15 December 2022
EMA/41550/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Invented name: Kerendia

International non-proprietary name: finerenone

Procedure No. EMEA/H/C/005200/II/0001/G

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ACEI	angiotensin-converting enzyme inhibitor
ANCOVA	analysis of covariance
ARB	angiotensin receptor blocker
AUC	area under the plasma concentration vs time curve from zero to infinity after single (first) dose
AUC(0-96h)	AUC from time 0 to time 96 h after dosing
BID	bis in die (twice daily)
BMI	body mass index
BP	blood pressure
CEC	Clinical Event Committee
CHF	chronic heart failure
CI	confidence interval
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL	clearance
CL_{CR}	creatinine clearance
C_{max}	maximum observed drug concentration in measured matrix after single dose administration
$C_{max,md}$	C_{max} in measured matrix after multiple dose administration during a dosage interval (C_{max} under steady-state conditions)
COVID-19	coronavirus disease 2019
CV	cardiovascular
CYP	cytochrome P450
CYP3A4	cytochrome P450 isoenzyme 3A4
DBP	diastolic blood pressure
DKD	diabetic kidney disease
DM	diabetes mellitus
DN	diabetic nephropathy
DPP-4	dipeptidyl peptidase-4
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
E_{max}	maximum effect

EOS	end of study (visit)
EQ-5D-5L	EuroQol Group 5-dimension, 5-level questionnaire
ER	exposure / response
ESRD	end-stage renal disease
FAS	full analysis set
GLP-1	glucagon-like peptide-1
HbA1c	glycated hemoglobin
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
HR	hazard ratio
IC_{50}	concentration to inhibit 50% of an enzyme activity
IR	immediate release
ITT	intent to treat (principle)
IV	intravenous
K^+	potassium
KDIGO	Kidney Disease: Improving Global Outcomes
KDQOL-36	Kidney Disease Quality of Life-36
K_i	inhibitory constant
LS means	least square means
MI	myocardial infarction
MLG	medical labelling group
MR(A)	mineralocorticoid receptor (antagonist)
Na^+	sodium
NNT	number needed to treat
NT-proBNP	N-terminal prohormone B-type natriuretic peptide
NYHA	New York Heart Association
OATP	organic anion transporting polypeptide
OD	once daily
OE	outcome event
pH	negative log of hydrogen ion concentration
PEG	polyethylene glycol
PK	pharmacokinetic(s)
popPK	population pharmacokinetics

PPS	per protocol set
QT	QT interval
QTcB	QT interval corrected for heart rate according to Bazett
QTcF	QT interval corrected for heart rate according to Fridericia
QTcI	QT interval corrected for heart rate according to the individual method
RAS	renin-angiotensin system
RRR	Relative risk reduction
SAF	safety analysis set
SBP	systolic blood pressure
SD	standard deviation
SGLT2	sodium-glucose cotransporter-2
T2D(M)	Type 2 diabetes (mellitus)
TIA	transient ischemic attack
UACR	urinary albumin-to-creatinine ratio
UAE	urinary albumin excretion
t_{max}	time to reach maximum drug concentration in plasma after single (first) dose
vs	versus
WCHF	worsening chronic heart failure

1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Bayer AG submitted to the European Medicines Agency on 8 March 2022 an application for a group of variations.

The following variations were requested in the group:

Variations requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I
C.I.13	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	Type II	None

Extension of indication to include the treatment of chronic kidney disease (CKD) and for the prevention of cardiovascular (CV) events in adults with CKD (regardless of the stage of albuminuria) associated with type 2 diabetes, based on results from Study 17530 (FIGARO-DKD); a randomized, double-blind, placebo-controlled, parallel-group, multicenter, event-driven Phase III study to investigate the efficacy and safety of finerenone on the reduction of cardiovascular morbidity and mortality in subjects with type 2 diabetes mellitus and the clinical diagnosis of diabetic kidney disease in addition to standard of care. As a consequence, sections 4.1, 4.8, 5.1, 5.2 of the SmPC is being updated and the Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to make editorial changes in the SmPC. The updated RMP version 2.2 has also been submitted.

Update of the SmPC section 5.2 based on the results of Study 21429, a phase 1 drug interaction study of finerenone with rosuvastatin. The CSR PH-42032 was already submitted within the response to Day 180 List of Outstanding Issues of the initial MAA.

Submission of the results of Study 21325, a phase 1 bioequivalence study assessing BE between finerenone 2 x 10 mg tablets and 20 mg tablet in Japanese healthy male adult participants (required by the Japanese PMDA).

The group of variations requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0298/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0298/2021 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH received Scientific advice from the CHMP on 11 March 2015 (EMEA/H/SA/3096/1/2015/III). The Scientific advice pertained to quality, non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Kristina Dunder Co-Rapporteur: Armando Genazzani

Timetable	Actual dates
Submission date	8 March 2022
Start of procedure:	26 March 2022
CHMP Rapporteur Assessment Report	23 May 2022
PRAC Rapporteur Assessment Report	24 May 2022
CHMP Co-Rapporteur Critique	1 June 2022
PRAC members comments	1 June 2022
PRAC Outcome	10 June 2022
CHMP members comments	7 June 2022
Updated CHMP Rapporteur(s) (Joint) Assessment Report	17 June 2022
Request for supplementary information (RSI)	23 June 2022
CHMP Rapporteur Assessment Report	23 August 2022
CHMP members comments	6 September 2022
Updated CHMP Rapporteur Assessment Report	8 September 2022
2nd Request for supplementary information (RSI)	15 September 2022
CHMP Rapporteur Assessment Report	23 November 2022
CHMP members comments	06 December 2022
Updated CHMP Rapporteur Assessment Report	08 December 2022
CHMP Opinion	15 December 2022

2. Scientific discussion

2.1. Introduction

Finerenone (company research code: BAY 94-8862) is a non-steroidal and selective mineralocorticoid receptor antagonist. The steroidal hormones, aldosterone and cortisol, are natural ligands of the MR. Overactivation of the MR contributes to organ damage found in CKD, HF and hypertension, through mediation of pro-inflammatory and pro-fibrotic effects, as well as via sodium retention and endothelial dysfunction.

Finerenone was approved in the European Union, Iceland, Liechtenstein and Norway on February 16, 2022.

In the EU, finerenone is approved for the treatment of chronic kidney disease (stage 3 and 4 with albuminuria) associated with type 2 diabetes in adults.

With the present variation the applicant proposes to include information from the FIGARO-DKD study in the SmPC.

The applicant further proposes to extend the indication to prevention of cardiovascular events and to enable treatment of patients with less severe renal function. In addition, the applicant proposes to include a reference to section 5.1. The submission consists of the following study:

• FIGARO-DKD (Study 17530): "A randomized, double-blind, placebo-controlled, parallel-group, multicenter, event driven Phase III study to investigate the efficacy and safety of finerenone on the reduction of cardiovascular morbidity and mortality in subjects with type 2 diabetes mellitus and the clinical diagnosis of diabetic kidney disease in addition to standard of care"

2.1.1. Problem statement

Disease or condition

The proposed indication was:

Kerendia is indicated for the treatment of chronic kidney disease *(CKD) and for the prevention of cardiovascular (CV) events in adults with CKD* (~~stage 3 and 4~~ with albuminuria) associated with type 2 diabetes~~ in adults~~.
For study results with respect to renal and CV events in the population studied, see section 5.1.

During the procedure the Applicant's updated the proposed indication:

Kerendia is indicated for the treatment of chronic kidney disease (~~stage 3 and 4~~ with albuminuria) associated with type 2 diabetes in adults.
For study results with respect to renal and cardiovascular events, see section 5.1.

Epidemiology

CKD and T2D are each independently major global health concerns. In 2017, approximately 451 million patients worldwide were diagnosed with T2D, and this number is expected to grow to 693 million by 2045[1]. An estimated 20 to 40% of T2D patients develop CKD[2], which is characterized by progressive damage and irreversible loss of function in the kidney eventually leading to kidney failure. T2D is the leading cause of kidney failure in developed countries[3]. Worldwide rates of ESRD are projected to rise in parallel with the substantial increase in T2D prevalence[4]. CKD is also associated with increased risks of CV mortality and morbidity, as well as impaired quality of life[5].

[1] Cho NH, Shaw JE, Karuranga S, Huang Y, da Rocha Fernandes JD, Ohlrogge AW, et al. IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. Diabetes Res Clin Pract. 2018 Apr;138:271-81.
[2] Persson F, Rossing P. Diagnosis of diabetic kidney disease: state of the art and future perspective. Kidney Int Suppl (2011). 2018 Jan;8(1):2-7.
[3] Tuttle KR, Alicic RZ, Duru OK, Jones CR, Daratha KB, Nicholas SB, et al. Clinical Characteristics of and Risk Factors for Chronic Kidney Disease Among Adults and Children: An Analysis of the CURE-CKD Registry. JAMA Netw Open. 2019 Dec 2;2(12):e1918169.
[4] Liyanage T, Ninomiya T, Jha V, Neal B, Patrice HM, Okpechi I, et al. Worldwide access to treatment for end-stage kidney disease: a systematic review. Lancet. 2015 May 16;385(9981):1975-82.
[5] Hill NR, Fatoba ST, Oke JL, Hirst JA, O'Callaghan CA, Lasserson DS, et al. Global Prevalence of Chronic Kidney Disease - A Systematic Review and Meta-Analysis. PLoS One. 2016;11(7):e0158765.

Biologic features

The pathophysiology underlying CKD in T2D is complex and there are multiple factors involved in the progression of CKD and its associated morbidity[6]. Contemporary models of CKD in T2D posit hemodynamic, metabolic, inflammatory and fibrotic factors as interrelated pathophysiological drivers of CKD progression[7].

Clinical presentation

Diagnosis, risk stratification and monitoring of CKD is based on assessments of kidney damage using urinary albumin excretion, and kidney function using estimations of the GFR[8]. Increasing albuminuria and decreasing eGFR are robust independent and additive predictors of increasing risk of CV events, mortality and accelerated progression of kidney disease. Widespread screening and utilization of these simple laboratory measures, in accordance with clinical guideline recommendations, has facilitated earlier recognition of CKD and has formed the basis for clinical staging for risk stratification. Nevertheless, CKD in T2D remains underdiagnosed and the true scale of disease burden is likely underestimated.

Individuals with T2D have an increased risk of premature CV disease, and in those who develop CKD, this risk is further exacerbated[9,10]. There is a 3-fold to 6-fold increase in the risk of CV mortality and CV events, respectively, in T2D patients with CKD compared to those with T2D alone[11].

Although often insidious and asymptomatic, manifesting with vague non-specific symptoms at early stages, more advanced CKD is associated with deteriorating physical function and quality of life[12,13,14]. The onset of ESRD is associated with high individual and socioeconomic burden and necessitates renal replacement therapy with chronic dialysis or kidney transplantation to manage kidney failure. Chronic dialysis is associated with considerable morbidity and mortality[15,16], and although kidney transplantation patients have improved prognosis there is often a prolonged time until transplantation.

