Finerenone
(stage 1 and 2 renal insufficiency)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

The questionnaire on the disease and its treatment was answered by one person.

IQWiG thanks the respondent for participating in the written exchange about how she experienced the disease and its treatment and about the treatment goals. The respondent was not involved in the actual preparation of the dossier assessment.

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Part I: Benefit assessment

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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

I List of abbreviations

Abbreviation	Meaning
ACE	angiotensin-converting enzyme
ACT	appropriate comparator therapy
ARB	angiotensin receptor blocker
CKD	chronic kidney disease
eGFR	estimated glomerular filtration rate
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GLP-1	glucagon-like peptide 1
HbA1c	glycated haemoglobin
IPD	individual patient data
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
KDIGO	Kidney Disease: Improving Global Outcomes
NVL	Nationale VersorgungsLeitlinie (German National Care Guideline)
NYHA	New York Heart Association
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SGLT2	sodium-glucose cotransporter 2
SPC	Summary of Product Characteristics
UACR	urine albumin creatinine ratio

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug finerenone. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 27 February 2023.

Research question

The aim of this report is to assess the added benefit of finerenone compared with optimized standard therapy as an appropriate comparator therapy (ACT) in patients with stage 1 and 2 chronic kidney disease (CKD) with albuminuria in combination with type 2 diabetes mellitus.

The research question presented in Table 2 results from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of finerenone

Therapeutic indication	**ACT**[a]
Adults with CKD (stage 1 and 2 with albuminuria) associated with type 2 diabetes mellitus	Optimized standard therapy for the treatment of CKD and type 2 diabetes mellitus, taking into account the underlying disease(s) and common comorbidities (such as dyslipoproteinaemia, hypertension, anaemia)[b]

a. Presented is the ACT specified by the G-BA.
b. Comments of the G-BA:

- It is assumed that, according to the current state of medical knowledge, treatment of CKD includes the use of ACE inhibitors or AT1 antagonists, if they are an option and not contraindicated or intolerable. ACE inhibitors or AT1 antagonists are thus to be used (in the treatment situation of the add-on therapy) in both study arms.
- Within the framework of the ACT, it is assumed that individualized treatment of the underlying disease, in particular type 2 diabetes mellitus, and any comorbidities that may be present, is carried out in accordance with the current state of medical knowledge, avoiding the use of nephrotoxic drugs in both treatment arms. There is a discrepancy between drugs for the treatment of CKD recommended in the guidelines and approved drugs.
- Placebo or the unchanged continuation of an inadequate treatment of the underlying disease does not correspond to an ACT if there are still further options for treatment optimization.
- For the target population to be treated, target values for comorbidities (such as diabetes mellitus, hypertension, dyslipoproteinaemia, anaemia) are to be defined before the start of the study, which the patients should reach before the start of the study or, if applicable, during a run-in phase and which they should maintain during the study by means of individualized treatment (e.g. dose adjustments). The target values should be based on the treatment standards of the corresponding diseases and, if applicable, take multiple comorbidities into account.
- It is assumed that the goal of the patients in the planned therapeutic indication still is a slowdown of disease progression, so that renal replacement therapy in the form of dialysis or transplantation is not yet indicated for the patients.

ACE: angiotensin-converting enzyme; AT1: angiotensin receptor subtype 1; G-BA: Federal Joint Committee

The company followed the G-BA's specification of the ACT.

In its dossier, the company also addresses the research question on adult patients with stage 3 and 4 CKD with albuminuria in combination with type 2 diabetes mellitus. This research question is part of the benefit assessment A23-15 and this part of the dossier is assessed there.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data presented by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks are used for the derivation of the added benefit. This concurs with the company's inclusion criteria.

Hereinafter, the terms CKD and renal insufficiency are used synonymously.

Results

The check of completeness of the study pool did not reveal any relevant study for assessing the added benefit of finerenone in comparison with the ACT for the present research question. This deviates from the assessment of the company, whose information retrieval identified the RCTs FIDELIO-DKD and FIGARO-DKD. For each of these studies, it presented subpopulations as well as a prespecified meta-analysis based on individual patient data (IPD), which it used to assess the added benefit of finerenone.

The studies FIDELIO-DKD and FIGARO-DKD included by the company are not suitable for the assessment of the added benefit of finerenone versus the ACT because the ACT was not implemented. This is justified below.

