Finerenone
(renal insufficiency, stage 3 and 4 1)

Addendum to Project A23-15
(dossier assessment)[1]

ADDENDUM

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CKD	chronic kidney disease
eGFR	estimated glomerular filtration rate
ESRD	end-stage renal disease
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
KDQOL-36	Kidney Disease Quality of Life Instrument-36
MCS	Mental Component Summary
MMRM	mixed-effects model repeated measures
PCS	Physical Component Summary
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SGLT-2	sodium-glucose cotransporter 2
VAS	visual analogue scale

1 Background

On 11 July 2023, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A23-15 (Finerenone – Benefit assessment according to § 35a Social Code Book V) [1].

The commission comprises the assessment of the data of the studies FIGARO-DKD and FIDELIO-DKD [2] presented in the dossier, taking into account the information from the commenting procedure [3,4].

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

As explained in detail in dossier assessment A23-15 [1], the studies FIDELIO-DKD and FIGARO-DKD presented by the pharmaceutical company (hereinafter referred to as "the company") comparing finerenone versus the appropriate comparator therapy (ACT) were not included in the benefit assessment because the ACT in the sense of an optimized standard therapy was not implemented.

On the one hand, this was due to the fact that in the relevant subpopulation (stages 3 and 4) of the studies FIDELIO-DKD and FIGARO-DKD, chronic kidney disease (CKD) was not treated to a sufficient extent with sodium/glucose cotransporter 2 (SGLT-2) inhibitors. In addition, optimized treatment of arterial hypertension was not guaranteed, especially for patients in the comparator arms of the two studies. Moreover, several drugs for the treatment of oedema or of heart failure that might occur in the course were not available. These points of criticism have not been resolved even after completion of the commenting procedure. In particular, it became clear in the oral hearing [5] that the use of SGLT-2 inhibitors in CKD is the current standard of care. Therefore, the studies FIDELIO-DKD and FIGARO-DKD are still not rated as relevant for the benefit assessment.

However, the proportionally small subpopulation (4% and 6%) of patients who received an SGLT-2 inhibitor from the start of the study is potentially relevant for the benefit assessment. However, the uncertainties described above regarding the optimized treatment of arterial hypertension as well as oedema or potentially occurring heart failure in the course also apply to this population. The company did not present the subgroup analyses on the use of SGLT-2 inhibitors at baseline (yes vs. no), which were pre-specified in the statistical analysis plan, in the dossier or in the comments [4], but submitted them subsequently to the oral hearing [3]. However, the subsequently submitted subgroup analyses are incomplete (data on health status and health-related quality of life are missing) and were consequently not used for the benefit assessment. There were therefore no suitable data for the benefit assessment. Results for selected benefit outcomes for the population of patients using SGLT-2 inhibitors at baseline are presented in Appendix B.

In the following, the studies FIDELIO-DKD and FIGARO-DKD are described in accordance with the commission, taking into account the information from the commenting procedure, and the results are presented.

2.1 Study characteristics

Detailed characteristics of the studies FIDELIO-DKD and FIGARO-DKD can be found in dossier assessment A23-15 [1]. In the following, the risk of bias across outcomes not yet presented in dossier assessment A23-15 is described for both studies.

Risk of bias across outcomes (study level)

Table 1 shows the risk of bias across outcomes (risk of bias at study level).

Table 1: Risk of bias across outcomes (study level) – randomized controlled trial (RCT), direct comparison: finerenone vs. placebo

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	Absence of other aspects	Risk of bias at study level
			Patients	Treatment providers			
FIDELIO-DKD	Yes	Yes	Yes	Yes	Yes	Yes	Low
FIGARO-DKD	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes was rated as low for both studies.

2.1 Results

2.1.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
  - All-cause mortality
- Morbidity
  - Renal morbidity with decrease in estimated glomerular filtration rate (eGFR) ≥ 57%
  - cardiovascular morbidity/severe cardiovascular events
  - Health status, recorded using the EQ-5D visual analogue scale (VAS)
- Health-related quality of life
  - Measured with the Kidney Disease Quality of Life Instrument (KDQOL)-36
- Side effects
  - Serious adverse event (SAEs)
  - Discontinuation due to adverse events (AEs)
  - Hyperkalaemia (Preferred Term [PT], SAE)
  - Further specific AEs, if any

The choice of patient-relevant outcomes deviates from that by the company, which used further outcomes in the dossier (Module 4 A).

Table 2 shows the outcomes for which data were available in the included study.

Table 2: Matrix of outcomes – RCT, direct comparison: finerenone versus placebo

Study	Outcomes									
	All-cause mortality	Renal morbidity with eGFR decrease ≥ 57%[a]	Cardiovascular morbidity (composite outcome)	Severe cardiovascular events[b]	Health status (EQ-5D VAS)	Health-related quality of life (KDQOL-36)	SAEs	Discontinuation due to AEs	Hyperkalaemia (PT, SAEs)	Further specific AEs
FIDELIO-DKD	Yes	Yes	No[c]	No[d]	Yes	Yes	No[e]	No[e]	No[e]	No[e]
FIGARO-DKD	Yes	Yes	No[c]	No[d]	Yes	Yes	No[e]	No[e]	No[e]	No[e]

a. Composite renal outcome, consisting of renal insufficiency (defined as confirmed sustained decrease in eGFR to < 15 ml/min/1.73m^2 or end-stage renal disease [ESRD] [need for chronic dialysis treatment > 30 days unless it is apparent that dialysis treatment can be terminated after 90 days, or renal transplantation]), eGFR reduction ≥ 57% and renal death.
b. Operationalized as cardiovascular hospitalization. This includes hospitalization for heart failure, other cardiovascular hospitalization (unstable angina pectoris, arrhythmias, peripheral arterial occlusive disease) or adjudicated cardiovascular event involving hospitalization (cardiovascular death, newly occurred atrial fibrillation or flutter, non-fatal myocardial infarction, non-fatal stroke, transient ischaemic attack).
c. No suitable data available; the composite cardiovascular outcome presented by the company, consisting of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke and severe heart failure events (operationalized as hospitalization due to heart failure), is only presented as supplementary information; for reasons, see the following text section.
d. No suitable data available; for reasons, see the following text section.
e. No suitable analyses on superordinate AE outcomes available (see following text section); selection of specific AEs is therefore also not possible.