Management

Alongside dietary and lifestyle interventions, current proven pharmacological strategies for CKD prevention and treatment in T2D patients include optimization of glycaemic control, blood pressure and

[6] Vallon V, Komers R. Pathophysiology of the diabetic kidney. Compr Physiol. 2011 Jul;1(3):1175-232.
[7] Alicic RZ, Rooney MT, Tuttle KR. Diabetic Kidney Disease: Challenges, Progress, and Possibilities. Clin J Am Soc Nephrol. 2017 Dec 7;12(12):2032-45.
[8] Molitch ME, Adler AI, Flyvbjerg A, Nelson RG, So WY, Wanner C, et al. Diabetic kidney disease: a clinical update from Kidney Disease: Improving Global Outcomes. Kidney Int. 2015 Jan;87(1):20-30.
[9] Hudspeth B. The burden of cardiovascular disease in patients with diabetes. Am J Manag Care. 2018 Aug;24(13 Suppl):S268-S72.
[10] Leon BM, Maddox TM. Diabetes and cardiovascular disease: Epidemiology, biological mechanisms, treatment recommendations and future research. World J Diabetes. 2015 Oct 10;6(13):1246-58.
[11] Afkarian M, Sachs MC, Kestenbaum B, Hirsch IB, Tuttle KR, Himmelfarb J, et al. Kidney disease and increased mortality risk in type 2 diabetes. J Am Soc Nephrol. 2013 Feb;24(2):302-8.
[12] Aggarwal HK, Jain D, Pawar S, Yadav RK. Health-related quality of life in different stages of chronic kidney disease. QJM. 2016 Nov;109(11):711-6.
[13] Mujais SK, Story K, Brouillette J, Takano T, Soroka S, Franek C, et al. Health-related quality of life in CKD Patients: correlates and evolution over time. Clin J Am Soc Nephrol. 2009 Aug;4(8):1293-301.
[14] Pagels AA, Soderkvist BK, Medin C, Hylander B, Heiwe S. Health-related quality of life in different stages of chronic kidney disease and at initiation of dialysis treatment. Health Qual Life Outcomes. 2012 Jun 18;10:71.
[15] Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM. Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. J Am Soc Nephrol. 2004 Aug;15(8):2208-18.
[16] Foley RN, Murray AM, Li S, Herzog CA, McBean AM, Eggers PW, et al. Chronic kidney disease and the risk for cardiovascular disease, renal replacement, and death in the United States Medicare population, 1998 to 1999. J Am Soc Nephrol. 2005 Feb;16(2):489-95.

blood lipid levels. RAS-inhibition using an ACEI or ARB constitute the current standard of care according to KDIGO 2020, ADA 2019 and joint ESC/EASD 2019 guidelines[17,18,19,20,21].

In placebo-controlled studies in patients with early CKD (i.e. high albuminuria at baseline), ACEis were found to significantly reduce the risk of all-cause and CV mortality, and of CV morbidity[22]; however, they were not prospectively investigated in more advanced stages of CKD.

In T2D patients with CKD and very high albuminuria (UACR ≥300 mg/g), losartan reduced the incidence of ESRD and a doubling of serum creatinine compared to placebo, but had no effect on CV mortality and CV morbidity[23]. Irbesartan was also shown to be effective in delaying the progression of kidney disease, but no significant differences in the rates of CV morbidity or mortality were observed compared to placebo[24].

Recent clinical studies with SGLT2 inhibitors showed a benefit on cardiorenal outcomes in patients with or without T2D and CKD, with UACR >300 mg/g or >200 mg/g in the CREDENCE[25] and DAPA-CKD trials[26]. According to recent updates in KDIGO 2020[27], ADA and joint ESC/EASD guidelines from 2019[28,29], the use of SGLT2 inhibitors is recommended for patients with T2D and CKD.

Despite treatment with ACEis or ARBs and the concomitant use of SGLT-2 inhibitors, there remains a high residual risk of cardiorenal outcome events, with more than twice the normal observed age-related decline in kidney function[30].There remains a need for further effective therapies to address the complex multifactorial underlying disease mechanisms including inflammation and fibrosis in CKD in a growing global T2D population..

2.1.2. About the product

Finerenone (company research code: BAY 94-8862) is a novel, non-steroidal and selective mineralocorticoid receptor antagonist. The steroidal hormones, aldosterone and cortisol, are natural

[17] American Diabetes Association. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2019. Diabetes Care. 2019a Jan;42(Suppl 1):S90-S102.
[18] American Diabetes Association. 10. Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes-2019. Diabetes Care. 2019b Jan;42(Suppl 1):S103-S23
[19] American Diabetes Association. 11. Microvascular Complications and Foot Care: Standards of Medical Care in Diabetes-2020. Diabetes Care. 2020 Jan;43(Suppl 1):S135-S51.
[20] Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J. 2020 Jan 7;41(2):255-323.
[21] KDIGO. Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease, published January 2013. 2012.
[22] Investigators of HOPE. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Heart Outcomes Prevention Evaluation Study Investigators. Lancet. 2000 Jan 22;355(9200):253-9.
[23] Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med. 2001 Sep 20;345(12):861-9.
[24] Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. . N Engl J Med 2001;345(12):851-60.
[25] Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. N Engl J Med. 2019 Jun 13;380(24):2295-306.
[26] Heerspink HJL, Stefansson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, et al. Dapagliflozin in Patients with Chronic Kidney Disease. N Engl J Med. 2020 Oct 8;383(15):1436-46.
[27] de Boer IH, Caramori ML, Chan JCN, Heerspink HJL, Hurst C, Khunti K, et al. Executive summary of the 2020 KDIGO Diabetes Management in CKD Guideline: evidence-based advances in monitoring and treatment. Kidney Int. 2020 Oct;98(4):839-48.
[28] American Diabetes A. 6. Glycemic Targets: Standards of Medical Care in Diabetes-2019. Diabetes Care. 2019 Jan;42(Suppl 1):S61-S70.
[29] Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J. 2020 Jan 7;41(2):255-323.
[30] Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. N Engl J Med. 2019 Jun 13;380(24):2295-306.

ligands of the MR. Overactivation of the MR contributes to organ damage found in CKD, HF and hypertension, through mediation of pro-inflammatory and pro-fibrotic effects, as well as via sodium retention and endothelial dysfunction.

Finerenone is supplied as immediate-release tablets with non-functional film coating for oral once daily administration in the dose strengths 10 and 20 mg.

In the EU, finerenone is approved for the treatment of chronic kidney disease (stage 3 and 4 with albuminuria) associated with type 2 diabetes in adults.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

This application of variation is based on efficacy and safety data from the FIGARO-DKD study. Prospective regulatory guidance concerning the clinical development program was obtained from the EMA (EMEA/H/SA/3096/1/2015/III).

Clinically, in order to claim that finerenone results in both (1) a reduction of CV mortality and morbidity and (2) a reduction in the rate of progression of kidney disease, a significant reduction in both the CV and renal events has to be demonstrated in the Phase 3 program. However, because the time to renal events is expected to be significantly longer than the time to CV events in the DKD population, the probability of showing a balanced reduction in renal and CV events when both are part of a composite endpoint, or when early and advanced DKD sub-populations are investigated in a single trial, is considered to be low. Therefore, the Applicant planned to conduct two separate studies:

- FIDELIO-DKD (16244): To demonstrate a beneficial effect on CKD progression in type 2 diabetic patients with advanced stages of CKD *(submitted in support for the initial market authorisation application)*.
- FIGARO-DKD (17530): to demonstrate a beneficial effect on CV events in type 2 diabetic patients with moderate CKD *(submitted with the present application for variation)*

CHMP considered this approach in principle acceptable and the similarity in CV and CKD effects in both studies should support that both studies are complementary for a renal indication. This implies that in both studies the primary endpoints should be positive, but at least the secondary endpoints should show a positive trend. This is considered important in terms of the requirement for two pivotal studies in the EMA guideline recommendations, considering that both a CV and DKD treatment indication are implicitly requested in the proposed indication. In a scenario with only one successful study, the evidence generated may not allow to support positive benefit/risk even if compelling data would be available from one trial, since both studies were seen to complement each other.

The CV primary endpoint in the FIGARO-DKD study was discussed at the advice. The inclusion of hospitalisation for heart failure in the otherwise thrombotic 'MACE' endpoint is not in line with the CV prevention guideline that recommends a composite of all cause death or cardiovascular death and non-fatal MI and non-fatal stroke [EMEA/CHMP/EWP/311890/2007] and there were concerns that the additional component 'unplanned hospitalization for heart failure' is sensitive to differences in local practice. However, finerenone is expected to influence the pathophysiology of heart failure by antagonizing aldosterone, its effects are not purely anti-atherothrombotic. The Applicant presented data indicating also that the weight of hospitalisation for HF is considerable, quoting mortality rates for patients with HFpEF and HFrEF of 22% and 25% at one year (Bhatia et al NEJM 2006). Additionally, as patients with symptomatic HFrEF are excluded as this is a class 1A recommendation for MRA (spironolactone / eplerenone) treatment an HF hospitalisation would be a first manifestation of HF disease. While the Applicant presented data to suggest that HF hospitalisations will significantly contribute

to the primary event rate they are not expected to be the driving force of the composite events, but be in the same order as MI's or CV deaths. CHMP agreed that an endpoint consisting of CV death, non-fatal MI, non-fatal stroke and hospitalisation for heart failure is considered acceptable.

2.1.4. General comments on compliance with GCP

The clinical study was conducted in accordance with the Declaration of Helsinki ethical principles and the ICH GCP guideline.

2.2. Non-clinical aspects

This Type II variation contains data from the second pivotal finerenone Phase 3 study, FIGARO-DKD study 17530, that completed in 2021. No new non-clinical data have been submitted in this application, which is considered acceptable.

2.2.1. Ecotoxicity/environmental risk assessment

The European 'Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use' (EMEA/CHMP/SWP/4447/00, London, June 2006) stipulates the requirement for an ERA for medicinal products licensed in the EU after 2006.

In the EU, the medicinal product Kerendia® with 10 mg and 20 mg finerenone is already authorized for the treatment of chronic kidney disease (CKD) associated with type 2 diabetes. The applicant now requests the modification of indication via this type II variation procedure, i.e., the proposed indication includes the prevention of cardiovascular (CV) events in adults with CKD associated with type 2 diabetes. The CKD population is proposed to be extended to all stages of the disease. The treatment area remains the same (cardiorenal). The recommended dose is 20 mg and remains unchanged compared to the already authorized treatment and ERA as of November 23, 2021. In this ERA in phase II, tier B the risks calculated for environmental compartments were all well below 1 revealing no risk to the environment. These calculations were based on the dose of 20 mg of finerenone and would thus not change due to the new extended indication of finerenone.

Therefore, the current ERA as of November 23, 2021, is up to date and the recent new authorization application does not require a revision of the ERA.

The present Type II variation will extend the CKD indication to all stages of the disease, but the recommended dose remains the same. According to the Applicant, this extension of the indication will not push the RQ above 1 for the environmental compartments. As initially no calculations have been made available, this position was not accepted. The Applicant was asked to provide with detailed justifications to support the position that no new risks to the environment are anticipated due to the extended indication. The Applicant has provided an updated ERA in which the Fpen has been refined based on a European prevalence of CKD with T2D of 17 125 000 patients. The data used for the Fpen refinement is based on a publication by Deng et. al in Frontiers in Endocrinology where CKD-DM burden (incidence, prevalence, deaths, and DALYs) was investigated in four world regions using the Global Health Data Exchange (GHDx) query tool (doi: 10.3389/fendo.2021.672350). The peer-reviewed publication is considered an independent and reliable source why the data is considered adequate for the Fpen refinement exercise.

The refined Fpen (0.0229) was used to calculate the risk quotients for the environmental compartments. All risk quotients are below 1 why no risks to the surface water, sediment, or soil compartments are anticipated. The general statements aimed at minimising discharge of unused medicine into the

environment have already been included in the PIL and SmPC 6.6.

2.2.2. Discussion on non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable. However, a new ERA statement has been provided. According to the Applicant, this extension of the indication will not push the RQ above 1 for the environmental compartments. As no calculations had been made available, this position could not be be agreed. The Applicant was therefore asked to provide with detailed justifications (including RQ calculations) to support the position that no new risks to the environment are anticipated due to the extended indication.

In the response, the Applicant provided an updated ERA in which the Fpen has been refined based on a European prevalence of CKD with T2D of 17 125 000 patients. The data used for the Fpen refinement was based on a publication by Deng et. al in Frontiers in Endocrinology where CKD-DM burden (incidence, prevalence, deaths, and DALYs) was investigated in four world regions using the Global Health Data Exchange (GHDx) query tool (doi: 10.3389/fendo.2021.672350). The peer-reviewed publication was considered an independent and reliable source why the data was considered adequate for the Fpen refinement exercise.