Evidence presented by the company – FIDELIO-DKD study

The FIDELIO-DKD study is a placebo-controlled, double-blind, randomized parallel-group study on finerenone. Patients with type 2 diabetes mellitus according to the American Diabetes Association and CKD with a urine albumin creatinine ratio (UACR) ≥ 30 to < 300 mg/g and an estimated glomerular filtration rate (eGFR) of ≥ 25 to ≤ 60 ml/min/1.73m^2 or a UACR of ≥ 300 mg/g and an eGFR of ≥ 25 to ≤ 75 ml/min/1.73m^2 were included. At least 4 weeks before screening, patients had to be treated with a maximum tolerated and stable dose of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), which was ensured as part of treatment optimization during the run-in phase. Patients with known non-diabetic kidney disease or class II to IV symptomatic heart failure (according to the New York Heart Association [NYHA]) and reduced ejection fraction were excluded. Patients with uncontrolled arterial hypertension of ≥ 160/100 mmHg at the time of screening or glycated haemoglobin (HbA1c) levels of > 12% were also excluded. Eplerenone, spironolactone, renin inhibitors and potassium-sparing diuretics were not allowed from 4 weeks before screening. A total of 5734 patients were included and assigned in a 1:1 ratio to treatment with finerenone (N = 2866) or to the placebo group (N = 2868). According to the

study protocol, the study participants were to be treated with an individually adapted therapy according to local guidelines and recommendations for CKD, type 2 diabetes mellitus and, if applicable, further comorbidities.

The primary outcome of the study was the composite outcome consisting of the components "renal insufficiency", "persistent decrease of eGFR by ≥ 40%" and "renal death". Patient-relevant outcomes were recorded in the categories of mortality, morbidity, health-related quality of life and side effects.

Evidence presented by the company – FIGARO-DKD study

The FIGARO-DKD study is a placebo-controlled, double-blind, randomized parallel-group study on finerenone. Patients with type 2 diabetes mellitus according to the American Diabetes Association and CKD with a UACR of ≥ 30 to < 300 mg/g and an eGFR of ≥ 25 to ≤ 90 ml/min/1.73m^2 or a UACR of ≥ 300 mg/g and an eGFR of ≥ 60 ml/min/1.73m^2 were included. At least 4 weeks before screening, patients had to be treated with a maximum tolerated and stable dose of ACE inhibitors or ARBs, which was ensured as part of treatment optimization during the run-in phase. Patients with known non-diabetic kidney disease or class II to IV symptomatic heart failure (according to the NYHA) and reduced ejection fraction were excluded. Patients with uncontrolled arterial hypertension of ≥ 160/100 mmHg at the time of screening or HbA1c levels of > 12% were also excluded . Eplerenone, spironolactone, renin inhibitors and potassium-sparing diuretics were not allowed from 4 weeks before screening. A total of 7437 patients were included and assigned in a 1:1 ratio to treatment with finerenone (N = 3723) or to the placebo group (N = 3714). According to the study protocol, the study participants were to be treated with an individually adapted therapy according to local guidelines and recommendations for CKD, type 2 diabetes mellitus and, if applicable, further comorbidities.

The study's primary outcome was the composite outcome of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke or hospitalization for heart failure. Further patient-relevant outcomes were recorded in the categories of mortality, morbidity, health-related quality of life and side effects.

Subpopulations of the studies FIDELIO-DKD and FIGARO-DKD presented by the company

To answer the research question of the G-BA, the company formed subpopulations of the studies FIDELIO-DKD and FIGARO-DKD based on the diagnostic criteria of the guideline "Kidney Disease: Improving Global Outcomes" (KDIGO). The criteria used for stage 1 and 2 CKD are an eGFR ≥ 60 ml/min/1.73m^2 and a UACR ≥ 30 mg/g. As both studies only included patients with albuminuria (UACR ≥ 30 mg/g), the company classified the patients exclusively according to the criterion "eGFR ≥ 60 ml/min/1.73m^2". This approach is generally appropriate. The company's classification results in a subpopulation with 432 patients (211 in the

intervention arm and 221 in the comparator arm) from the FIDELIO-DKD study and a subpopulation with 4631 patients (2327 in the intervention arm and 2304 in the comparator arm) from the FIGARO-DKD study.

ACT specified by the G-BA not implemented

As ACT in the present therapeutic indication, the G-BA specified optimized standard therapy for the treatment of CKD and type 2 diabetes mellitus, taking into account the underlying disease(s) and common comorbidities (such as dyslipoproteinaemia, hypertension, anaemia).