AE: adverse event; eGFR: estimated glomerular filtration rate; ESRD: end stage renal disease; KDQOL: Kidney Disease Quality of Life Instrument; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

Composite outcome on renal morbidity

The composite outcome of the studies on renal morbidity comprises the individual components of renal insufficiency (defined as confirmed sustained decrease in eGFR to < 15 ml/min/1.73m^2 or end-stage renal disease [ESRD] [need for chronic dialysis treatment > 30

days unless it is apparent that dialysis treatment can be terminated after 90 days, or renal transplantation]), eGFR reduction ≥ 57% and renal death. Due to the mean eGFR baseline values (approx. 43 ml/min/1.73m^2) of the patients, sufficient patient relevance of the component "eGFR decrease ≥ 57%" is not assumed in the present data situation and the composite outcome is used.

Renal insufficiency (component of the composite outcome of renal morbidity)

In Module 4 A, the company presents analyses on the outcome of renal insufficiency, consisting of the components ESRD and a sustained decrease in eGFR to < 15 ml/min/1.73m². Dossier assessment A23-15 describes that the definition of the component ESRD in the study documents deviates from the one provided in to Module 4 A [1].

In its comments, the company states that the definitions and criteria for the identification of events for renal and cardiovascular outcomes described in Module 4 A and Module 4 B correspond to the specifications determined a priori for the FIDELIO-DKD and FIGARO-DKD studies, which are described in detail in the Clinical Event Committee Charter across studies [6].

The analyses on the outcome of renal insufficiency are used as sufficiently suitable analyses in this addendum.

Cardiovascular morbidity/severe cardiovascular events

The composite outcome of the studies on cardiovascular morbidity includes the individual components of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke and severe heart failure events (operationalized as hospitalization due to heart failure). However, the analyses do not include hospitalizations for other cardiovascular reasons (e.g. hospitalization due to atrial fibrillation, unstable angina pectoris or arrhythmias), which, for example, occurred more than twice as often as hospitalizations due to heart failure in the FIDELIO-DKD study. The composite outcome on cardiovascular morbidity thus covers only part of the relevant cardiovascular events.

In its comments, the company subsequently submitted analyses for cardiovascular hospitalization that are basically suitable for depicting severe cardiovascular events. However, these analyses are incomplete (results for the individual studies are lacking, and there is no information for the relevant subpopulations on how the included events are distributed among the different components [e.g. cardiovascular mortality, transient ischaemic attack, other cardiovascular hospitalizations]).

Overall, the results of the composite outcome "cardiovascular morbidity" as well as of severe cardiovascular events, operationalized as cardiovascular hospitalization, are only presented as supplementary information in this addendum due to the shortcomings described.

Other morbidity outcomes

The composite outcome of renal morbidity, consisting of the individual components "renal insufficiency", "renal death" and "eGFR decrease ≥ 40%", the outcome of confirmed deterioration of CKD to stage 4 or 5, and total hospitalization are each presented as supplementary information in Appendix A.

Health status (EQ-5D VAS) and health-related quality of life (KDQOL-36)

For the outcomes of health status (recorded with the EQ-5D VAS) and health-related quality of life (recorded with the KDQOL-36), the company presented responder analyses on deterioration and improvement, respectively, with the response criterion 15% of the scale range (EQ-5D VAS: 15 points; KDQOL-36: Physical Component Summary [PCS]) = 8 points; Mental Component Summary [MCS] = 9 points; burden of the kidney disease, symptoms and problems of kidney disease and effects of kidney disease on daily life 15 points each). Although the response criteria used correspond to the specifications of the General Methods 6.1 of the Institute [7], the company calculates the relative risk for deterioration or improvement compared to baseline over the entire documentation period and not at a defined time point of documentation, e.g. at month 24. A patient is thus considered a responder in the analyses of the company if he/she showed deterioration or improvement at (any) time point in the course of the study. This analysis is not informative because the time of deterioration or improvement is not taken into account in the analyses submitted by the company. The mixed-effects model repeated measures (MMRM) analyses submitted by the company are therefore used for this addendum.

SAEs, discontinuation due to AEs, hyperkalaemia (PT, SAE) and specific AEs

In the studies FIDELIO-DKD and FIGARO-DKD, AEs were recorded over the entire observation period, regardless of whether the patients were still receiving treatment with the study medication. However, only events that occurred during treatment with the study medication and up to 3 days after a treatment interruption or treatment discontinuation were included in the analyses on AEs, SAEs and discontinuation due to AEs submitted by the company. The company provided no data on the proportion of patients with treatment interruption (> 3 days) and the corresponding duration of the interruption. In the total population of the FIDELIO-DKD study, a proportion of 53.6% in the intervention arm and 45.0% in the comparator arm interrupted treatment; in the total population of the FIGARO-DKD study, a proportion of 50.3% in the intervention arm and 47.4% in the comparator arm interrupted treatment [1]. This proportion is not expected to differ in the subpopulation relevant to this addendum. AEs that occurred during a treatment interruption of more than 3 days are therefore not included in the analyses for a relevant proportion of patients. Likewise, patients who discontinued treatment with the study medication (29-30% in the FIDELIO-DKD study and 31-34% in the FIGARO-DKD study, see dossier assessment A23-15 [1] are not included in the analyses with their entire observation period. This approach is not appropriate. In principle,

analyses that include all events in the observation period are necessary for the benefit assessment.

The company subsequently submitted data with its comment in which, according to its information, all AEs up to 30 days after the last intake of the study medication are taken into account. However, effect estimates and p-values are only available for the overall rate of SAEs; data on discontinuation due to AEs and specific AEs are completely missing. The subsequently submitted data are therefore incomplete. It should be noted, however, that this analysis shows no statistically significant advantage for the intervention (0.97 [0.92; 1.02]; p = 0.2992) in SAEs (deviating from the analysis in Module 4 A).

Therefore, no suitable data are available for the outcomes of SAEs, discontinuation due to AEs, hyperkalaemia (PT, SAE) and other specific AEs. The results of the - unsuitable - data submitted with the dossier (AEs that occurred up to 3 days after treatment interruption or discontinuation) are presented as supplementary information in Appendix A.