The refined Fpen (0.0229) was used to calculate the risk quotients for the environmental compartments. All risk quotients were below 1 why no risks to the surface water, sediment, or soil compartments are anticipated. The general statements aimed at minimising discharge of unused medicine into the environment have already been included in the PIL and SmPC 6.6.

2.2.3. Conclusion on the non-clinical aspects

There are no non-clinical objections to approve the present type II variation.

2.3. Clinical aspects

2.3.1. Introduction

The application is based on data from the FIGARO-DKD study.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.3.2. Pharmacokinetics

Apart from the FIGARO Phase III study which only included sparse pharmacokinetic (PK) sampling, there are no new dedicated clinical PK studies conducted/submitted by the Applicant for the purpose of the

current Var 2 procedure. The Applicant proposes several SmPC updates in 5.2 section, most of which are representing editorial changes. Overall, all proposed PK updates in the SmPC are evaluated as acceptable.

It is also worth noting that the Applicant is updating SmPC 5.2 section with the new information about finerenone interaction with rosuvastatin (BCRP and OATP substrate). This clinical DDI study with rosuvastatin (denoted as study 21429) was already submitted and assessed within the initial regulatory procedure Kerendia EMEA/H/C/005200/0000 | 5.4.1-2020-95063 | PRAC Co-Rapp + CHMP Rapp | CP | 5.4.1 | Complete | NCE 8(3)/12(3). More details are available within the corresponding previous PK Assessment Reports D150 and D180. Therefore, no re-assessment of the mentioned DDI study was performed for the purpose of the present Var 2 procedure.

Finally, the Applicant has also submitted a new biopharmaceutic study within the module 5 of the present Var 2 application. This was a study 21325: Bioequivalence (BE) study (tablet: 2 × 10 mg vs 20 mg) in Japanese healthy subjects. This BE study appears to be outside of scope of the current Var 2 procedure, and results in no updates of the SmPC text. According to the Applicant, as stated in the Summary of Biopharmaceutics: "*The study was conducted based on regional requests (BE study in Japan)*." Therefore, no regulatory assessment of the mentioned BE study was performed for the purpose of the present Var 2 procedure.

2.3.3. Population PK

a. Objectives

The objectives of the PopPK analysis were to:

- Characterize the PK of finerenone in patients from the Phase 3 Study 17530 (FIGARO-DKD, referred to as FIGARO) and identify relevant covariate effects to support the finerenone submission and labelling.
- Provide posthoc estimates for exposure-response analyses, which are reported separately.

b. Data

The PopPK analysis was based on FIGARO, a Phase 3 study to investigate the efficacy and safety of finerenone in T2D patients with CKD. The primary objective of this study was to demonstrate whether finerenone is superior to placebo in delaying the progression of kidney disease on top of standard of care. A graphical representation of the study design is presented in *Figure 1*.

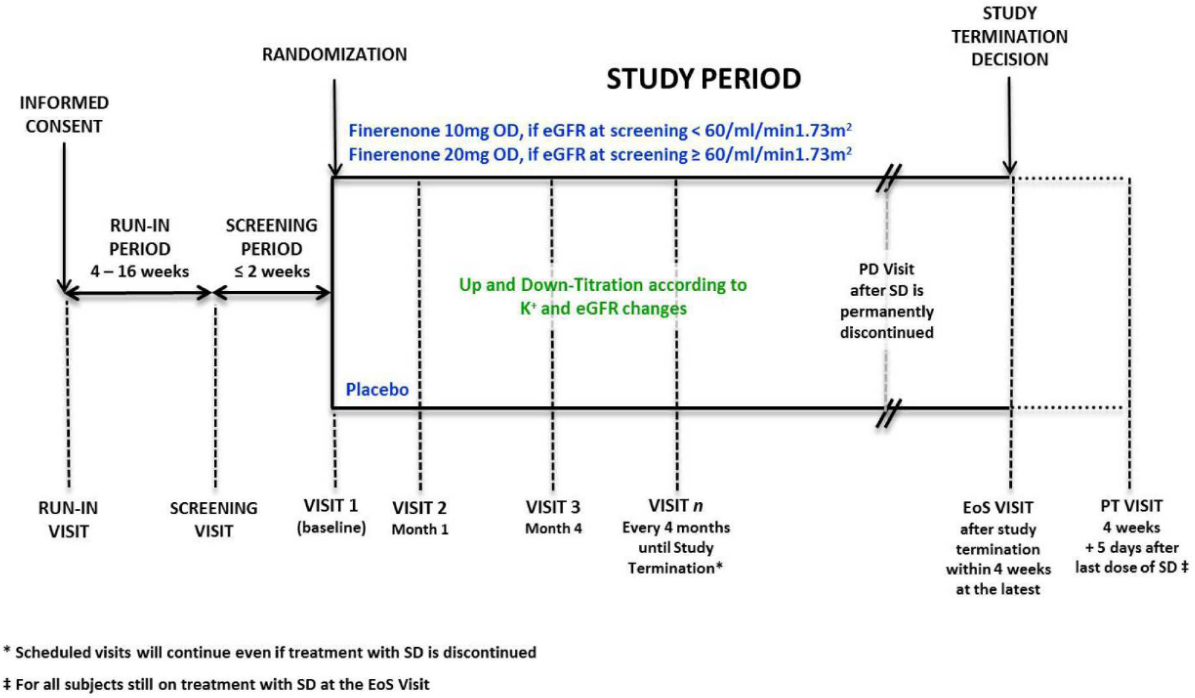


Figure 1 Study design Study 17530 (FIGARO-DKD)

Eligible patients were randomized 1:1 to receive either once daily (OD) oral doses of finerenone (10 mg or 20 mg based on their eGFR value at screening) or placebo in addition to their SoC therapy. Each patient in the Kerendia arm received 10 mg finerenone tablet OD (starting dose for patients with an eGFR between 25 to <60 mL/min/1.73m2 at the Screening Visit or 20 mg finerenone tablet OD (starting dose for patients with an eGFR ≥60 mL/min/1.73m2 at the Screening Visit).

There were two scheduled visits in the first four months after the baseline visit (Visit 1); thereafter visits took place every four months until the end of the study. Study drug could be up-titrated from 10 mg to 20 mg from Visit 2 (Month 1) onwards, provided that potassium from the local laboratory was ≤4.8 mmol/L and eGFR-EPI decrease was ≤30% below the value last measured. Down-titration or interruption of study drug was permitted at any time during the study for safety reasons.

Plasma concentrations of finerenone were determined for PK samples taken at different time points using a sparse sampling approach in all patients. Trough samples were collected at Visit 3 (Month 4). At each of the yearly visits, one blood sample for the determination of finerenone plasma concentrations was drawn during the visit after intake of study drug at home.

The final PK data dataset contained 8142 valid finerenone concentrations from 3102 subjects after flagging flagged to be ignored in the analysis (e.g. outliers, BLQ samples [labelled as MDV=1], etc) as shown in *Table 1*.

Table 1 Overview of number of observations and subjects ignored in the analysis (Final PK dataset)

Step	description	Obs in	IDs in	Obs dropped	IDs dropped
0	Original dataset	11681	3478	0	0
1	Ignore all records which were NOT defined as members of the analysis dataset by the sponsor (PMAS=0).	11109	3253	572	225
2	Ignore outliers with DV/PRED<0.02 (FLDVP=1), DV/PRED>50 (FLDVP=2), DV=2630 mcg/L (FLDVP=3), and TADGT0=386.55h (FLDVP=4)	9691	3214	1418	39
3	Ignore records flagged by sponsor as: Irrelevant for statistical evaluation, exclude from statistics	9508	3214	183	0
4	Ignore records flagged by sponsor as: Kinetically implausible, exclude from statistics	9072	3214	436	0
5	Ignored missing DV (MDV)	8142	3102	930	112
6	Total	8142	3102	3539	376

Dropped records are listed sequentially. This means that for each step the number of dropped records opposed to the previous step is displayed. This does not take into account an overlap in dropped records

Figure 2 shows the observed data with the excluded data points highlighted by different colours.

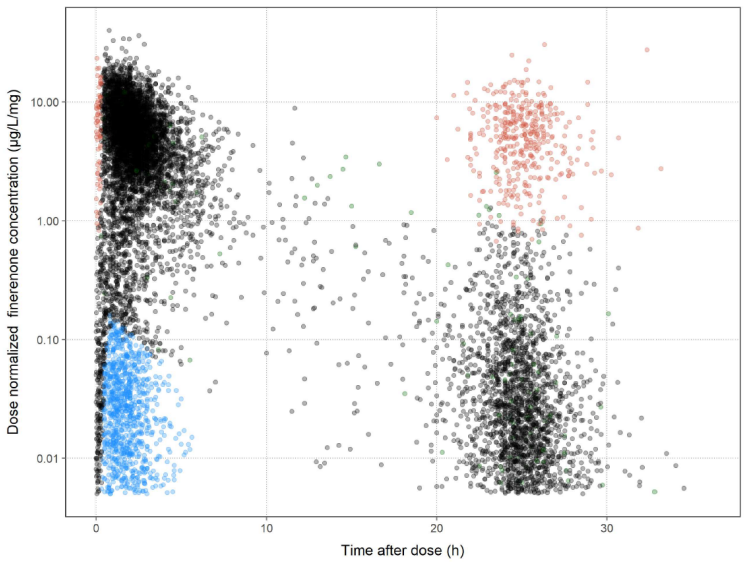


Figure 2 Overview of measured finerenone concentrations in the final PK dataset.

black symbols: non-outliers (0.02<DV/PRED<50); red symbols: outliers identified with DV/PRED>50; blue symbols: outliers identified with DV/PRED<0.02; green symbols: outliers identified by the sponsor after evaluating final batch of data which were not already labeled as outliers based on DV/PRED ratio; x-axis truncated at 36h

The model was mainly developed on an interim PK dataset including a total of 6337 finerenone concentrations from 3026 subjects with a data cut-off on Oct 7 2019. As the final final PK dataset (data cut-off on May 04 2021) became available, limited model development was performed to achieve a final model.

The CHMP concluded that the database appears to be overall reasonable for developing a PopPK model. The study design included a different starting dose depending on the estimated eGFR at baseline. Furthermore, the study included a design element resulting in interruptions, discontinuations, and/or alteration of the dosing regimen, at the individual patient level, guided by measured variables (e.g. potassium). This should not have overall meaningful impact on the development of the PopPK model, however, this should be considered when assessing the subsequent exposure-response models.

Approximately 14.5% of PK observations were identified as outliers. These numbers were higher than those identified in the analysis of Study 16244 (FIDELIO-DKD) (12%) and Phase 1 and Phase 2 studies (3-4%). Outliers identified in Study 17530 (FIGARO-DKD) could not be explained by any of the available covariates and the Applicant assumed they were caused by deviations between recorded and actual dosing and/or sampling times. The most common reason for excluding observations were identified outliers based on a DV:PRED ratio outside of defined margins of 0.02 to 50. An additional reason for exclusion was observations flagged by the sponsor as “kinetically implausible”. These deviations should be better justified, since they could arise doubts regarding the appropriate data recording and collection. However, despite a large number of outliers, the data from Study 17530 (FIGARO-DKD) contained a similar pattern of outliers as observed previously in historical Phase 2a, Phase 2b and Phase 3 analyses. For this reason, the issue was not further pursued. Approximately 10% of the observations were excluded since they were below the lower limit of quantification which is considered acceptable.

c. Methods

A previous model based on data from the Phase 2b studies 16243 (ARTS-DN global) and 16816 (ARTS-DN Japan) from PopPK report R-9603 was used as starting point for the analysis.