In both studies, FIDELIO-DKD and FIGARO-DKD, patients were to receive individualized standard treatment according to the recommendations of the local guidelines. This applied to the treatment of CKD and type 2 diabetes mellitus and to the treatment of comorbidities such as e.g. hypertension. In both studies, there were no restrictions regarding treatment switching and dose adjustments of concomitant treatment after randomization. However, the studies FIDELIO-DKD and FIGARO-DKD included by the company are not suitable for the assessment of the added benefit versus the ACT for the present research question, as particularly the treatment of type 2 diabetes mellitus and hypertension (especially in the comparator arms) does not correspond to an optimized standard treatment. This is justified below.

Treatment of type 2 diabetes mellitus

According to the current German National Care Guideline (Nationale VersorgungsLeitlinie, NVL), patients with type 2 diabetes mellitus and concomitant cardiovascular disease should additionally be offered sodium-glucose cotransporter 2 (SGLT2) inhibitors or glucagon-like peptide 1 (GLP-1) receptor agonists.

Overall, about 35% of the patients in the subpopulations of interest had a pre-existing cardiovascular disease at baseline. For these patients, treatment with SGLT2 inhibitors or GLP-1 receptor agonists would thus have been indicated. According to the data provided by the company, only 9.8% of the patients received an SGLT2 inhibitor and 7.6% received a GLP-1 receptor agonist at baseline. It is not clear from the study documents which patients (with or without cardiovascular disease) were receiving SGLT2 inhibitors or GLP-1 receptor agonists. During the course of the study, treatment with SGLT2 inhibitors was initiated in 17.4% of the patients and treatment with GLP-1 receptor agonists was initiated in 10.7%. Even assuming that treatment with SGLT2 inhibitors or GLP-1 receptor agonists was exclusively carried out in patients with pre-existing cardiovascular disease at the start of the study, only a small proportion would have been treated according to the treatment algorithm of the current NVL on type 2 diabetes mellitus.

According to the NVL, the remaining 65% of patients in the relevant subpopulations of the studies FIDELIO-DKD and FIGARO-DKD were at high risk of diabetes-associated cardiovascular and/or renal events due to the existing clinically relevant renal disease and other

cardiovascular risk factors such as hypertension. According to the NVL, treatment with SGLT2 inhibitors or GLP-1 receptor agonists can also be indicated for these patients. Thus, patients at high risk of diabetes-associated cardiovascular and/or renal events should be offered either metformin in combination with SGLT2 inhibitors or GLP-1 receptor agonists, or initially metformin alone, after individual assessment and joint decision-making. If the patient is initially treated with metformin alone and does not achieve the desired treatment goal after 3 to 6 months, a new evaluation is carried out with the option of adding another drug. The choice of a further drug should be based on the corresponding effects on prioritised outcomes. In the respective studies (EMPA-REG Outcome, DECLARE-TIMI 58 and LEADER), a reduction in the risk of severe cardiovascular events was only shown for SGLT2 inhibitors (empagliflozin, dapagliflozin) and GLP-1 receptor agonists (liraglutide). These should therefore be used preferentially. Overall, treatment with SGLT2 inhibitors or GLP-1 receptor agonists would therefore also have been indicated for a large proportion of patients without pre-existing cardiovascular disease, but with a high cardiovascular risk, in the relevant subpopulations.

Analyses of patients with SGLT2 inhibitors and GLP-1 receptor agonists at baseline would be potentially relevant for the benefit assessment. These must therefore be submitted for the benefit assessment.

In summary, only a small proportion of patients with pre-existing cardiovascular disease or at high cardiovascular risk were treated with SGLT2 inhibitors or GLP-1 receptor agonists in compliance with the guidelines. Thus, treatment of the type 2 diabetes mellitus in these studies neither corresponded to the treatment algorithm of the current NVL on type 2 diabetes mellitus nor to an optimized standard therapy in the sense of the ACT. The company did not provide analyses in the form of subgroup analyses for patients who were treated according to the ACT.

Treatment of arterial hypertension

According to the notes of the G-BA, target values for the comorbidities should be defined and achieved before the start of the study and maintained during the course of the study by means of individualized treatment. In its study documents for both studies, the company follows the recommendation of the KDIGO guideline of 2012 with a target value of 130/80 mmHg with individual adjustment, if applicable. However, according to the exclusion criteria, blood pressure values of up to 160/100 mmHg were allowed for patients to be included in the study. Moreover, treatment with aldosterone antagonists (eplerenone and spironolactone) and other potassium-sparing diuretics was not allowed from 4 weeks before screening and during treatment with the study medication. Overall, there was inadequate blood pressure control at baseline. In the subpopulations presented, 25% of the patients had a systolic blood pressure of > 146 mmHg at baseline. The company provided information on blood pressure values during the course of the study only for the total populations of the studies. There was no

relevant improvement in blood pressure values during the course of the study. Notably, blood pressure in the comparator arm remained consistently 2 to 3 mmHg higher on average than in the intervention arm, potentially due to the blood pressure-lowering effect of finerenone.