2.1.2 Risk of bias

Table 3 describes the risk of bias for the results of the considered outcomes.

Table 3: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: finerenone versus placebo

Study	Study level	Outcomes									
		All-cause mortality	Renal morbidity with eGFR decrease ≥ 57%[a]	Cardiovascular morbidity (composite outcome)	Severe cardiovascular events[b]	Health status (EQ-5D VAS)	Health-related quality of life (KDQOL-36)	SAEs	Discontinuation due to AEs	Hyperkalaemia (PT, SAEs)	Further specific AEs
FIDELIO-DKD	L	L	L	–[c]	–[d]	H[e]	H[e]	–[f]	–[f]	–[f]	–[f]
FIGARO-DKD	L	L	L	–[c]	–[d]	H[e]	H[e]	–[f]	–[f]	–[f]	–[f]

a. Composite renal outcome, consisting of renal insufficiency (defined as confirmed sustained decrease in eGFR to < 15 ml/min/1.73m^2 or end-stage renal disease [ESRD] [need for chronic dialysis treatment > 30 days unless it is apparent that dialysis treatment can be terminated after 90 days, or renal transplantation]), eGFR reduction ≥ 57% and renal death.
b. Operationalized as cardiovascular hospitalization.
c. No suitable data available (see Section 2.1.1); the composite cardiovascular outcome presented by the company, consisting of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke and severe heart failure events (operationalized as hospitalization due to heart failure), is only presented as supplementary information.
d. No suitable data (see Section 2.1.1).
e. Decreasing questionnaire response rate over the course of the study.
f. No suitable analyses on superordinate AE outcomes available (see Section 2.1.1); selection of specific AEs is therefore also not possible.

AE: adverse event; eGFR: estimated glomerular filtration rate; ESRD: end-stage renal disease; KDQOL: Kidney Disease Quality of Life Instrument; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

The risk of bias for the results of the outcomes on all-cause mortality and renal insufficiency with decrease in eGFR by ≥ 57% was rated as low. The results of the outcomes on health status, recorded using the EQ-5D VAS, and on health-related quality of life, recorded with the KDQOL-36, show a high risk of bias due to decreasing questionnaire response rates over the course of the study. No suitable data are available for the outcomes on cardiovascular morbidity (as well as on serious cardiovascular events) and side effects (for reasons, see Section 2.1.1).

2.1.3 Results

Table 4 and Table 5 summarize the results comparing finerenone with placebo in adult patients with stage 3 and 4 CKD with albuminuria associated with type 2 diabetes mellitus. Outcomes on renal morbidity with eGFR decline ≥ 40%, on confirmed worsening of CKD to stage 4 or 5, total hospitalization and data on side effects are presented as supplementary information in Appendix A of the full dossier assessment and outcomes for the subpopulation with concomitant treatment of SGLT-2 inhibitors at baseline are presented in Appendix B of the full dossier assessment. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier. The Kaplan-Meier curves on the event time analyses of the outcomes can be found in dossier assessment A23-15 [1].

Table 4: Results (mortality, morbidity, time to event) – RCT, direct comparison: finerenone vs. placebo (multipage table)

Outcome category outcome study	Finerenone N	Finerenone median time to event in months [95% CI] patients with event n (%)	Placebo N	Placebo median time to event in months [95% CI] patients with event n (%)	Finerenone vs. placebo HR [95% CI]; p-value[a]
Mortality					
All-cause mortality					
FIDELIO-DKD	2622	NA 202 (7.7)	2620	NA 230 (8.8)	0.87 [0.72; 1.05]; 0.157
FIGARO-DKD	1359	NA 167 (12.3)	1362	NA 159 (11.7)	1.05 [0.85; 1.31]; 0.648
Total[b]					0.94 [0.82; 1.09]; 0.421
Morbidity					
Renal morbidity					
Renal morbidity with eGFR decrease ≥ 57% (composite outcome)					
FIDELIO-DKD	2622	NA 245 (9.3)	2620	NA 310 (11.8)	0.78 [0.66; 0.92]; 0.004
FIGARO-DKD	1359	NA 35 (2.6)	1362	NA 31 (2.3)	1.15 [0.71; 1.87]; 0.569
Total[b]					0.82 [0.70; 0.96]; 0.014
Renal insufficiency[c, d]					
FIDELIO-DKD	2622	NA 206 (7.9)	2620	NA 227 (8.7)	0.89 [0.74; 1.08]; 0.228
FIGARO-DKD	1359	NA 24 (1.8)	1362	NA 24 (1.8)	0.96 [0.54; 1.70]; 0.887
Total[b]					0.90 [0.75; 1.07]; 0.233
Sustained decrease in eGFR to < 15 ml/min/1.73 m² [c]					
FIDELIO-DKD	2622	NA 166 (6.3)	2620	NA 193 (7.4)	0.84 [0.69; 1.04]; 0.108
FIGARO-DKD	1359	NA 16 (1.2)	1362	NA 17 (1.2)	0.90 [0.45; 1.81]; 0.772
Total[b]					0.85 [0.70; 1.04]; 0.105
ESRD[c,e]					
FIDELIO-DKD	2622	NA 118 (4.5)	2620	NA 134 (5.1)	0.88 [0.69; 1.13]; 0.316

Table 4: Results (mortality, morbidity, time to event) – RCT, direct comparison: finerenone vs. placebo (multipage table)