First, the existing PK model was applied to the interim data (MAXEVAL=0 run) to evaluate its predictive power on FIGARO data. Subsequently, the model was optimized to the data from FIGARO, while keeping the previously identified covariate effects. Subsequently, the inter-individual variability (IIV) structure was re-evaluated and it was evaluated whether the covariate EGFRMD0 (on CL/F and F) could be replaced by eGFR values calculated according to the CKD Epidemiology Collaboration (EGFREP0 (baseline), EGFREPI (time-varying)) formula. The covariate effect relationships were described using a power function.

Covariates were tested in a step-wise covariate modelling approach (see below). Potential time-dependent changes in PK that could not be explained by time-varying covariates were investigated in a last step.

The final PK dataset become available approximately at this stage where the comedication implementation was updated, re-investigating covariate effects for three comedication categories: CYP3A4-inhibitors (CYPINH), CYP3A4-inducers (CYPIND) and Sodium Glucose Transporter 2 inhibitors (SGLT), via a reduced forward inclusion-backward deletion procedure to result in a final PK model.

The analysis was performed in NONMEM 7.5.0 using the first-order conditional estimation with interaction as estimation method.

PopPK model 20957 (report 13322) was overall well constructed according to the EMA guidelines relevant to population PK modelling & simulation (i.e. step-wise covariate analysis approach, model selection and acceptance criteria, simulation approach, reporting). Handling of missing data, data below LLOQ, outliers was described as well.

The final popPK model was built on the basis of the one already run for ARTs-DN and ARTS-DN Japan phase II studies (report-9603, assessed within Kerendia initial MAA), which was subsequently optimized to fit with data collected through FIGARO phase III study. Model 20957 development strategy was also similar to the one already applied to perform PK analysis for FIDELIO study.

Purely in terms of popPK model building and construction, the approach of the Applicant is considered acceptable.

Covariate model development

The testing of covariates was performed using a step-wise covariate modelling approach. The covariates were divided in two groups, namely: covariates of category 1 which were to be included in the covariate analysis, and covariates of category 2 which were to be included in the statistical evaluation only if graphical exploration shows a potential effect of a covariate on the model parameter of interest (*Table 2*).

Table 2 Overview of covariates of interest for finerenone PK, including variable names and aliases used in the analysis

Covariate[a]	Abbreviation (interim dataset)	Abbreviation (final and interim dataset)	Category[b]	Type [c]
Albumin	ALB0	ALB	2	continuous
Alcohol consumption	ALC	ALC	2	categorical
Alkaline phosphatase	ALP0	ALP	2	continuous
Alanine aminotransferase	ALT0	ALT	2	continuous
Aspartate aminotransferase	AST0	AST	2	continuous
Age	AGE	AGE	1	continuous
Body Height	HGHT0	HGHT	2	continuous
Bilirubin	BILI0	BILI	2	continuous
Body Mass Index	BMI0	BMI	2	continuous
Body Surface Area	BSA0	BSA	2	continuous
Body Weight	WGHT0	BW0	1	continuous
Child-Pugh score	CHILDPSC	CPGH	1	categorical
CKD Stage (renal impairment cat.)	RENALIM0	CKDS	2	categorical
Co-medication of CYP3A4 inducers	CYPINDN	CYPIND	1	categorical
Co-medication of CYP3A4 inhibitors	CYPINHN	CYPINH	1	categorical
eGFR-EPI at baseline	EGFREPI0	EGFREP0	1	continuous
eGFR-EPI time dependent	EGFREPI	EGFREP	1	continuous
eGFR-MDRD at baseline	EGFRMDR0	EGFRMD0	1	continuous
eGFR-MDRD time dependent	EGFRMDRD	EGFRMD	1	continuous
Ethnic group	ETHNICIT	ETHN	1	categorical
Gamma Glutamyl Transpeptidase	GGT0	GGT	2	continuous
Gender	SEX	SEX	1	categorical
Lean Body Mass	LBM0	LBM	1	continuous
Race/ethnicity incl. detailed spec. for Asian race	RACEASIA	RACA	1	categorical
Serum creatinine	CREA0	CREA	2	continuous
Co-medication of Sodium Glucose Transporter Inhibitors	GLYCSICN	SGLT	1	categorical
Smoking status	SMOK	SMOK	2	categorical
Total protein	PROT0	PROT	2	continuous

[a]Covariates at baseline were investigated, unless indicated as time dependent
[b]1 = test, 2 = graphically explored and only tested if indication from visual inspection of EBE plots
[c]Links to the source data and the definition of the categories for categorical covariates were provided in the dataset documentation provided by the Sponsor

The main covariate analysis was performed on the interim PK dataset. The comedication variables were re-evaluated using the final PK dataset.

Correlated covariates have been tested, such as several highly correlated body size descriptors. This could potentially lead to selection bias and correlated covariate effects if two (or more) correlated covariates are included on a single parameter. The Applicant is strongly recommended to make pre-specified decisions to include only one of several correlated covariates.

Model selection and acceptance criteria

Technical and/or statistical criteria were applied during model development and acceptance of a final model where appropriate. These could be customised based on the objectives of the analysis, limitations of the available data, and computational limitations, but in general the following criteria were upheld:

- A convergence criterion of preferably 3 or more significant digits in the parameter estimation.
- The model fit converged successfully to a minimum objective function value with, if feasible, a successful covariance step.

- The standard error of a structural parameter estimate reported by NONMEM was preferably less than 50% of the estimated parameter value. This would imply the 95% confidence interval of the parameter estimate does not include zero, assuming normality.
- The correlation between parameter estimates (structural and stochastic) as reported by NONMEM in the correlation matrix of the model output was preferably between -0.95 and 0.95.
- The values estimated for η and ε, for each random effect, was preferably adequately centred around zero (with a reported p-value in the NONMEM output file of at least 0.05).
- Shrinkage of the random effects as reported by NONMEM was preferably below 30% (η-shrinkage and ε-shrinkage).
- Standard Goodness-of-Fit (GoF) plots, and other diagnostic plots relevant to the project, were inspected visually to evaluate the model fit, including Observations versus individual and typical predictions, Conditional weighted residuals versus time and Conditional weighted residuals versus population predictions

The obtained minimum value of objective functions was used to statistically compare nested models via the likelihood ratio test. In case of adding one parameter to the model (1 degree of freedom), a decrease of 3.84 points was considered statistically significant (which theoretically coincides with a p-value of 0.05). In case of a comparison of models that were structurally different (and thus not nested), the models were compared using the Akaike Information Criterion (AIC).

In addition to inspection of parameter estimates and goodness-of-fit plots, according to the criteria described above, the predictive performance and robustness of the developed PK model was evaluated using prediction-corrected Visual Predictive Checks (pcVPC).

Overall standard model selection and model evaluations were applied which is considered acceptable.

Simulations

Two types of model-based simulations were then performed; 1) simulations to assess the magnitude and uncertainty of the pure covariate effects, and 2) simulations to compare the finerenone exposure at steady-state in subgroups of interest taking combined individual covariate effects into account.

The posthoc estimates of the final PK model and simulated finerenone exposure parameters were used to predicted the area under the curve at steady state ($AUC_{\tau,md}$ or AUCss) and maximum concentration at steady state ($C_{max\tau,md}$ or $C_{max,ss}$) in subsequent exposure-response analyses.

The workflow of the simulations is considered acceptable.

d. Results

Model development

The existing PK model slightly underpredicted data from Study 17530 (FIGARO-DKD). Other than that, the data were already captured fairly well by the Phase 2b model. Subsequently, model parameters were optimized to data from the interim PK dataset. IIV in Ka caused model instability, high standard errors (low precision) and high asymmetric shrinkage for the IIV term (η) on Ka. Therefore, the stochastic model was reduced by excluding the IIV term on Ka. The stochastic model included IIV on CL/F and Vc/F with a correlation (block) between them.

The log-linear covariate effect relationships in the existing PK model were replaced by power functions which did not have a relevant influence on the model fit. In addition to this, covariate EGFRMD0 on CL/F and F was replaced by EGFREP0 (used in E-R analyses) which resulted in only a minor decrease in MVOF.

Baseline eGFR-EPI (EGFREP0) was replaced by time varying eGFR-EPI values (EGFREPI) which resulted in a significant decrease in MVOF (ΔMVOF or dOFV=-49.0). The log-linear covariate effect relationship between WGHT0 and Vc/F was replaced by a power function which led to a minor decrease in MVOF of 2.74 points, referred to as the base model. Reducing the model structure to a one compartment model significantly worsened the model fit resulting in an increase in MVOF of 483 points and was therefore rejected.

Covariates ALP, SMOK, HGHT, ALC, PROT, BMI, BSA, CREA and GGT were all included in the model based covariate evaluation, in addition to the predefined type one covariates (AGE, BW0, CPGH, CYPIND, CYPINH, EGFREPI0, EGFREPI, EGFRMD0, EGFRMD, ETHN, SEX, LBM, RACA and SGLT). The identified covariates were:

- body weight and CYP inhibitor on Vc/F.
- BSA, time-varying eGFR, SGLT, PROT and a reduced CYP inhibitor variable on both CL/F and F
- ALP on CL/F

The development of the base model was based on a previous model as a starting point. The previous model was optimized and adapted to the current dataset. This considered a reasonable approach given the objectives of the analysis.

The covariate analysis identified several covariates where most are considered overall reasonable. However, CYP inhibitor on Vc/F is not considered biologically plausible and is likely a chance finding, identified as a consequence of the observed data sample. Potentially, CYP inhibitor on Vc/F is confounded with an underlying effect on F, although it is highly questionable whether CYP inhibitor is identifiable on CL/F, F and Vc/F. A more reasonable approach would have been to not test CYP inhibitor on Vc/F. However, this is considered acceptable for descriptive purposes and for predicting individual level exposures for subsequent exposure-response analyses, and therefore, this issue is not further pursued. In case this model is used e.g. to predict the effect of CYP inhibition in settings outside of the current study, an updated model may be needed.

Another limitation of the covariate model is the Applicants' approach of including body size. Different body size descriptors are used for CL (BSA) vs Vc and Vp (weight). Preferably, the same body size descriptor should be used both CL and V. Within PopPK, body weight is the most frequently applied body size descriptor and is considered good enough for most situations. Furthermore, a standard approach is to include body size using an allometric scaling approach where all clearance terms (e.g. Cl and Q) are scaled using a single exponent. Despite these limitations, the developed model is considered acceptable for descriptive purposes in the setting of this trial, and to derive individual exposures for performing exposure-response analyses. However, these aspects should be resolved in case the model is used for extrapolation outside the setting of the clinical study which the model is based on (e.g. exposure predictions in paediatric patients or patients with high weight). The Applicant is strongly recommended to make pre-specified decisions to include only one of several correlated covariates in future applications.

Final model

The final PK model described all data from the final PK dataset adequately as shown in pcVPC plots (*Figure 3*) and GoF plots (not shown). All fixed-effect and random-effect parameters of the final PK model could be identified with reasonable precision, since the estimated uncertainty in all parameter estimates,

expressed as RSE was ≤31.3% for all parameters (see *Table 3*). The degree of η-shrinkage for CL/F was acceptable (24.4%) whereas Vc/F had a larger shrinkage of 46.6%. The relationship between preselected covariates listed in *Table 2* and estimated ETA (η) values from the final PK model did not reveal any remaining trends of concern (not shown).