Overall, optimized treatment of arterial hypertension in the sense of the ACT was not guaranteed in the subpopulations of the studies FIDELIO-DKD and FIGARO-DKD presented by the company, especially in the comparator arms.

Conclusion

A large proportion of patients with pre-existing cardiovascular disease or at cardiovascular risk in the subpopulation of the studies FIDELIO-DKD and FIAGRO-DKD relevant for the present benefit assessment were not treated with SGLT 2 inhibitors or GLP-1 receptor agonists according to the treatment algorithm of the current NVL on type 2 diabetes mellitus. In addition, optimized treatment of arterial hypertension was not guaranteed, especially for patients in the comparator arms of the two studies. Several drugs for the treatment of oedema or of heart failure that might occur in the course were not available. In summary, the ACT of an optimized standard therapy was not implemented in the studies FIDELIO-DKD and FIGARO-DKD.

Results on added benefit

As no suitable data are available for the benefit assessment of finerenone in patients with stage 1 and 2 CKD with albuminuria in combination with type 2 diabetes mellitus, there is no hint of an added benefit of finerenone compared with the ACT; an added benefit is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Table 3 shows a summary of probability and extent of the added benefit of finerenone.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

Table 3: Finerenone – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adults with CKD (stage 1 and 2 with albuminuria) associated with type 2 diabetes mellitus	Optimized standard therapy for the treatment of CKD and type 2 diabetes mellitus, taking into account the underlying disease(s) and common comorbidities (such as dyslipoproteinaemia, hypertension, anaemia)	Added benefit not proven
a. Presented is the ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The G-BA decides on the added benefit.

I 2 Research question

The aim of this report is to assess the added benefit of finerenone compared with optimized standard therapy as an ACT in patients with stage 1 and 2 CKD with albuminuria in combination with type 2 diabetes mellitus.

The research question presented in Table 4 results from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of finerenone

Therapeutic indication	**ACT**[a]
Adults with CKD (stage 1 and 2 with albuminuria) associated with type 2 diabetes mellitus	Optimized standard therapy for the treatment of CKD and type 2 diabetes mellitus, taking into account the underlying disease(s) and common comorbidities (such as dyslipoproteinaemia, hypertension, anaemia)[b]

a. Presented is the ACT specified by the G-BA.
b. Comments of the G-BA:

- It is assumed that, according to the current state of medical knowledge, treatment of CKD includes the use of ACE inhibitors or AT1 antagonists, if they are an option and not contraindicated or intolerable. ACE inhibitors or AT1 antagonists are thus to be used (in the treatment situation of the add-on therapy) in both study arms.
- Within the framework of the ACT, it is assumed that individualized treatment of the underlying disease, in particular type 2 diabetes mellitus, and any comorbidities that may be present, is carried out in accordance with the current state of medical knowledge, avoiding the use of nephrotoxic drugs in both treatment arms. There is a discrepancy between drugs for the treatment of CKD recommended in the guidelines and approved drugs.
- Placebo or the unchanged continuation of an inadequate treatment of the underlying disease does not correspond to an ACT if there are still further options for treatment optimization.
- For the target population to be treated, target values for comorbidities (such as diabetes mellitus, hypertension, dyslipoproteinaemia, anaemia) are to be defined before the start of the study, which the patients should reach before the start of the study or, if applicable, during a run-in phase and which they should maintain during the study by means of individualized treatment (e.g. dose adjustments). The target values should be based on the treatment standards of the corresponding diseases and, if applicable, take multiple comorbidities into account.
- It is assumed that the goal of the patients in the planned therapeutic indication still is a slowdown of disease progression, so that renal replacement therapy in the form of dialysis or transplantation is not yet indicated for the patients.

ACE: angiotensin-converting enzyme; AT1: angiotensin receptor subtype 1; G-BA: Federal Joint Committee

The company followed the G-BA's specification of the ACT.