Outcome category outcome study	Finerenone N	Finerenone median time to event in months [95% CI] patients with event n (%)	Placebo N	Placebo median time to event in months [95% CI] patients with event n (%)	Finerenone vs. placebo HR [95% CI]; p-value[a]
FIGARO-DKD	1359	NA 15 (1.1)	1362	NA 15 (1.1)	0.98 [0.48; 2.01]; 0.964
Total[b]					0.89 [0.70; 1.12]; 0.325
Decrease in eGFR by ≥ 57%[c]					
FIDELIO-DKD	2622	NA 161 (6.1)	2620	NA 229 (8.7)	0.70 [0.57; 0.85]; < 0.001
FIGARO-DKD	1359	NA 21 (1.5)	1362	NA 19 (1.4)	1.11 [0.59; 2.07]; 0.746
Total[b]					0.73 [0.60; 0.89]; 0.001
Renal death[c,f]					
FIDELIO-DKD	2622	NA 2 (< 0.1)	2620	NA 2 (< 0.1)	1.02 [0.14; 7.24]; 0.985
FIGARO-DKD	1359	NA 0 (0)	1362	NA 1 (< 0.1)	NC; 0.296
Total[b]					0.69 [0.12; 4.14]; 0.685
Cardiovascular morbidity			No suitable data		
Cardiovascular morbidity (composite outcome[g]) (supplementary information)					
FIDELIO-DKD	*2622*	*NA* *333 (12.7)*	*2620*	*NA* *387 (14.8)*	*0.84 [0.73; 0.97]; 0.020*
FIGARO-DKD	*1359*	*NA* *195 (14.3)*	*1362*	*NA* *228 (16.7)*	*0.84 [0.69; 1.02]; 0.072*
Total[b]					0.84 [0.74; 0.94]; 0.003
Cardiovascular death[c]					
FIDELIO-DKD	*2622*	*NA* *115 (4.4)*	*2620*	*NA* *138 (5.3)*	*0.83 [0.65; 1.06]; 0.140*
FIGARO-DKD	*1359*	*NA* *89 (6.5)*	*1362*	*NA* *90 (6.6)*	*0.99 [0.74; 1.32]; 0.932*
Total[b]					0.89 [0.74; 1.08]; 0.234
Nonfatal myocardial infarction[c]					

Table 4: Results (mortality, morbidity, time to event) – RCT, direct comparison: finerenone vs. placebo (multipage table)

Outcome category **outcome** **study**	**Finerenone**		**Placebo**		**Finerenone vs. placebo**
	N	**median time to event in months [95% CI]** **patients with event n (%)**	**N**	**median time to event in months [95% CI]** **patients with event n (%)**	**HR [95% CI]; p-value[a]**
FIDELIO-DKD	*2622*	*NA* *62 (2.4)*	*2620*	*NA* *78 (3.0)*	*0.78 [0.56; 1.09]; 0.146*
FIGARO-DKD	*1359*	*NA* *48 (3.5)*	*1362*	*NA* *53 (3.9)*	*0.89 [0.60; 1.31]; 0.548*
Total[b]					0.83 [0.64; 1.06]; 0.138
Nonfatal stroke[c]					
FIDELIO-DKD	*2622*	*NA* *82 (3.1)*	*2620*	*NA* *76 (2.9)*	*1.06 [0.78; 1.45]; 0.700*
FIGARO-DKD	*1359*	*NA* *32 (2.4)*	*1362*	*NA* *46 (3.4)*	*0.70 [0.44; 1.10]; 0.116*
Total[b]					0.92 [0.71; 1.19]; 0.531
Severe heart failure events (operationalized as hospitalization for heart failure)[c]					
FIDELIO-DKD	*2622*	*NA* *130 (5.0)*	*2620*	*NA* *149 (5.7)*	*0.87 [0.69; 1.10]; 0.242*
FIGARO-DKD	*1359*	*NA* *58 (4.3)*	*1362*	*NA* *72 (5.3)*	*0.79 [0.56; 1.12]; 0.187*
Total[b]					0.84 [0.69; 1.02]; 0.085
Severe cardiovascular events (presented as supplementary information)[c]					
FIDELIO-DKD	*2622*	*ND[h]*	*2620*	*ND[h]*	*ND*
FIGARO-DKD	*1359*	*ND[h]*	*1362*	*ND[h]*	*ND*
Total[d]					*0.90 [0.81; 0.99]; 0.028*
Side effects	No suitable data				

Table 4: Results (mortality, morbidity, time to event) – RCT, direct comparison: finerenone vs. placebo (multipage table)

Outcome category outcome study	Finerenone		Placebo		Finerenone vs. placebo
	N	median time to event in months [95% CI] patients with event n (%)	N	median time to event in months [95% CI] patients with event n (%)	HR [95% CI]; p-value[a]

a. For the individual studies, HR [95% CI] from Cox regression model, stratified by region, eGFR category at the time of screening and, for the FIDELIO-DKD study, additionally by urine albumin-creatinine ratio (UACR) at the time of screening and, for the FIGARO-DKD study, additionally by cardiovascular history; p-value: log-rank test, stratified by the same factors.

b. Calculation from IPD metaanalysis with factor study as fixed effect (for model see footnote "a"); stratified by region, eGFR category at the time of screening, UACR at time of screening and cardiovascular history.

c. The presentation of the individual components does not comprise the qualifying events, but all events that occurred during the course of the study.

d. Renal insufficiency was defined as the occurrence of ESRD or an eGFR < 15 ml/min/1.73m², confirmed by a 2nd measurement ≥ 4 weeks after the 1st measurement.

e. According to Module 4 A ESRD was defined as:

- Kidney transplant
- Peritoneal dialysis or haemodialysis required for at least 30 days and for which it is not apparent that treatment can be stopped after 90 days.
- acute kidney injury resulting in dialysis or death and occurring during dialysis treatment
- Renal replacement therapy indicated for symptomatic uraemia (eGFR of < 15 ml/min/1.73m^2 for at least 30 days) or asymptomatic uraemia (eGFR of < 8 ml/min/1.73m^2) but not available or accessible, refused or considered futile; ESRD is then diagnosed even without initiation of renal replacement therapy.

f. A death was classified as renal death if the patient died and had not received clinically indicated renal replacement therapy and there is no other probable cause of death.

g. Composite outcome, consisting of hospitalization for heart failure, other cardiovascular hospitalization (unstable angina pectoris, arrhythmias, peripheral arterial occlusive disease) or adjudicated cardiovascular event involving hospitalization (cardiovascular death, newly occurred atrial fibrillation or flutter, non-fatal myocardial infarction, non-fatal stroke, transient ischaemic attack).

h. In the IPD metaanalysis, 780 (19.6%) patients in the intervention arm and 849 (21.3%) patients in the comparator arm had an event.