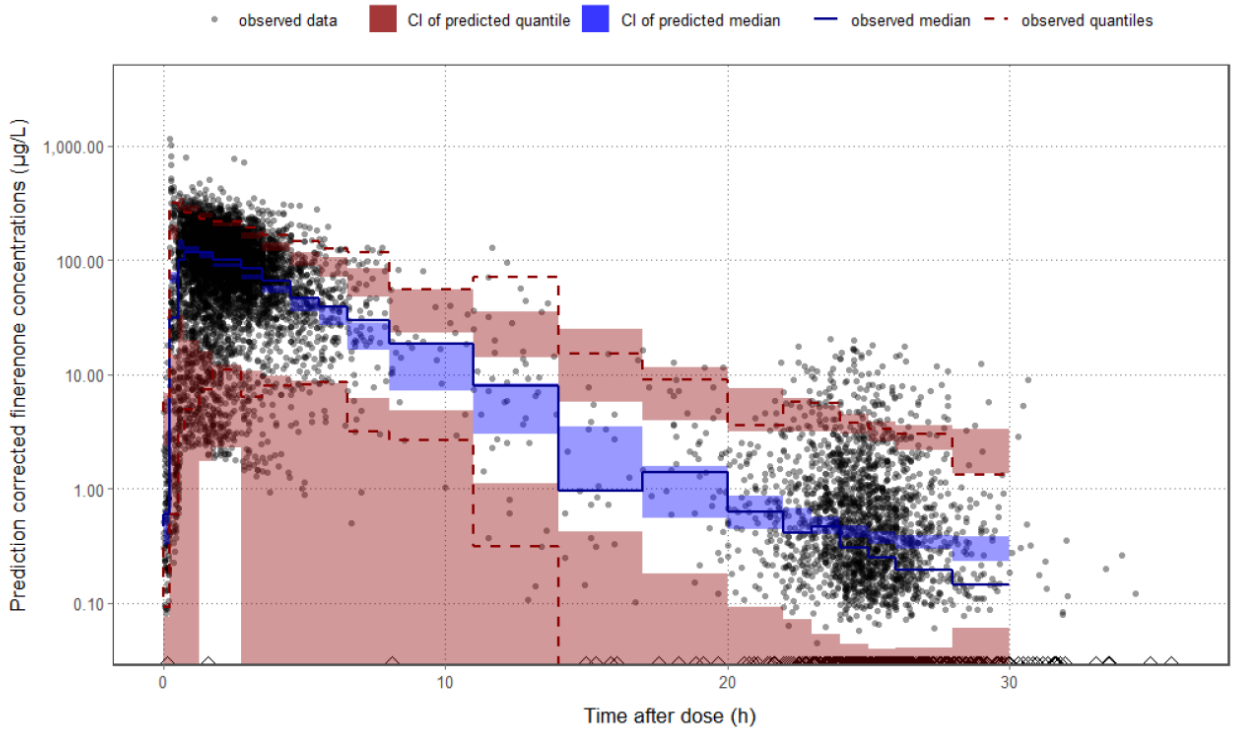


Figure 3 pcVPC plot of the final PK model applied to FIGARO data from the final PK dataset.

black/grey dots: prediction-corrected observations; blue line: observed median; red dashed lines: 2.5th and 97.5th percentiles of observations; red area: 95% variability-based prediction interval of the simulated 2.5th and 97.5th percentiles (excluding parameter uncertainty); blue area: 95% prediction interval of the simulated median; diamond symbols: observations below LLOQ

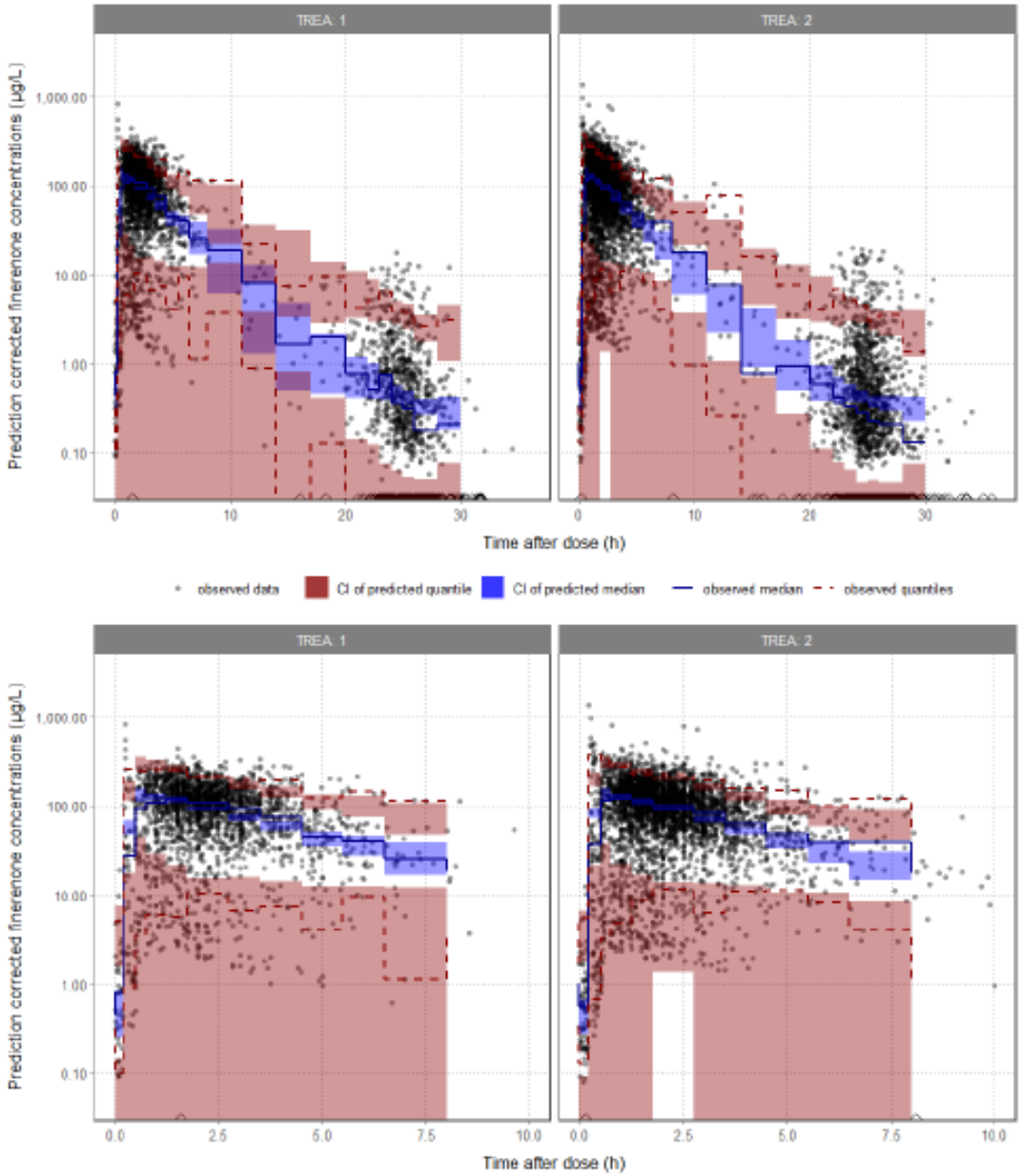


Figure 4 pcVPC plot of the final PK model applied to FIGARO data from the final PK dataset per starting dose.

TREA=1: starting dose 10 mg; TREA=2: starting dose 20 mg. Upper plot: 0-36h after last dose. Bottom plot: 0-10h after last dose. black/grey dots: prediction-corrected observations; blue line: observed median; red dashed lines: 2.5th and 97.5th percentiles of observations; red area: 95% variability-based prediction interval of the simulated 2.5th and 97.5th percentiles (excluding parameter uncertainty); blue area: 95% prediction interval of the simulated median; diamond symbols: observations below LLOQ

Table 3 Parameter estimates and uncertainties of the final PK model (Final PK dataset)

Parameter Name	Estimate	SE	RSE (%)	95% CI
Ka (1/h)	20.1	2.14	10.6	(15.9, 24.3)
CL/F (L/h)	34.9	0.927	2.66	(33.0, 36.7)
Vc/F (L)	135	3.67	2.73	(128, 142)
Q/F (L/h)	0.348	0.0387	11.1	(0.272, 0.424)
Ratio between Vp/F and Vc/F (fixed)	1.00	-	-	-
Absorption lagtime (h) (fixed)	0.215	-	-	-
Relative bioavailability (fixed)	1.00	-	-	-
effect of WGHT0 on Vc/F	0.647	0.0408	6.30	(0.567, 0.727)
effect of EGFREP on CL/F and F	0.118	0.0143	12.1	(0.0902, 0.146)
effect of ALP0 on CL/F	-0.0914	0.0246	26.9	(-0.140, -0.0432)
effect of BSA0 on CL/F and F	0.483	0.0377	7.82	(0.409, 0.557)
effect of PROT0 on CL/F and F	-0.249	0.0777	31.3	(-0.401, -0.0963)
effect of SGLT (chronic SGLT-2 inhibitor use) on CL/F and F	1.06	0.0138	1.31	(1.03, 1.08)
effect of Cyp3A4 inhibitor use (Weak Moderate or Strong Cyp3A4 inhibitors for more than 50% of time (CYPINH 8 6 or 4)) on V/F	0.904	0.0216	2.39	(0.861, 0.946)
effect of Cyp3A4 inhibitor use (Weak Moderate or Strong Cyp3A4 inhibitors for more than 50% of time (CYPINH 8 6 or 4) on CL/F and F	0.938	0.0102	1.09	(0.918, 0.958)
effect of other Cyp3A4 inhibitor use (CYPINH 1 or 2 or 3 or 5 or 7) on CL/F and F	0.980	0.0151	1.54	(0.950, 1.01)
effect of other Cyp3A4 inhibitor use (CYPINH 1 or 2 or 3 or 5 or 7) on V/F	0.970	0.0316	3.26	(0.908, 1.03)
Variability	**Estimate**	**SE**	**RSE (%)**	**%CV**
CL/F	0.0979	0.00635	6.49	32.1
Vc/F and Vp/F	0.0904	0.0147	16.3	30.8
covariance CL/FxV/F	0.0333	0.00736	22.1	0.338
Residual Error	**Estimate**	**SE**	**RSE (%)**	**stDev**
RES ERR residual error	0.313	0.00704	2.25	0.560

RSE (%) is calculated as SE/Estimate*100; 95% CI is calculated as Estimate +/- 1.96*SE; for back-transformed parameters 95% CI is back-transformed values of 95% CI; %CV is calculated as sqrt(exp(OM)-1)*100 in case of exponential variability or sqrt(OM)/TH*100 in case of additive variability, or presents the correlation coefficient (OMx,y / (sqrt(exp(OMx)-1) * sqrt(exp(OMy)-1))) for the covariance between parameters; StDev is calculated as sqrt(SIG), if SIG is defined already as StDev it will be the same as estimate

The Applicant states that all PK data were described adequately by a final model pcVPC. However, not all data are well described. At the later time points (~25-30 h after the most recent dose), the model slightly overpredicts the observed data whereas the drug concentrations during ~1-5 hours after the last dose, there is a trend of underpredicting the observed drug concentrations. One concern raised by the CHMP is that a two-compartment model is not fully supported by the observed dataset. Despite these signs of model misspecification, the model is considered acceptable for descriptive purposes and

for deriving individual exposures for exposure-response analyses. The outlined limitations will be kept in mind when making labelling claims for Kerendia and when predicting drug concentrations beyond ~24 hours after the last dose.

The final model parameters were estimated with overall reasonable precision.

Simulations from the final model

The impact of these covariate effects on finerenone exposure at steady-state is illustrated in *Figure 5*. For continuous covariates, Cmax,md and AUCτ,md at the 5th-95th percentiles of the covariate distribution were within 80-125% of the exposure at the median of the covariate distribution. These 80-125% references were chosen as typical equivalence ranges. For the categorical covariates, the largest effects were found for CYP3A4 inhibitor use for >50% of the at-risk time when compared to no CYP3A4 inhibitor use (17.4% increase in Cmax,md , 13.8% increase in AUCτ,md).

