before entering the model), whereas the ERG preferred to model this using the total patient history. The ERG explained that the company used external evidence to inform mortality and that this had a substantial effect on the cost-effectiveness estimates. So, there was a risk that estimates would be biased if the proportion of people with a history of cardiovascular disease was not accurate. The company explained that the model was structured in a way that meant that if it included total cardiovascular history, a considerable part of any cardiovascular protective benefit of finerenone would be lost. The ERG suggested that it would be ideal to have 3 sub-models, reflecting:

- people with no cardiovascular history
- people entering the model with cardiovascular history but yet to experience a further cardiovascular event

- people who experienced a cardiovascular event in the model.

The committee agreed that in the company's 2 sub-models, the company and the ERG had valid reasons to support the different approaches, and that neither approach was optimal. It agreed that it would not be fair to lose any cardiovascular benefit of finerenone, but noted that this benefit was not statistically significant in the trial. The committee also noted that any limitations in the company's sensitivity analyses (see section 3.19) meant that uncertainties around this benefit could not be analysed with a valid probabilistic sensitivity analysis. The committee considered that the company's approach likely resulted in optimistic cost-effectiveness results, and recommended that restructuring the model into 3 sub-models would reduce uncertainty. During consultation, the company updated its model to account for the impact of recorded cardiovascular history on costs, utilities and mortality. The company felt that the 3 sub-model approach suggested by the committee would not be informative. Despite this, it created the sub-models and provided the results as scenario analyses. The ERG highlighted that the company's approach to the 3 sub-models did not align with the committee's request; the company's approach did not track patients over time in each of the 3 subgroups, but instead modelled 3 independent populations over time. The ERG did not consider these scenario analyses relevant to decision making. The committee concluded that modelling of previous cardiovascular disease remains an outstanding area of uncertainty.

## Utility values used in the company's updated model are appropriate

3.18 The company initially used empirical data from FIDELIO-DKD to inform the utilities in its model because they were trial-based and it considered them to be conservative. But after technical engagement, the company decided to use utility sources from the literature. This was because the ERG was concerned about an apparent increase in utility from CKD stages 1 to 2, to CKD stage 3. The company still used FIDELIO-DKD to inform CKD stage 1 to 2 utilities, but used disutilities for all other CKD health states to be consistent with NICE's technology appraisal guidance on tolvaptan for treating autosomal dominant polycystic kidney disease (TA358). This was because it included the necessary utilities for the health states, and it was previously accepted by NICE. The ERG noted

that it had merely raised questions about some utility values used in the company's submission, and it had not directed the company to completely revise its approach. It noted that the CKD-based health utilities from TA358 were from a study from 2005, with a small relevant population, and it did not use the EQ-5D. The company reviewed relevant literature in its submission that included more recent studies to inform comparable health states in the NICE guideline on type 2 diabetes in adults: management (NG28), acute kidney injury: prevention, detection and management (NG148) and chronic kidney disease (NG203). But it did not appear to have used them to inform its model. The ERG preferred using modified trial-based utilities, despite some imperfections. The utilities from the trial and updated utilities from the literature were similar for CKD stages 3 and 4, but lower for the subsequent stages from TA358. The company acknowledged that the CKD health states were taken from TA358, which evaluated a different indication, but it had advice from clinicians that it is not CKD stage 5 and dialysis, but being on dialysis itself, that has a large impact on quality of life. The clinical experts explained that there is not a large difference in the quality of life between CKD stage 1 to 2 and CKD stage 3, because CKD stages 3a and 3b are generally asymptomatic, although renal function is affected physiologically. But the clinical experts noted that with CKD and type 2 diabetes, there are more comorbidities, with a greater burden, and therefore a lower quality of life. In addition, in people with CKD and type 2 diabetes, their CKD tends to progress through stages at a faster rate for any given eGFR level. The ERG and the committee acknowledged that in the trial, the utilities for dialysis, post-dialysis and transplant were higher than expected. The committee considered that both approaches to utilities in the model have advantages and disadvantages, so a base case with trial-based utilities, and another with utilities from more recent and relevant literature sources than those currently used in the model, such as utilities from NG28, would be informative. During consultation, the company updated the model's utility values for dialysis and kidney transplant and cardiovascular events to reflect those in NG28. The ERG accepted the updated utility values. The committee concluded that the utility values used in the company's updated model were appropriate.