CI: confidence interval; eGFR: estimated glomerular filtration rate; ESRD: end-stage renal disease; HR: hazard ratio; IPD: individual patient data; n: number of patients with (at least 1) event; N: number of analysed patients; NA: not achieved; NC: not calculable; RCT: randomized controlled trial; UACR: urine albumin creatinine ratio

Table 5: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: finerenone versus placebo (multipage table)

Study outcome category outcome	Finerenone			Placebo			Finerenone vs. placebo
	N[a]	values at baseline mean (SD)	mean change in the course of the study mean[b] (95% CI)	N[a]	values at baseline mean (SD)	mean change in the course of the study mean[b] (95% CI)	MD [95% CI]; p-value[b]
Morbidity							
Health status (EQ-5D VAS)[c]							
FIDELIO-DKD	2386	73.58 (16.77)	–[d]	2366	72.94 (16.80)	–[d]	–[d]
FIGARO-DKD	1245	73.78 (15.96)	-0.58 [-1.42; 0.26]	1234	72.92 (17.07)	-0.42 [-1.29; 0.46]	-0.16 [-1.18; 0.86]; 0.758
Total							–
Health-related quality of life							
KDQOL-36[e]							
PCS							
FIDELIO-DKD	2360	42.04 (10.09)	-0.81 [-1.26; -0.35]	2333	42.09 (9.99)	-1.29 [-1.75; -0.83]	0.49 [0.04; 0.93]; 0.032
FIGARO-DKD	1237	41.35 (10.22)	-1.30 [-1.79; -0.80]	1223	41.60 (10.30)	-1.39 [-1.89; -0.90]	0.10 [-0.49; 0.68]; 0.748
Total[f]							0.38 [0.04; 0.72]; 0.030 SMD: 0.04 [0.00; 0.09]
MCS							
FIDELIO-DKD	2360	51.30 (9.66)	-1.14 [-1.64; -0.64]	2333	51.20 (9.70)	-1.03 [-1.52; -0.53]	-0.11 [-0.59; 0.37]; 0.650
FIGARO-DKD	1237	52.18 (9.39)	-0.98 [-1.51; -0.45]	1223	51.83 (9.59)	-1.50 [-2.03; -0.98]	0.53 [-0.10; 1.15]; 0.100
Total[f]							0.02 [-0.34; 0.39]; 0.894
Disease burden of kidney disease							
FIDELIO-DKD	2381	71.62 (25.77)	0.93 [-0.34; 2.21]	2361	71.51 (26.46)	0.67 [-0.59; 1.94]	0.26 [-0.96; 1.48]; 0.674
FIGARO-DKD	1247	77.96 (24.02)	-0.68 [-1.92; 0.56]	1236	77.20 (24.07)	-0.30 [-1.52; 0.91]	-0.37 [-1.81; 1.07]; 0.613
Total[f]							0.08 [-0.83; 0.99]; 0.863

Table 5: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: finerenone versus placebo (multipage table)

Study outcome category / outcome	Finerenone N[a]	Finerenone values at baseline mean (SD)	Finerenone mean change in the course of the study mean[b] (95% CI)	Placebo N[a]	Placebo values at baseline mean (SD)	Placebo mean change in the course of the study mean[b] (95% CI)	Finerenone vs. placebo MD [95% CI]; p-value[b]
Symptoms and problems of kidney disease							
FIDELIO-DKD	2383	82.69 (14.54)	-2.15 [-2.82; -1.49]	2366	82.58 (14.56)	-1.93 [-2.59; -1.26]	-0.23 [-0.87; 0.41]; 0.485
FIGARO-DKD	1248	82.88 (14.36)	-1.54 [-2.20; -0.88]	1238	83.24 (13.95)	-1.68 [-2.36; -1.00]	0.14 [-0.65; 0.93]; 0.722
Total[f]							-0.18 [-0.67; 0.30]; 0.454
Effects of kidney disease on everyday life							
FIDELIO-DKD	2375	85.78 (15.94)	-0.40 [-1.17; 0.38]	2358	85.89 (15.60)	-1.04 [-1.83; -0.24]	0.64 [-0.13; 1.41]; 0.102
FIGARO-DKD	1246	87.79 (15.15)	-0.92 [-1.69; -0.15]	1236	87.48 (14.87)	-0.74 [-1.49; 0.00]	-0.18 [-1.07; 0.71]; 0.694
Total[f]							0.29 [-0.29; 0.87]; 0.331[g]

a. Number of patients taken into account in the analysis for calculating the effect estimation; baseline values may rest on different patient numbers.
b. Changes and mean difference of the individual studies: MMRM with the covariates treatment group, region, eGFR at the time of screening, time, interaction from treatment and time, baseline value and interaction from baseline value and time, as well as for the study FIDELIO-DKD, additionally the covariate UACR at the time of screening or, for the study FIGARO-DKD, additionally the covariate history of cardiovascular disease.
c. Higher (increasing) values indicate improved symptoms; positive effects (intervention minus control) indicate an advantage for the intervention (scale range 0 to 100).
d. According to the company, no results are available due to convergence problems.
e. Higher (increasing) values mean improved symptoms/health-related quality of life; positive effects (intervention minus control) mean an advantage for the intervention (scale range: Physical Component Summary (PCS) 13 to 69 points; Mental Component Summary (MCS) 10 to 70 points; disease burden of kidney disease, symptoms and problems of kidney disease, and effects of kidney disease on everyday life 0 to 100 points each).
f. Calculation from IPD metaanalysis: MMRM with the covariates study, treatment group, region, eGFR at time of screening; UACR at time of screening, history of cardiovascular disease, time, interaction from treatment and time, baseline value and interaction from baseline value and time.
g. Institute's calculation from aggregate data. Results from IPD metaanalysis are not available.

CI: confidence interval; eGFR: estimated glomerular filtration rate; IPD: individual patient data; KDQOL: Kidney Disease Quality Of Life; MCS: Mental Component Summary; MD: mean difference; MMRM: mixed-effects model repeated measures; N: number of analysed patients; PCS: Physical Component Summary; RCT: randomized controlled trial; SD: standard deviation; SMD: standardized mean difference; UACR: urine albumin creatinine ratio; VAS: visual analogue scale

Mortality

All-cause mortality

For the outcome of all-cause mortality, the metaanalysis of the studies FIDELIO-DKD and FIGARO-DKD does not show any statistically significant differences between treatment groups. There is an effect modification by the characteristic of region for this outcome (see Section 2.1.4). For patients in the "Asia" category, there is a statistically significant difference in favour of, and in the "Other" category, there is a statistically significant difference to the disadvantage of finerenone compared to placebo. However, there was no statistically significant difference between the treatment groups for patients in the categories “Europe”, “North America” and “Latin America”.