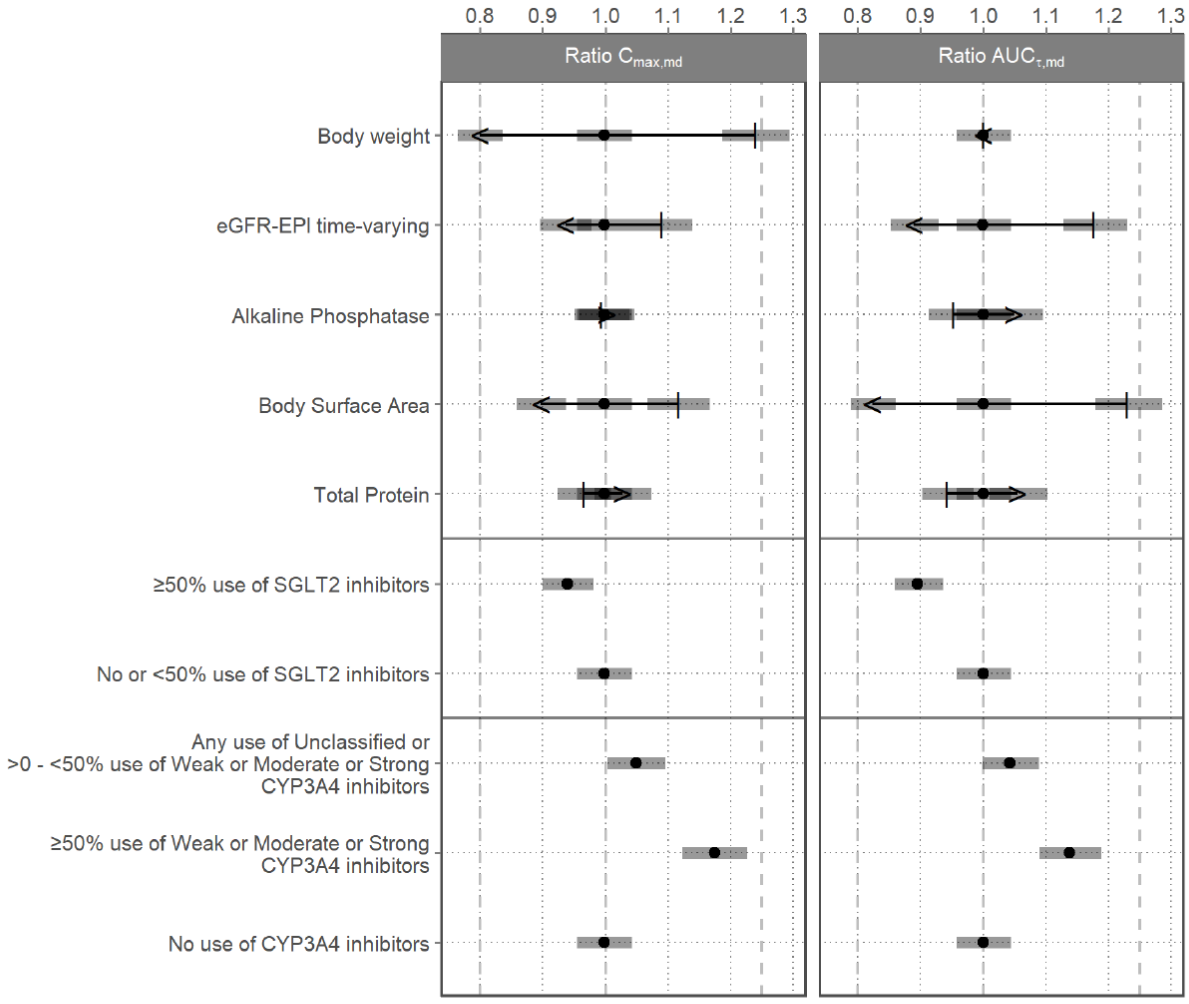


Figure 5 Forest plots illustrating the influence of the identified covariate effects on Cmax,md and AUCτ,md relative to the median covariate value (continuous covariates) or reference subgroup (categorical covariates).

Black dots indicate the reference or the fold change relative to the reference. Whiskers, shaped as an arrow, indicate the PK parameter values at the 5th-95th percentiles of the covariate distribution, where the rear end of the arrow corresponds to the 5th percentile and the tip of the arrow corresponds to the

95th percentile of the covariate distribution. Grey bars indicate the uncertainty (5th-95th percentiles of the simulated 5th percentile, median and 95th percentile based on 10000 simulated PK curves). Vertical dashed lines indicate unity and general acceptance range for equivalence of 80-125%.

Model-based simulations were performed to compare the finerenone exposure at steady-state in subgroups of interest. Of particular interest were potential differences in exposure between races and ethnic backgrounds. These are graphically represented in Figure xxx. Although no RACE-based covariate effects were identified, differences between (sub)groups may arise from other covariates such as body weight, body height or eGFR-EPI. The ratio of the median exposure ($C_{max,md}$ and $AUC_{\tau,md}$) for a specific racial or ethnic group, and the reference (subject with median exposure) is generally contained within the 80-125% range for both the posthoc based exposure as well as the exposure based on 1000 trial simulations. The one exception to this is the "Other Asians" subgroup, for which both median $C_{max,md}$ and median $AUC_{\tau,md}$ are just outside the 125% boundary. However, both values are within the 5-95% variability range of the population. It should be noted that this is a relatively small subgroup representing only 2.2% of the total number of subjects included in the analysis. Other subgroups were explored in the same way and did not identify any differences of particular concern (not shown).

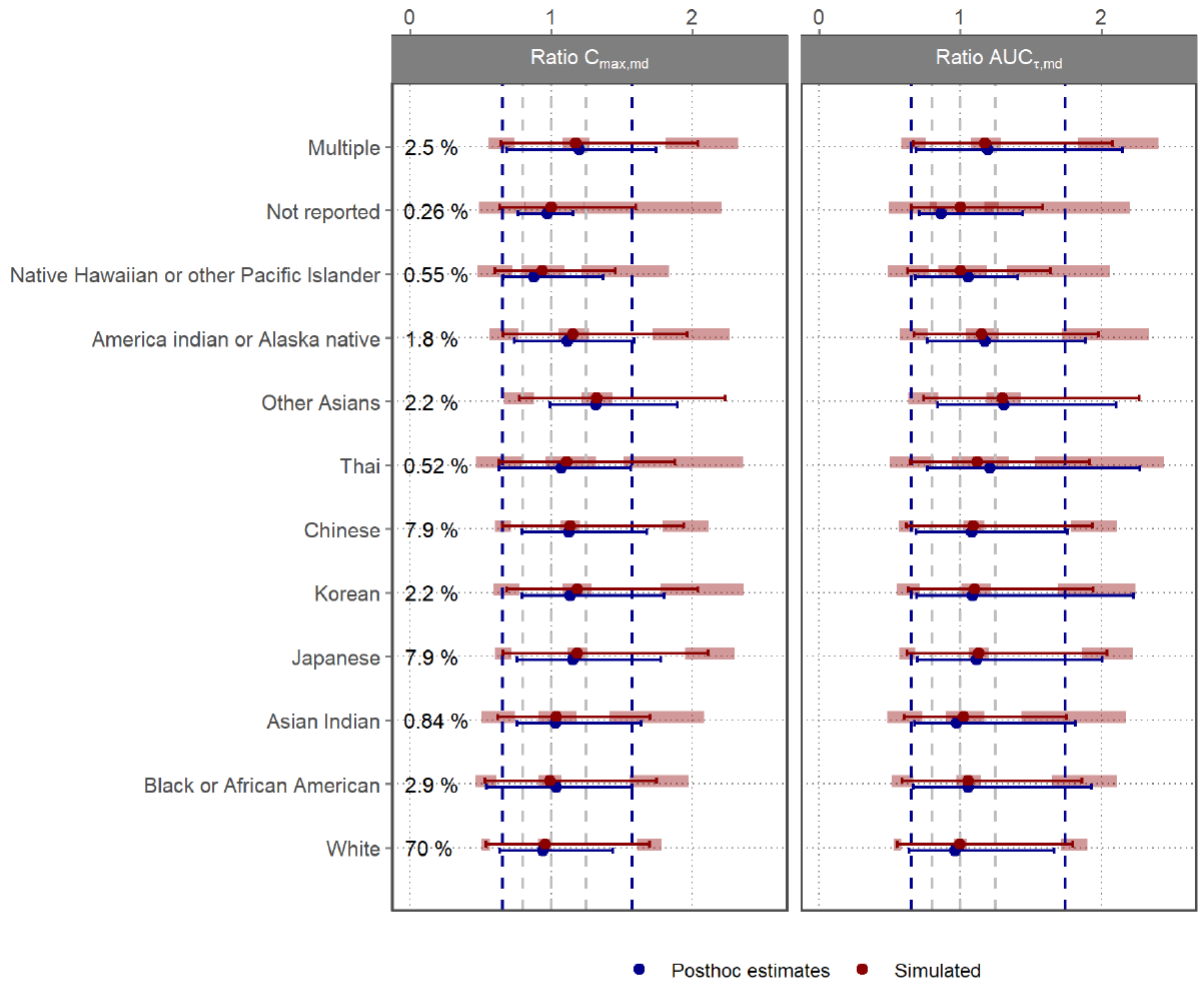


Figure 7.7:6: Comparison of $C_{max,md}$ and $AUC_{\tau,md}$ between racial and ethnic groups

The % indicates the percentage of subjects in each group. Red dots and whiskers represent the median and 5^{th}-95^{th} percentiles of the $C_{max,md}$ or $AUC_{\tau,md}$ ratio using a subject with median $C_{max,md}$ or $AUC_{\tau,md}$ as reference, based on 1000 trial simulations. The red areas indicate the uncertainty (5^{th}-95^{th} percentiles of the simulated 5^{th} percentile, median and 95^{th} percentile). Blue dots and whiskers represent the median and 5^{th}-95^{th} percentiles of the $C_{max,md}$ or $AUC_{\tau,md}$ ratio using a subject with median $C_{max,md}$ or $AUC_{\tau,md}$ as reference, based on the *posthoc* estimates. Grey dashed lines indicate 0.8, 1, and 1.25 boundaries while blue dashed lines indicate 5^{th} and 95^{th} percentiles of $C_{max,md}$ or $AUC_{\tau,md}$ values.

Figure 6 Comparison of Cmax,md and AUCτ,md between racial and ethnic groups

The % indicates the percentage of subjects in each group. Red dots and whiskers represent the median and 5th-95th percentiles of the Cmax,md or AUCτ,md ratio using a subject with median Cmax,md or AUCτ,md as reference, based on 1000 trial simulations. The red areas indicate the uncertainty (5th-95th percentiles of the simulated 5th percentile, median and 95th percentile). Blue dots and whiskers represent the median and 5th-95th percentiles of the Cmax,md or AUCτ,md ratio using a subject with median Cmax,md or AUCτ,md as reference, based on the posthoc estimates. Grey dashed lines indicate 0.8, 1, and 1.25 boundaries while blue dashed lines indicate 5th and 95th percentiles of Cmax,md or AUCτ,md values.

The distribution of the individually predicted AUCss and Cmax,ss which was used are shown in Figure xxx.