In its dossier, the company also addresses the research question on adult patients with stage 3 and 4 CKD with albuminuria in combination with type 2 diabetes mellitus. This research question is part of benefit assessment A23-15 [3] and this part of the dossier is assessed there.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data presented by the company in the dossier. RCTs with a minimum duration of 24 weeks are used for the derivation of added benefit. This concurs with the company's inclusion criteria.

Hereinafter, the terms CKD and renal insufficiency are used synonymously.

I 3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on finerenone (status: 16 December 2022)
- bibliographical literature search on finerenone (last search on 16 December 2022)
- search in trial registries/trial results databases for studies on finerenone (last search on 16 December 2022)
- search on the G-BA website for finerenone (last search on 16 December 2022)

To check the completeness of the study pool:

- search in trial registries for studies on finerenone (last search on 13 March 2023); for search strategies, see Appendix I A of the full dossier assessment

The check of completeness of the study pool did not reveal any relevant study for assessing the added benefit of finerenone in comparison with the ACT for the present research question. This deviates from the assessment of the company, which identified the RCTs FIDELIO-DKD [4-16] and FIGARO-DKD [17-23] with its information retrieval. For each of these studies, it presented subpopulations as well as a prespecified meta-analysis based on IPD, which it used to assess the added benefit of finerenone.

The studies FIDELIO-DKD and FIGARO-DKD included by the company are not suitable for the assessment of the added benefit of finerenone versus the ACT because the ACT was not implemented. This is justified below. For this purpose, the studies and subpopulations considered by the company are first described. Thereafter, it will be explained why the studies are not suitable for assessing the added benefit of finerenone compared to the ACT. Further information on the characteristics of the studies FIDELIO-DKD und FIGARO-DKD, the interventions used, and the included patients are found in I Appendix B of this benefit assessment.

Evidence provided by the company

FIDELIO-DKD

The FIDELIO-DKD study is a placebo-controlled, double-blind, randomized parallel-group study on finerenone. Patients with type 2 diabetes mellitus according to the American Diabetes Association and CKD with a UACR of ≥ 30 to < 300 mg/g and an eGFR of ≥ 25 to ≤ 60 ml/min/1.73m^2 or a UACR of ≥ 300 mg/g and an eGFR of ≥ 25 to ≤ 75 ml/min/1.73m^2 were included. At least 4 weeks before screening, patients had to be treated with a maximum tolerated and stable dose of ACE inhibitors or ARBs, which was ensured as part of treatment

optimization during the run-in phase. Patients had to have a serum potassium level of ≤ 4.8 mmol/L for screening. Patients with known non-diabetic kidney disease or class II to IV symptomatic heart failure (according to the NYHA) and reduced ejection fraction were excluded. Patients with uncontrolled arterial hypertension of ≥ 160/100 mmHg at the time of screening or glycated haemoglobin (HbA1c) levels of > 12% were also excluded. Eplerenone, spironolactone, renin inhibitors and potassium-sparing diuretics were also not allowed from 4 weeks before screening.

A total of 5734 patients were included and assigned in a 1:1 ratio to treatment with finerenone (N = 2866) or to the placebo group (N = 2868). Patients were stratified by region (North America vs. Latin America vs. Europe vs. Asia vs. other), UACR at the time of screening (30 to < 300 mg/g [high albuminuria] vs. ≥ 300 mg/g [very high albuminuria]) and eGFR at the time of screening (25 to < 45 ml/min/1.73m^2 vs. 45 to < 60 ml/min/1.73m^2 vs. ≥ 60 ml/min/1.73m^2).

Treatment with finerenone was administered in compliance with the approval in the FIDELIO-DKD study [24]. According to the study protocol, the study participants were to be treated with an individually adapted therapy according to local guidelines and recommendations for CKD, type 2 diabetes mellitus and, if applicable, further comorbidities. A detailed discussion on the implementation of the ACT can be found below.

The study was event-driven and was planned to end after 1068 events of the primary outcome. Patients who discontinued the study medication prematurely were followed up until the end of the study. Patients who were still on treatment with finerenone at the end of the study were followed up until 33 days after the end of the study.

The primary outcome of the study was the composite outcome consisting of the components “renal insufficiency”, “persistent decrease of eGFR by ≥ 40%” and “renal death”. Patient-relevant outcomes were recorded in the categories of mortality, morbidity, health-related quality of life and side effects.