Morbidity

Renal morbidity with eGFR decrease ≥ 57%

For the composite outcome of renal morbidity with decrease in eGFR by ≥ 57% as well as for the single component decrease in eGFR ≥ 57%, the metaanalysis of the studies FIDELIO-DKD and FIGARO-DKD each showed a statistically significant difference in favour of finerenone compared to placebo. The metaanalysis of the studies FIDELIO-DKD and FIGARO-DKD shows no statistically significant difference between the treatment groups for the individual components renal insufficiency, sustained decrease in eGFR to < 15 ml/min/1.73m^2, ESRD and renal death.

Cardiovascular morbidity (composite outcome) and severe cardiovascular events (operationalized as cardiovascular hospitalization)

No suitable data are available for the composite outcome of cardiovascular morbidity and severe cardiovascular events (operationalized as cardiovascular hospitalization).

Health status (EQ-5D VAS) analysed using MMRM

For the outcome of health status measured using the EQ-5D VAS, no result is available for the metaanalysis of the studies FIDELIO-DKD and FIGARO-DKD.

Health-related quality of life

KDQOL-36 analysed using MMRM

PCS

For the dimension PCS of the KDQOL-36, the metaanalysis of the studies FIDELIO-DKD and FIGARO-DKD shows a statistically significant difference in favour of finerenone over placebo. However, the effect is not outside the irrelevance range (standardized mean difference [-0.2; 0.2]). It can therefore not be inferred that the effect was relevant.

MCS, disease burden of kidney disease, symptoms and problems of kidney disease and impact of kidney disease on everyday life

For each of the domains of the KDQOL-36 MCS, burden of kidney disease, symptoms and problems of kidney disease and impact of kidney disease on everyday life, the metaanalysis of the studies FIDELIO-DKD and FIGARO-DKD shows no statistically significant difference between the treatment groups.

Side effects

No suitable data are available for outcomes of the category of side effects.

2.1.4 Subgroups and other effect modifiers

The following subgroup characteristics are relevant for the present analysis:

- Age (< 65 years versus ≥ 65 years)
- Sex (male versus female)
- Region (Europe vs. North America vs. Asia vs. Latin America vs. other)
- eGFR (ml/min/1.73 m²) at the screening visit (25 to < 45 vs. 45 to < 60)
- Albuminuria at screening visit (high albuminuria vs. very high albuminuria)

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. Moreover, for binary data, there had to be at least 10 events in at least 1 subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are presented only if there is a statistically significant and relevant effect in at least one subgroup.

The results are presented in Table 6. Kaplan-Meier curves for the subgroup results of the individual studies are not available.

Table 6: Subgroups (mortality, morbidity, time to event) – RCT, direct comparison: finerenone vs. placebo (multipage table)

Outcome characteristic study subgroup	Finerenone N	Finerenone median time to event in months [95% CI] patients with event n (%)	Placebo N	Placebo median time to event in months [95% CI] patients with event n (%)	Finerenone vs. placebo HR [95% CI][a]	Finerenone vs. placebo p-value[b]
All-cause mortality						
Region						
FIDELIO-DKD						
Europe	1078	ND 93 (8.6[a])	1064	ND 115 (10.8[a])	0.80 [0.60; 1.04]	
North America	425	ND 40 (9.4[a])	437	ND 32 (7.3[a])	1.28 [0.81; 2.04]	
Asia	751	ND 34 (4.5[a])	748	ND 51 (6.8[a])	0.65 [0.42; 1.01]	
Latin America	274	ND 20 (7.3[a])	274	ND 26 (9.5[a])	0.76 [0.42; 1.36]	
Other	94	ND 15 (16.0[a])	97	ND 6 (6.2[a])	2.68 [1.04; 6.92]	
FIGARO-DKD						
Europe	640	ND 92 (9.8[a])	639	ND 85 (13.3[a])	1.08 [0.80; 1.45]	
North America	267	ND 32 (12.0[a])	271	ND 31 (11.4[a])	1.08 [0.66; 1.76]	
Asia	288	ND 13 (4.5[a])	292	ND 23 (7.9[a])	0.55 [0.28; 1.09]	
Latin America	102	ND 16 (15.7[a])	101	ND 16 (15.8[a])	1.00 [0.50; 2.00]	
Other	62	ND 14 (22.6[a])	59	ND 4 (6.8[a])	3.44 [1.13; 10.5]	
Total					Interaction:	0.002[b]
Europe					0.92 [0.75; 1.12][c]	0.405
North America					1.18 [0.84; 1.65][c]	0.349
Asia					0.61 [0.42; 0.88][c]	0.008
Latin America					0.85 [0.54; 1.33][c]	0.470
Other					2.94 [1.43; 6.07][c]	0.002

a. Institute's calculation.
b. p-value from Wald test in Cox regression model stratified by region, eGFR category at time of screening, UACR at time of screening and cardiovascular history.
c. IPD metaanalysis: Cox regression model with factor study as fixed effect stratified by region, eGFR category at the time of screening, UACR at time of screening and cardiovascular history.

Table 6: Subgroups (mortality, morbidity, time to event) – RCT, direct comparison: finerenone vs. placebo (multipage table)

Outcome characteristic study subgroup	Finerenone		Placebo		Finerenone vs. placebo	
	N	median time to event in months [95% CI] patients with event n (%)	N	median time to event in months [95% CI] patients with event n (%)	HR [95% CI][a]	p-value[b]
CI: confidence interval; eGFR: estimated glomerular filtration rate; HR: hazard ratio; IPD: individual patient data; ND: no data; N: number of analysed patients; n: Number of patients with event; RCT: randomized controlled trial; UACR: urine albumin-creatinine ratio						

All-cause mortality

The metaanalysis showed an effect modification by the characteristic “region" for the outcome "all-cause mortality". For patients in the "Asia" category, there is a statistically significant difference in favour of, and in the "Other" category, there is a statistically significant difference to the disadvantage of finerenone compared to placebo. However, there was no statistically significant difference between the treatment groups for patients in the categories “Europe”, “North America” and “Latin America”.