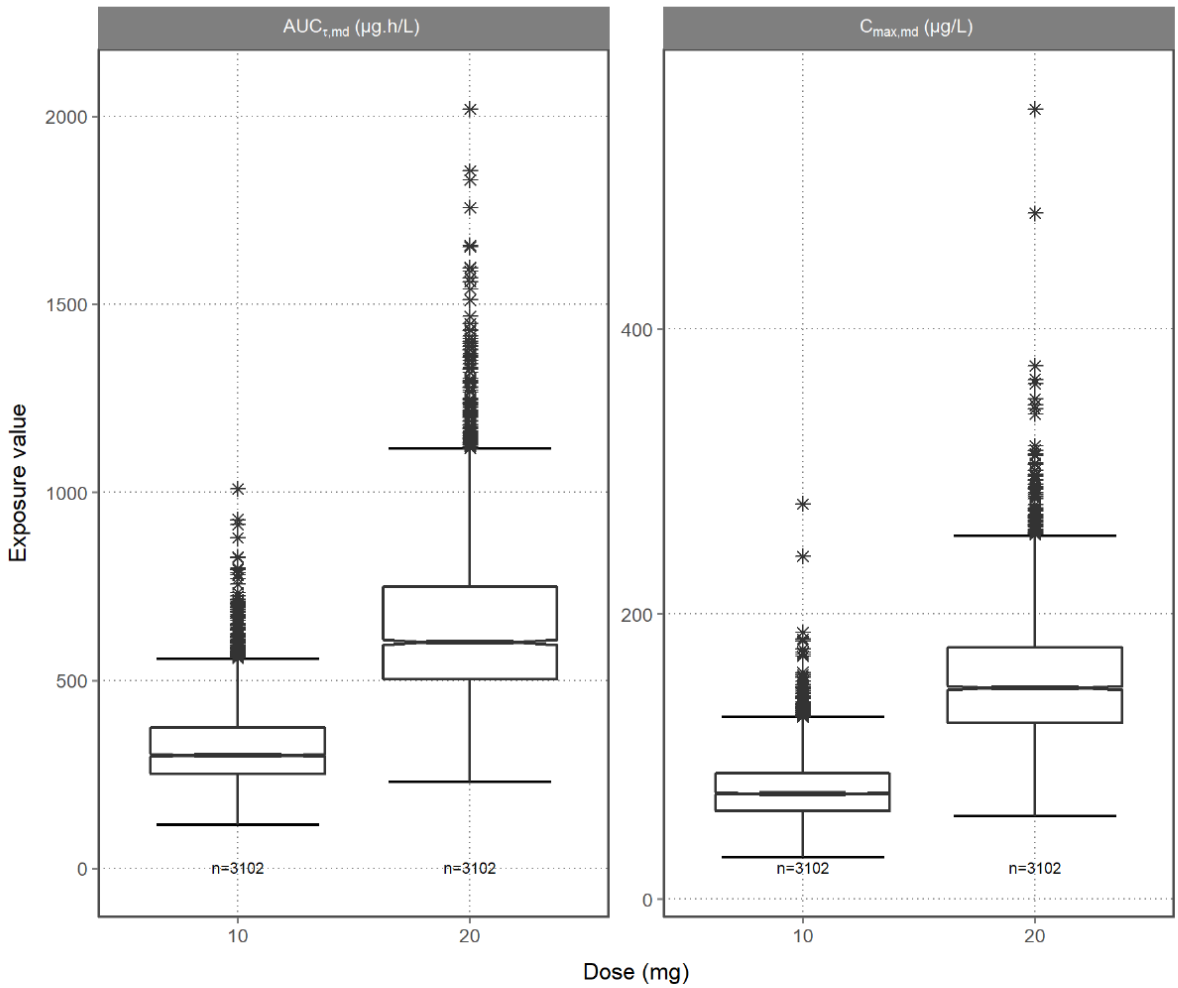


Figure 7 Box plots of finerenone exposure at steady-state based on the final PK model

Whiskers (Black bars): Range between the lowest observation still within 1.5 x the interquartile range (IQR) of the lower quartile and the highest observation still within 1.5 x interquartile range (IQR) of the upper quartile. Box: Range between lower and upper quartile. Box width reflects number of observations. Notches: 95% confidence interval of the median. Black horizontal line: Median. Grey dots: Outliers (individual values outside of whiskers).

The Applicant has performed various simulations using the final model. The difference in AUC and Cmax at extreme values of the included covariates (5^{th} and 95^{th} percentiles) were presented as forest plots in *Figure 5*. In general, no differences were seen which would require an update of the dosing recommendations in the SmPC. Race was considered a subgroup of interest by the Applicant and the difference in AUC and Cmax for the available race categories were predicted. Overall, the exposures appear overall comparable between the race categories. As FIGARO includes more CKD stages compared to FIDELIO (considerably more patients with CKD stages I and II), the potential difference in exposure between CKD stages are considered important. An increase of trough concentrations of ~60-70% were seen between moderate and severe groups compared to normal and mild groups which is considered reasonable given the study design and patient population.

The individually predicted exposures which was used for the exposure-response analysis appears to be reasonable.

e. MAH conclusion

The final PK model adequately captures the PK of finerenone in FIGARO. The PK of finerenone is linear over the studied dose and time range, as was previously observed in Phase 1, Phase 2a, Phase 2b, and Phase 3 (FIDELIO-DKD) studies. Apart from the influence of EGFREPI on CL/F and F, the PK of finerenone in FIGARO was not found to be time-dependent.

For continuous covariates, Cmaxmd and $AUC_{\tau,md}$ at the 5th-95th percentiles of the covariate distribution were within 80-125% of the exposure at the median of the covariate distribution. For the categorical covariates, the largest effects were found for CYP3A4 inhibitor use.

Based on simulations, taking the individual values of all covariates into account, median exposure for all subgroups of interest was generally contained within the 80-125% range, when normalized to a subject with median exposure in the FIGARO population.

The final PK model for finerenone allows estimation of the individual $C_{max,md}$ and $AUC_{\tau,md}$ and can be used for subsequent exposure-response analyses.

The CHMP concluded that overall the final popPK model appears to be well constructed and suitable for a description of PK main parameters of finerenone in the context of FIGARO study, albeit some limitations found also in terms of exclusion of about 14.5% of PK observations, identified as outliers. However, such trend is in line with the previous model run for FIDELIO 16244 study (12% outliers). Also, the pcVPC for the final model shows a slight under-prediction in terms of 97,5th percentile observations around 10 hours after administration (this is more evident in patients assuming a 20 mg finerenone starting dose) and an over-prediction trend for median values after about 25 hours from last dose. As these limitations are not considered crucial for the benefit/risk assessments of the current submission, these issues are not pursued further.

In conclusion, the presented model describes the observed data sufficiently well and the analysis appears overall adequate for descriptive purposes and for predicting individual exposures for subsequent exposure-response analyses. In case the current PopPK model is used e.g. for extrapolation (simulations) in future Type II variations outside of the setting of the FIGARO-DKD study, such as paediatric patients or patients with higher-than-studied body weight, these issues will most likely have to be addressed.

2.3.4. PK/PD modelling

Several different exposure-response analyses were performed as described below.

2.3.4.1. TTE analysis

The objectives of this analysis were to characterize the relationship between finerenone exposure and the time to reach CV composite and renal composite endpoints, in combination with selected prognostic factors (PFs) in FIGARO. The following endpoints were investigated:

- CV composite endpoint, which is the first occurrence of:
    - CV death
    - Non-fatal myocardial infarction
    - Non-fatal stroke

- Hospitalization for HF

- Renal composite endpoint, which is the first occurrence of:
  - Kidney failure (end-stage renal disease or eGFR<15 mL/min/1.73m2)
  - A sustained decrease of eGFR≥40% from baseline over at least 4 weeks
  - Renal death

The objectives are considered relevant. However, it should be noted that this exposure-response analysis is not considered pivotal for the overall benefit-risk assessment in the current application. Consequently, this exposure-response analysis is seen as supportive and therefore, the analysis was not subject to a detailed assessment.

a. Data

The analysis was based on interim (containing approximately 2/3 of the events) and final datasets, respectively. The model developments were mainly performed on the interim dataset and the models were then confirmed and finalized on the final dataset. The interim dataset and final TTE dataset used for the analyses contained all subjects in the full analysis set (FAS, 7354 subjects in the interim dataset and 7352 subjects in the final dataset with two additional subjects prospectively excluded due to critical GCP violations). An overview of the event data used for the interim and final analyses is given in *Table 4*. Only the first occurrence of an event was taken into consideration. The dataset was adjusted to allow the use of interval-censoring in the analysis. As the day of a CV event was captured in the dataset, but the time was not, the interval was set to 24 hours (the day of the event). Renal events were visit related (i.e. mainly based on eGFR measurements). As, in theory, the renal event could have happened between visits, the interval was set to the last central lab eGFR measurement before the event until the event. As eGFR measurements at unscheduled visits were not included in the dataset, these were not taken into account for the interval. The observed KM curves for the renal endpoint stratified on UACR at baseline are shown in *Figure 8*.

Table 4 Overview of event data

	Interim Analysis		Final Analysis	
Event type	Placebo	Active	Placebo	Active
	N,events/N,subjects (% of subjects)	N,events/N,subjects (% of subjects)	N,events/N,subjects (% of subjects)	N,events/N,subjects (% of subjects)
CV composite	346/3666 (9.4%)	301/3688 (8.2%)	519/3666 (14.2%)	458/3686 (12.4%)
Renal composite	189/3666 (5.2%)	181/3688 (4.9%)	395/3666 (10.8%)	350/3686 (9.5%)

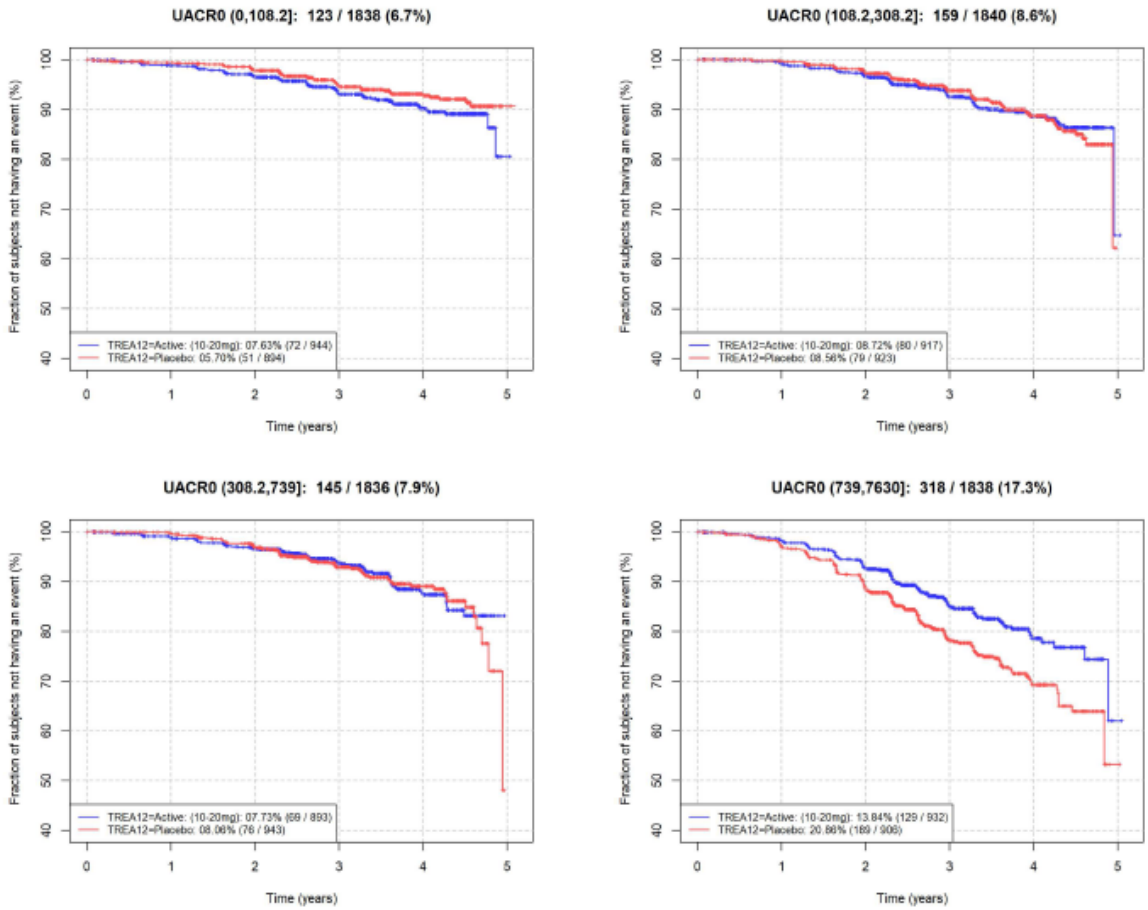


Figure 8 Observed KM curves for the renal composite endpoint by treatment group and UACR at baseline quartiles (final TTE dataset)
Upper left plot: UACR at baseline quartile 1 (0, 108.2]. Upper right plot: UACR at baseline quartile 2 (108.2-308.2]. Lower left plot: UACR at baseline quartile 3 (308.2-739]. Lower right plot: UACR at baseline quartile 4 (739-7630]. Solid lines indicate the observed KM curve, number above the figures and in the legends represent N,events/N,subjects.