FIGARO-DKD

The FIGARO-DKD study is a placebo-controlled, double-blind, randomized parallel-group study on finerenone. Patients with type 2 diabetes mellitus according to the American Diabetes Association and CKD with a UACR of ≥ 30 to < 300 mg/g and an eGFR of ≥ 25 to ≤ 90 ml/min/1.73m^2 or a UACR of ≥ 300 mg/g and an eGFR of ≥ 60 ml/min/1.73m^2 were included. At least 4 weeks before screening, patients had to be treated with a maximum tolerated and stable dose of ACE inhibitors or ARBs, which was ensured as part of treatment optimization during the run-in phase. Patients had to have a serum potassium level of ≤ 4.8 mmol/L for screening. Patients with known non-diabetic kidney disease or class II to IV symptomatic heart failure (according to the NYHA) and reduced ejection fraction were excluded from participation in the study. Patients with uncontrolled arterial hypertension of ≥ 160/100

mmHg at the time of screening and HbA1c levels of > 12% were also excluded . Eplerenone, spironolactone, renin inhibitors and potassium-sparing diuretics were also not allowed from 4 weeks before screening.

A total of 7437 patients were included and assigned in a 1:1 ratio to treatment with finerenone (N = 3723) or to the placebo group (N = 3714). Patients were stratified by region (North America vs. Latin America vs. Europe vs. Asia vs. other), history of a cardiovascular disease (present vs. not present), UACR at the time of screening (30 to < 300 mg/g [high albuminuria] vs. ≥ 300 mg/g [very high albuminuria]) and eGFR at the time of screening (25 to < 45 ml/min/1.73m^2 vs. 45 to < 60 ml/min/1.73m^2 vs. ≥ 60 ml/min/1.73m^2).

Finerenone was administered in compliance with the approval in the FIGARO-DKD study [24]. According to the study protocol, the study participants were to be treated with an individually adapted therapy according to local guidelines and recommendations for CKD, type 2 diabetes mellitus and, if applicable, further comorbidities. A detailed discussion on the implementation of the ACT can be found below.

The study was event-driven and was planned to end after 976 events of the primary outcome. Patients who discontinued the study medication prematurely were followed up until the end of the study. Patients who were still on treatment with finerenone at the end of the study were followed up until 33 days after the end of the study.

The study's primary outcome was the composite outcome of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke or hospitalization for heart failure. Further patient-relevant outcomes were recorded in the categories of mortality, morbidity, health-related quality of life and side effects.

Subpopulations of the studies FIDELIO-DKD and FIGARO-DKD presented by the company

To answer the research question of the G-BA, the company formed subpopulations of the studies FIDELIO-DKD and FIGARO-DKD based on the diagnostic criteria of the KDIGO guideline" [25]. The criteria used for stage 1 and 2 CKD are an eGFR ≥ 60 ml/min/1.73m^2 and a UACR ≥ 30 mg/g. As both studies only included patients with albuminuria (UACR ≥ 30 mg/g), the company classified the patients exclusively according to the criterion "eGFR ≥ 60 ml/min/1.73m^2". This approach is appropriate. The company's classification results in a subpopulation with 432 patients (211 in the intervention arm and 221 in the comparator arm) from the FIDELIO-DKD study and a subpopulation of 4631 patients (2327 in the intervention arm and 2304 in the comparator arm) from the FIGARO-DKD study.

It should be noted that the company used the eGFR at the time of screening instead of the eGFR at baseline to form the subpopulations. As a result, a total of 10% of the patients were allocated to the therapeutic indication "stage 1 and 2 CKD" relevant to the present benefit

assessment, although the eGFR at baseline was < 60 ml/min/1.73m^2 (stage 3) (see Table 8 of the full dossier assessment). The company did not justify its approach. In addition, according to the Summary of Product Characteristics (SPC), finerenone therapy should not be initiated in patients with a serum potassium level ≥ 5 mmol/L. At baseline, about 4% of the patients showed a serum potassium level above this benchmark. It is unclear whether treatment was initiated in these patients or whether the initiation of treatment was delayed. These two aspects have no consequence for the present benefit assessment, as they affect less than 20% of the relevant patients and the ACT was not implemented in the subpopulations presented by the company (see following section).

ACT specified by the G-BA not implemented

As ACT in the present therapeutic indication, the G-BA specified optimized standard therapy for the treatment of CKD and type 2 diabetes mellitus, taking into account the underlying disease(s) and common comorbidities (such as dyslipoproteinaemia, hypertension, anaemia).