2.1.5 Summary of the results

Overall, the metaanalysis shows advantages of finerenone for the composite outcome on renal morbidity (with eGFR decrease ≥ 57%) and for the individual component eGFR decrease ≥ 57%. Suitable data for cardiovascular morbidity and side effects are lacking.

2.2 Summary

The data subsequently submitted by the company in the commenting procedure have not changed the conclusion on the added benefit of finerenone from dossier assessment A23-15.

The following Table 7 shows the result of the benefit assessment of finerenone under consideration of dossier assessment A23-15 and the present addendum.

Table 7: Finerenone – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adults with CKD (stage 3 and 4 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.

3 References

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

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6. Aci Clinical. CEC Charter 2019: Finerenone (BAY 94-8862) Phase III Program Clinical Event Committee Charter, Version 3.0.

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Appendix A Supplementary presentation of results on morbidity and side effects

Table 8: Supplementary presentation of results (morbidity, time to event) – RCT, direct comparison: finerenone vs. placebo

Study outcome category outcome	Finerenone N	Finerenone median time to event in months [95% CI] patients with event n (%)	Placebo N	Placebo median time to event in months [95% CI] patients with event n (%)	Finerenone vs. placebo HR [95% CI]; p-value[a]
Morbidity					
Renal morbidity with eGFR decrease ≥ 40% (composite outcome) (provided as supplementary information)[b, c]					
FIDELIO-DKD	*2622*	*NA* *470 (17.9)*	*2620*	*NA* *564 (21.5)*	*0.82 [0.72; 0.92]; 0.001*
FIGARO-DKD	*1359*	*NA* *133 (9.8)*	*1362*	*NA* *114 (8.4)*	*1.18 [0.92; 1.51]; 0.200*
Total[d]					*0.88 [0.79; 0.98]; 0.023*
Confirmed deterioration of CKD to stage 4 or 5 (supplementary information)[e]					
FIDELIO-DKD	*2622*	*NA* *386 (14.7)*	*2620*	*NA* *445 (17.0)*	*0.86 [0.75; 0.98]; 0.024*
FIGARO-DKD	*1359*	*NA* *104 (7.7)*	*1362*	*NA* *81 (5.9)*	*1.30 [0.97; 1.75]; 0.074*
Total[d]					*0.92 [0.82; 1.05]; 0.215*
Total hospitalization (supplementary information)					
FIDELIO-DKD	*2622*	*38.9 [36.5; 41.1]* *1176 (44.9)*	*2620*	*34.9 [32.7; 37.9]* *1227 (46.8)*	*0.95 [0.87; 1.03]; 0.184*
FIGARO-DKD	*1359*	*43.2 [39.4; 49.1]* *670 (49.3)*	*1362*	*41.2 [37.5; 45.7]* *687 (50.4)*	*0.97 [0.87; 1.07]; 0.521*
Total[d]					*0.95 [0.89; 1.01]; 0.116*

a. For individual studies, HR [95% CI] from Cox regression model, stratified by region, eGFR category at the time of screening and, for the FIDELIO-DKD study, additionally by urine albumin-creatinine ratio (UACR) at the time of screening and, for the FIGARO-DKD study, additionally by cardiovascular history; p-value: log-rank test, stratified by the same factors.

b. Composite outcome, consisting of renal insufficiency, sustained decrease in eGFR by ≥ 40% from baseline, with the decrease lasting at least 4 weeks, and renal death.

c. Data for the single component of sustained decrease in eGFR by ≥ 40% from baseline are not available. For results on the individual components of renal failure and renal death, see renal morbidity with a decrease in eGFR ≥ 57 % (Table 4).

d. Calculation from IPD metaanalysis with factor study as fixed effect (for model see footnote "a"); stratified by region, eGFR category at the time of screening, UACR at time of screening and cardiovascular history.

e. Decrease in eGFR by ≥ 25% to < 30 ml/min/1.73m^2 or to < 15 ml/min/1.73m^{2}compared to baseline, which had to be confirmed in a 2nd measurement ≥ 4 weeks after the 1st measurement.

CI: confidence interval; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; ESRD: end-stage renal disease; HR: hazard ratio; IPD: individual patient data; n: number of patients with (at least 1) event; N: number of analysed patients; NA: not achieved; RCT: randomized controlled trial; UACR: urine albumin creatinine ratio

Table 9: Results (side effects, dichotomous) – RCT, direct comparison: finerenone vs. placebo

Study outcome category outcome	Finerenone N	Finerenone patients with event n (%)	Placebo N	Placebo patients with event n (%)	Finerenone vs. placebo RR [95% CI]; p-value[a]
Side effects					
AEs (supplementary information)[b, c]					
FIDELIO-DKD	*2617*	*2263 (86.5)*	*2610*	*2281 (87.4)*	–
FIGARO-DKD	*1357*	*1186 (87.4)*	*1356*	*1183 (87.2)*	–
SAEs (supplementary information)[b, c]					
FIDELIO-DKD	*2617*	*814 (31.1)*	*2610*	*881 (33.8)*	*0.92 [0.85; 1.00]; 0.041*
FIGARO-DKD	*1357*	*484 (35.7)*	*1356*	*500 (36.9)*	*0.97 [0.88; 1.07]; 0.514*
Total[d]					*0.94 [0.88; 1.00]; 0.044*
Discontinuation due to AEs (supplementary information)[b]					
FIDELIO-DKD	*2617*	*197 (7.5)*	*2610*	*157 (6.0)*	*1.25 [1.02; 1.53]; 0.030*
FIGARO-DKD	*1357*	*122 (9.0)*	*1356*	*89 (6.6)*	*1.37 [1.05; 1.78]; 0.019*
Total[d]					*1.29 [1.10; 1.52]; 0.002*
Hyperkalaemia (PT, SAE) (supplementary information)[b]					
FIDELIO-DKD	*2617*	*40 (1.5)*	*2610*	*12 (0.5)*	*3.32 [1.75; 6.32]; < 0.001*
FIGARO-DKD	*1357*	*14 (1.0)*	*1356*	*2 (0.1)*	*7.00 [1.59; 30.72]; 0.010*
Total[d]					*3.85 [2.14; 6.91]; < 0.001*

a. RR for the individual studies calculated using log-binomial regression model, stratified by region, eGFR category at the time of screening and, for the FIDELIO-DKD study, additionally by UACR at the time of screening and, for the FIGARO-DKD study, additionally by cardiovascular history.