## The updated sensitivity analyses should still be interpreted with caution

3.19 The ERG described the company's sensitivity analyses as having multifaceted issues. These included issues of grouping parameters, having wide parameter bounds, parameters being sampled from user-specified limits, and the overestimation of uncertainty in utility values. Moreover, the critical transition probabilities were not only time-invariant, they were also not subject to any form of sensitivity analysis. The company attempted to address these uncertainties and its rationale during technical engagement. It explained that certain parameters were grouped to account for a higher utility being observed for CKD stage 3 than for CKD stage 1 to 2. But the company changed its utility source in the model (see section 3.18). The ERG did not agree with the approach because the differences in values in the probabilistic sensitivity analysis were not shown, only whether the values were all high or all low. The ERG highlighted that using very wide parameter bounds stress tests the deterministic sensitivity analyses to implausible limits. The company acknowledged that not including the uncertainty from its time-invariant transition probabilities was a limitation, but also that this concerned the impact of finerenone in delaying CKD progression, which was significant in the trial. The company described how the probabilistic sensitivity analysis could include the statistical impact of finerenone to translate to an improvement in benefit when randomisation occurs. The company acknowledged the limitations in the sensitivity analyses and mentioned that it would not be able to resolve all the problems, in particular those to do with utilities. During consultation, it updated the transition probabilities to account for parameter uncertainty in the probabilistic sensitivity analysis. Transition probabilities for the standard care arm were sampled in the probabilistic sensitivity analysis from the Dirichlet distribution. The ERG questioned why this approach was not considered for the finerenone arm as well. The committee recalled the ERG's concerns with both the original and updated approaches to estimating transition probabilities and that only the latter approach allowed for parameter uncertainty in the probabilistic sensitivity analyses (see section 3.14). It considered that, although the updated approach to sensitivity analyses was an improvement, the outputs of these remained uncertain. The committee concluded that the results of the updated

sensitivity analyses should be interpreted with caution.

# Cost-effectiveness estimates

## Finerenone is cost effective compared with standard care

3.20 The committee considered the cost-effectiveness estimates for finerenone compared with standard care. It acknowledged that, since the first committee meeting, the company had attempted to reduce the uncertainty in the clinical and cost-effectiveness evidence. But it noted the outstanding areas of uncertainty:

- missing comparison for finerenone use with SGLT2 inhibitors (see section 3.4)
- estimation of transition probabilities (see section 3.13 and section 3.14)
- treatment effect waning of finerenone (see section 3.15)
- modelling of previous cardiovascular disease (see section 3.17)
- sensitivity analyses results (see section 3.19).

For finerenone plus standard care compared with standard care alone (when standard care did not include SGLT2 inhibitors), the committee noted that the company's and the ERG's base-case ICERs were relatively low. It also noted that in all the company's scenario analyses, in which standard care included SGLT2 inhibitors, the ICER was less than £30,000 per quality-adjusted life year (QALY) gained. So, despite the uncertainties, it agreed that the most plausible ICER was within the range NICE normally considers an acceptable use of NHS resources. The committee concluded that finerenone is a cost-effective use of NHS resources compared with standard care with or without SGLT2 inhibitors.

# Other factors

## There are no equality issues

3.21 No equality or social value judgement issues were identified that were not captured in the modelling.

# Conclusion

## Finerenone is recommended as an add-on to optimised standard care including ACE inhibitors or ARBs, and SGLT2 inhibitors, unless these are unsuitable

3.22 For CKD associated with type 2 diabetes, finerenone is clinically effective compared with placebo, and improves outcomes when added to standard care (with or without SGLT2 inhibitors). Despite uncertainty in the economic modelling, the committee agreed that the most plausible ICER for finerenone plus standard care compared with standard care alone was within the range NICE normally considers to be a cost-effective use of NHS resources. It also took into account that finerenone had not been compared with SGLT2 inhibitors, so it could not be recommended instead of them. So the committee concluded that finerenone is recommended for stage 3 and 4 CKD (with albuminuria) associated with type 2 diabetes only as an add-on to optimised standard care including ACE inhibitors or ARBs, and SGLT2 inhibitors, unless these are unsuitable.

# 4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has chronic kidney disease associated with type 2 diabetes and the doctor responsible for their care thinks that finerenone is the right treatment, it should be available for use, in line with NICE's recommendations.

# 5 Appraisal committee members and NICE project team

## Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee B.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

## Chair

**Charles Crawley**
Chair, technology appraisal committee B

## NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

**Summaya Mohammadand Zain Hussain**
Technical leads

**Carl Prescott and Caron Jones**
Technical advisers

**Daniel Davies**

Project manager

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# Accreditation