In both studies, FIDELIO-DKD and FIGARO-DKD, patients were to receive individualized standard treatment according to the recommendations of the local guidelines. This applied to the treatment of CKD and type 2 diabetes mellitus and to the treatment of comorbidities such as e.g. hypertension. Guideline-compliant treatment with ACE inhibitors or ARBs in the maximum tolerated dose ≥ 4 weeks before screening was an inclusion criterion. In both studies, there were no restrictions regarding treatment switching and dose adjustments of concomitant treatment after randomization. The data presented on concomitant treatment at baseline and during the course of the study are presented in Table 9 and Table 10 of the full dossier assessment. However, the studies FIDELIO-DKD and FIGARO-DKD included by the company are not suitable for the assessment of the added benefit versus the ACT for the present research question, as particularly the treatment of type 2 diabetes mellitus and hypertension (especially in the comparator arms) does not correspond to an optimized standard therapy. This is justified below.

Treatment of type 2 diabetes mellitus

Elevated levels of HbA1c in patients with diabetes increase the risk of progression of the CKD. According to the current NVL, patients with type 2 diabetes mellitus and concomitant cardiovascular disease should additionally be offered SGLT2 inhibitors or GLP-1 receptor agonists [26].

Overall, about 35% of the patients in the subpopulations of interest had a pre-existing cardiovascular disease at baseline (see Table 8 of the full dossier assessment). For these patients, treatment with SGLT2 inhibitors or GLP-1 receptor agonists would thus have been indicated. According to the data provided by the company, only 9.8% of the patients received an SGLT2 inhibitor and 7.6% a GLP-1 receptor agonist at baseline (Table 9 of the full dossier

assessment). It is not clear from the study documents which patients (with or without cardiovascular disease) were receiving SGLT2 inhibitors or GLP-1 receptor agonists. During the course of the study, treatment with SGLT2 inhibitors was initiated in 17.4% of the patients and treatment with GLP-1 receptor agonists was initiated in 10.7%. The data on concomitant treatments also include treatment switching, so that it is unclear for how many patients a therapy with SGLT2 inhibitors or GLP-1 receptor agonists was newly initiated and for how many patients treatment switching between the two drug classes took place. In addition, it cannot be inferred from the information provided by the company which of the patients (with or without pre-existing cardiovascular disease) received SGLT2 inhibitors or GLP-1 receptor agonists during the course of the study. Overall, it is therefore unclear how many of the patients with pre-existing cardiovascular disease received guideline-compliant treatment with SGLT2 inhibitors or GLP-1 receptor agonists at baseline or during the course of the study. Even assuming that treatment with SGLT2 inhibitors or GLP-1 receptor agonists was exclusively carried out in patients with pre-existing cardiovascular disease at the start of the study, only a small proportion would have been treated according to the treatment algorithm of the current NVL on type 2 diabetes mellitus.

According to the NVL, the remaining 65% of patients in the relevant subpopulations of the studies FIDELIO-DKD and FIGARO-DKD were at high risk of diabetes-associated cardiovascular and/or renal events due to the existing clinically relevant renal disease and other cardiovascular risk factors such as hypertension. According to the NVL, treatment with SGLT2 inhibitors or GLP-1 receptor agonists can also be indicated for these patients. Thus, patients at high risk of diabetes-associated cardiovascular and/or renal events should be offered either metformin in combination with SGLT2 inhibitors or GLP-1 receptor agonists, or initially metformin alone, after individual assessment and joint decision-making. If the patient is initially treated with metformin alone and does not achieve the desired treatment goal after 3 to 6 months, a new evaluation is carried out with the option of adding another drug. The choice of a further drug should be based on the corresponding effects on prioritised outcomes. A reduction in the risk of severe cardiovascular events was shown for SGLT2 inhibitors (empagliflozin, dapagliflozin) and GLP-1 receptor agonists (liraglutide) in the respective studies (EMPA-REG Outcome, DECLARE-TIMI 58 and LEADER). These should therefore be used preferentially. In contrast, there is no evidence of a reduction in the risk of cardiovascular events for the drug classes of sulfonylureas and dipeptidyl peptidase-4 (DPP-4) inhibitors (see I Appendix B), which were the main drugs used alongside metformin in the studies FIDELIO-DKD and FIGARO-DKD. Overall, treatment with SGLT2 inhibitors or GLP-1 receptor agonists would therefore also have been indicated for a large proportion of patients without pre-existing cardiovascular disease, but at high cardiovascular risk, in the relevant subpopulations.