b. No meaningfully interpretable data available. However, only events that occurred during treatment with the study medication and up to 3 days after a treatment interruption or treatment discontinuation were included in the analyses. This is a relevant problem in the present data situation, as in the total population of the FIDELIO-DKD study a proportion of 53.6% in the intervention arm and 45.0% in the comparator arm, and in the total population of the FIGARO-DKD study 50.3% in the intervention arm and 47.4% in the comparison arm interrupted treatment (no data for the relevant subpopulation). Likewise, patients who discontinued treatment with the study medication (31-34% in the FIGARO-DKD study and 29-30% in the FIDELIO-DKD study, see dossier assessment A23-15 [1] are not included in the analyses with their entire observation period.

c. Excluding disease-related events.

d. Calculation from IPD metaanalysis with factor study as fixed effect (for model see footnote "a"); stratified by region, eGFR category at the time of screening, UACR at time of screening and cardiovascular history.

AE: adverse event; CI: confidence interval; IPD: individual patient data; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; UACR: urine albumin creatinine ratio

Appendix B Supplementary presentation of results of the subpopulation with concomitant treatment of SGLT-2 inhibitors at baseline

Table 10: Results (mortality, morbidity, time to event) - RCT, direct comparison: finerenone + optimized standard therapy vs. placebo + optimized standard therapy, population with concomitant treatment with SGLT-2 inhibitors at baseline (multipage table)

Outcome category **outcome** **study**	**Finerenone + optimized standard therapy**		**Placebo + optimized standard therapy**		**Finerenone + optimized standard therapy vs. placebo + optimized standard therapy**
	N	**median time to event in months [95% CI]** **patients with event n (%)**	**N**	**median time to event in months [95% CI]** **patients with event n (%)**	**HR [95% CI]; p-value[a]**
Mortality					
Overall survival					
FIDELIO-DKD	ND	ND	ND	ND	ND
FIGARO-DKD	ND	ND	ND	ND	ND
Total	186	ND 10 (5.4)	197	ND 17 (8.6)	0.53 [0.21; 1.34]; 0.174
Morbidity					
Renal morbidity with eGFR decrease ≥ 57% (composite outcome)					
FIDELIO-DKD	ND	ND	ND	ND	ND
FIGARO-DKD	ND	ND	ND	ND	ND
Total	186	ND 4 (2.2)	197	ND 5 (2.5)	0.60 [0.13; 2.79]; 0.514
Renal insufficiency[b,c]					
FIDELIO-DKD	ND	ND	ND	ND	ND
FIGARO-DKD	ND	ND	ND	ND	ND
Total	186	ND 4 (2.2)	197	ND 2 (1.0)	1.14 [0.18; 7.14]; 0.891
Sustained decrease in eGFR to < 15 ml/min/1.73m²	ND				
ESRD[d]	ND				
Decrease in eGFR by ≥ 57%	ND				
Renal death[e]	ND				
Cardiovascular morbidity (composite outcome) (supplementary information)					
FIDELIO-DKD	*ND*	*ND*	*ND*	*ND*	*ND*
FIGARO-DKD	*ND*	*ND*	*ND*	*ND*	*ND*
Total	*186*	*ND* *18 (9.7)*	*197*	*ND* *26 (13.2)*	*0.67 [0.34; 1.33];* *0.253*

Table 10: Results (mortality, morbidity, time to event) - RCT, direct comparison: finerenone + optimized standard therapy vs. placebo + optimized standard therapy, population with concomitant treatment with SGLT-2 inhibitors at baseline (multipage table)

Outcome category **outcome** **study**	**Finerenone + optimized standard therapy**		**Placebo + optimized standard therapy**		**Finerenone + optimized standard therapy vs. placebo + optimized standard therapy**
	N	**median time to event in months [95% CI]** **patients with event n (%)**	**N**	**median time to event in months [95% CI]** **patients with event n (%)**	**HR [95% CI]; p-value[a]**
Cardiovascular death				*ND*	
Nonfatal myocardial infarction				*ND*	
Nonfatal stroke				*ND*	
Severe heart failure events (operationalized as hospitalization for heart failure)				*ND*	

a. IPD meta-analysis: Cox regression model with factor "study" as fixed effect, stratified by region, eGFR category at the time of screening; UACR at the time of screening and cardiovascular history; as no information on the number of patients with events is available for the individual studies, these are presented for the metaanalysis.

b. The presentation of the individual components does not comprise the qualifying events, but all events that occurred during the course of the study.

c. Renal insufficiency was defined as the occurrence of ESRD or an eGFR < 15 ml/min/1.73m², confirmed by a 2nd measurement ≥ 4 weeks after the 1st measurement.

d. According to Module 4 A, ESRD was defined as:

- Kidney transplant
- Peritoneal dialysis or haemodialysis required for at least 30 days and for which it is not apparent that treatment can be stopped after 90 days.
- Acute kidney injury resulting in dialysis or death and occurring during dialysis treatment.
- Renal replacement therapy indicated for symptomatic uraemia (eGFR of < 15 ml/min/1.73m^2 for at least 30 days) or asymptomatic uraemia (eGFR of < 8 ml/min/1.73m^2) but not available or accessible, refused or considered futile; ESRD is then diagnosed even without initiation of renal replacement therapy.

e. A death was classified as renal death if the patient died and had not received clinically indicated renal replacement therapy and there was no other probable cause of death.

CI: confidence interval; eGFR: estimated glomerular filtration rate; ESRD: end-stage renal disease; HR: hazard ratio; IPD: individual patient data; ND: no data; n: Number of patients with event; N: number of analysed patients; RCT: randomized controlled trial; SGLT-2: sodium-glucose cotransporter 2; UACR: urine albumin-creatinine ratio