The company did not provide subgroup analyses pre-specified in the study documents of the studies FIDELIO-DKD and FIGARO-DKD on the use of SGLT2 inhibitors or GLP-1 receptor

agonists at baseline (yes vs. no) for the subpopulation under consideration. This approach is not appropriate. Analyses of patients with SGLT2 inhibitors and GLP-1 receptor agonists at baseline would be potentially relevant for the benefit assessment. These must therefore be submitted for the benefit assessment.

In summary, only a small proportion of patients with pre-existing cardiovascular disease or at high cardiovascular risk were treated with SGLT2 inhibitors or GLP-1 receptor agonists in compliance with the guidelines. Thus, the treatment of type 2 diabetes mellitus in these studies neither corresponded to the treatment algorithm of the current NVL on type 2 diabetes mellitus [26] nor to an optimized standard therapy in the sense of the ACT. The company did not provide analyses in the form of subgroup analyses for patients who were treated according to the ACT. Moreover, these subgroup analyses can basically only address the research question of finerenone as an add-on therapy (finerenone plus SGLT2 inhibitors or GLP-1-receptor agonists vs. SGLT2 inhibitors or GLP-1-receptor agonists) and not the comparison between finerenone and SGLT2 inhibitors or GLP-1-receptor agonists.

Treatment of arterial hypertension

According to the notes of the G-BA, target values for the comorbidities should be defined and achieved before the start of the study and maintained during the course of the study by means of individualized treatment. The KDIGO practice guideline on the management of blood pressure in CKD of 2012 [27] recommends a blood pressure of 130/80 mmHg for patients with CKD and type 2 diabetes mellitus including albuminuria (UACR ≥ 30 mg/g). According to the updated KDIGO practice guideline of 2021, a systolic blood pressure of < 120 mmHg [28] is even recommended for these patients.

In its study documents for both studies, the company follows the recommendation of the KDIGO guideline of 2012 [27] and specifies a target value of 130/80 mmHg with individual adjustment, if necessary. However, according to the exclusion criteria, blood pressure values of up to 160/100 mmHg were allowed for patients to be included in the study. Moreover, treatment with aldosterone antagonists (eplerenone and spironolactone) and other potassium-sparing diuretics was not allowed from 4 weeks before screening and during treatment with the study medication. This meant that several drugs for the treatment of arterial hypertension, but also of oedema and potentially occurring heart failure were not available for patients, especially in the comparator arm. Overall, there was inadequate blood pressure control at baseline. In the subpopulations presented, 25% of the patients had a systolic blood pressure of > 146 mmHg at baseline (see Table 8 of the full dossier assessment). The company only provided information on blood pressure values during the course of the study for the total populations of the studies. There was no relevant improvement in blood pressure values during the course of the study. Notably, blood pressure in the comparator

arm remained consistently 2 to 3 mmHg higher than in the intervention arm, potentially due to the blood pressure-lowering effect of finerenone [16,22].

Overall, an optimized treatment of arterial hypertension in the sense of the ACT was not guaranteed in the subpopulations of the studies FIDELIO-DKD and FIGARO-DKD presented by the company, especially in the comparator arms.

Conclusion

A large proportion of patients with pre-existing cardiovascular disease or at cardiovascular risk in the subpopulation of the studies FIDELIO-DKD and FIAGRO-DKD relevant for the present benefit assessment were not treated with SGLT-2 inhibitors or GLP-1 receptor agonists according to the treatment algorithm of the current NVL on type 2 diabetes mellitus. In addition, optimized treatment of arterial hypertension was not guaranteed, especially for patients in the comparator arms of the two studies. Several drugs for the treatment of oedema or of heart failure potentially occurring in the course were not available. In summary, the ACT of an optimized standard therapy was not implemented in the studies FIDELIO-DKD and FIGARO-DKD.

I 4 Results on added benefit

No suitable data are available for the assessment of the added benefit of finerenone compared to the ACT in patients with stage 1 and stage 2 CKD with albuminuria in connection with type 2 diabetes mellitus. There was no hint of an added benefit of finerenone in comparison with the ACT; an added benefit is therefore not proven for these patients.

I 5 Probability and extent of added benefit

Table 5 summarizes the result of the assessment of the added benefit for finerenone in comparison with the ACT.

Table 5: Finerenone – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adults with CKD (stage 1 and 2 with albuminuria) associated with type 2 diabetes mellitus	Optimized standard therapy for the treatment of CKD and type 2 diabetes mellitus, taking into account the underlying disease(s) and common comorbidities (such as dyslipoproteinaemia, hypertension, anaemia)	Added benefit not proven
a. Presented is the ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The assessment described above deviates from that of the company, which derived proof of considerable added benefit.

The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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