There were up to 4 planned visits (including randomization at Visit 1) in the first 4 months; thereafter visits took place every 4 months until the end of the study. Subjects could be seen at any time throughout the study, in addition to scheduled visits, at the discretion of the investigator.

The CHMP concluded that the observed data appears to be overall reasonable. Interval-censoring based on scheduled visits was applied for the composite renal endpoint, as the events were mainly based on eGFR measurements. Renal death is part of the composite endpoint which is an event expected to occur irrespective of scheduled visits. Therefore, the choice of applying an interval-censoring approach based on scheduled visits for the renal composite endpoint is not endorsed. However, since the events were reported to mainly be based on scheduled eGFR measurements, the overall impact of this issue is not considered to be major and this issue is not further pursued.

b. Methods

The model development procedure described below was applicable for the development of models for both endpoints (CV TTE model and renal TTE models). The analysis was conducted in NONMEM 7.5.0. First, a placebo model was developed using only data from patients in the placebo arm. Significant

prognostic factors (PFs) (at baseline, except for time-varying eGFR-EPI for the CV TTE model) at the 0.05 level, based on non-parametric Cox Proportional Hazard (CPH) analysis. This resulted in the full PF model.

Continuous PFs were included as exponential functions on the hazard. The explored covariates are shown in *Table 5*.

Table 5 Overview of candidate prognostic factors, including variable names and aliases used in the analysis

Prognostic Factor[a]	Variable name	Type [b]
Alcohol consumption	ALC	categorical
Age	AGE	continuous
Age Group	AGEGRP	categorical
Body Weight	WGHT0	continuous
Body Mass Index	BMI0	continuous
Likely Child-Pugh score at screening	CHILDPSC	categorical
CKD Stage / Renal impairment categories	RENALIM0	categorical
Co-medication of CYP3A4 inducers	CYPINDN	categorical
Co-medication of CYP3A4 inhibitors	CYPINHN	categorical
Cardiovascular disease history[c]	CVDHIST	categorical
eGFR-EPI at baseline	EGFREPI0	continuous
eGFR-EPI time dependent[c]	EGFREPI	continuous
Ethnic group	ETHNICIT	categorical
Gender	SEX	categorical
GLP-1 Agonist chronic co-medication	INJCGLCN	categorical
HbA1c	HBA1C0	continuous
K+	K0	continuous
Race/ethnicity including detailed spec. for Asian race	RACEASIA	categorical
SGLTi chronic co-medication	GLYCSICN	categorical
Smoking status	SMOK	categorical
UACR	UACR0	continuous

[a]PFs at baseline were investigated, unless indicated otherwise
[b]Links to the source data and the definition of the categories for categorical covariates were provided in the dataset documentation provided by the Sponsor
[c]CV composite endpoint only

The optimal parametric hazard model was then selected based on the Akaike Information Criterion (AIC). Tested distributions included exponential, Gompertz, Weibull, log-logistic and log-normal. Subsequently, non-significant PFs were removed via a backward deletion (BWD) procedure using a significance level of 0.01. This resulted in the interim placebo model.

Finerenone-treated patients were then included and the exposure-response relationship was implemented on the baseline hazard using the following Emax function:

$$h(t) = h(t)_{reference} \cdot PF \cdot (1 + \frac{Emax \cdot C^{\gamma}(t)}{EC50^{\gamma} + C^{\gamma}(t)})$$

Model-predicted exposure as the continuous individually predicted drug concentration was obtained from the interim and final finerenone population PK (PopPK) models. Emax and/or γ (Hill coefficient) were fixed to 1 or estimated, if supported by the data.

The CHMP concluded that the overall model development workflow is considered acceptable. Of note, both body weight and BMI were tested and as outlined for the PopPK analysis (see above) these variables are most likely highly correlated and testing of such correlated variables should preferably be avoided.

However, either variable was selected in the current analysis and therefore this issue is not further pursued.

CV ER model

For the CV endpoint, an exponential or power model were investigated as well for exposure-response. Subsequently, any removed PFs (during the PF backward deletion step) were re-evaluated in the model and the hazard shape was challenged.

The development of the CV ER model appears to be overall adequate.

Renal ER model

A single Emax model, with or without Hill coefficient, could not adequately capture the observed trend in the data. Therefore, an alternative approach was taken, which was based on a population pharmacokinetic-pharmacodynamic analysis of the effect of finerenone on UACR and eGFR-EPI in FIDELIO. In that analysis, the effect of finerenone on eGFR was described by a combined 'acute' eGFR-decreasing effect and a 'chronic' beneficial effect of finerenone on eGFR decline. To reflect this combined effect in the TTE analysis of the renal endpoint, a double Emax model was applied which consisted of a hazard increasing effect multiplied with a delayed hazard decreasing effect. The possible effects of UACR and eGFR-EPI at baseline were tested on the EC50.

The development of the renal ER model appears to be overall adequate.

Model selection and evaluation

The following criteria were applied during model development and acceptance of a final model:

- A convergence criterion of 2 significant digits
- The model should converge successfully to a minimum OFV with a successful covariance step
- The RSE of a structural parameter should preferably be <50%
- The correlation between parameter estimates in the correlation matric of the model output, should lie between -0.95 and 0.95

Renal and CV TTE models were evaluated by means of visual predictive checks (VPC) with 1000 replicates using observed dose titration, dropout and treatment discontinuation.

The model selections and evaluations appear to be overall acceptable.

c. Results

CV composite endpoint

The base hazard model was described by an exponential model. The exposure-response relationship was described by an Emax model. Age, UACR, body weight, time-varying eGFR-EPI, HbA1c, likely Child-Pugh Score, history of CV disease, CYP3A4 inhibitor use, SGLT-2 inhibitor use and GLP-1 agonist use were identified as significant covariates on the base hazard. The parameter estimates of the final model are shown in *Table 6*. A VPC stratified on exposure quantiles are shown in *Figure 9*.

Table 6 Parameter estimates and uncertainties of the final CV TTE model (final TTE dataset)

Parameter Name	Estimate	SE	RSE (%)	95% CI
Lambda (log scale, Exponential hazard)	-12.7	0.0903	0.708	(-12.9, -12.6)
E_{max}	-1 FIX	-	-	-
EC_{50} (μg/L)	9.69	2.09	21.6	(5.59, 13.8)
HILL	1 FIX	-	-	-
PFs on baseline hazard				
Age	0.0267	0.00409	15.4	(0.0186, 0.0347)
eGFR-EPI time-varying (log-transformed)	-0.556	0.0891	16.0	(-0.730, -0.381)
HbA1c	0.139	0.0247	17.7	(0.0910, 0.188)
UACR (log-transformed)	0.215	0.0302	14.1	(0.156, 0.274)
Body weight	0.00933	0.00173	18.6	(0.00594, 0.0127)
Likely / certain Child-Pugh B	1.05	0.322	30.6	(0.420, 1.68)
CV disease history present	1.11	0.145	13.1	(0.825, 1.39)
Weak CYP3A4 inhibitor use >0-<50% of at-risk period	1.34	0.296	22.1	(0.761, 1.92)
Weak CYP3A4 inhibitor use ≥50% of at-risk period	0.333	0.117	35.2	(0.103, 0.562)
Any Strong, Moderate or Unclassified CYP3A4-inhibitor use during at-risk period	0.506	0.187	36.9	(0.140, 0.872)
SGLT-2 inhibitor use > 0% of at-risk period	-0.249	0.0686	27.6	(-0.383, -0.114)
GLP-1 agonist use > 0% of at-risk period	-0.277	0.0756	27.3	(-0.425, -0.129)

RSE (%) is calculated as SE/Estimate×100; 95% CI is calculated as Estimate ± 1.96×SE

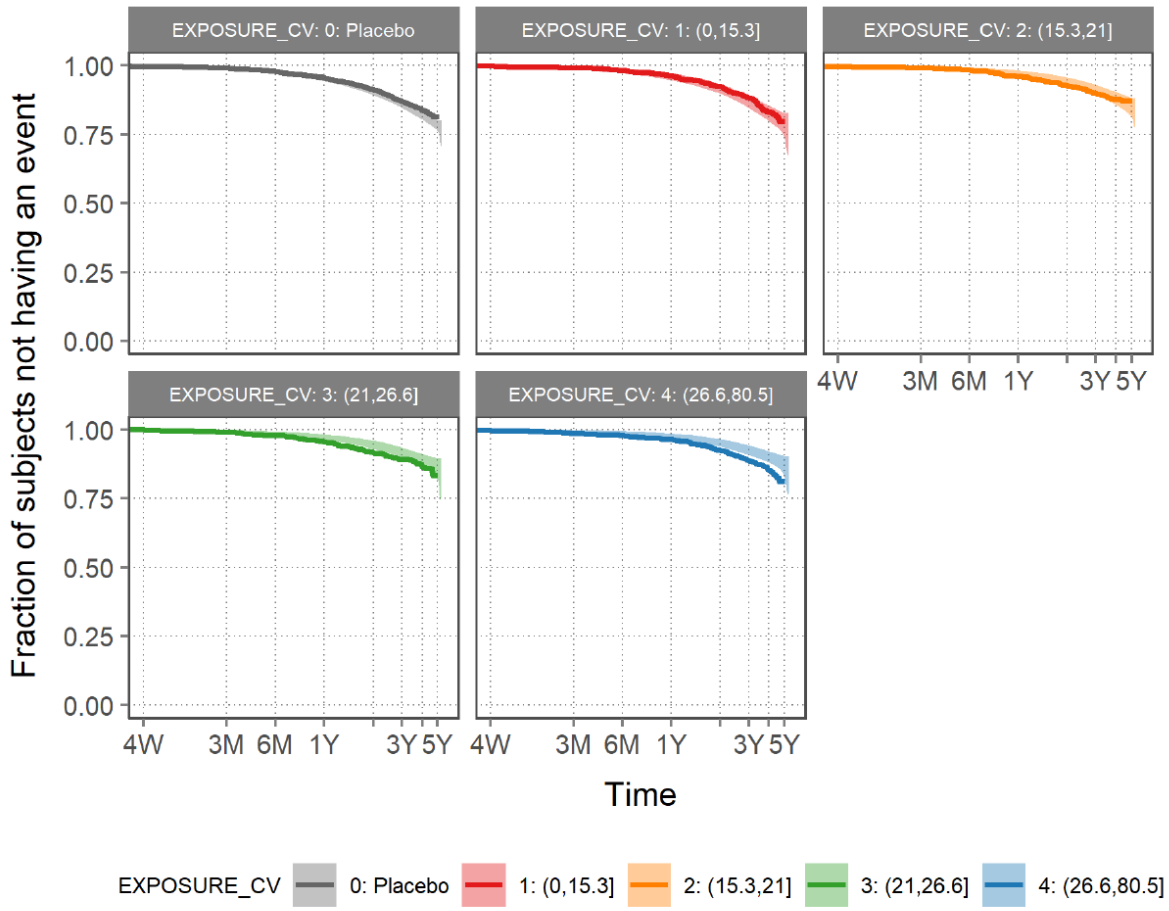


Figure 9 VPC of the final CV TTE model applied to FIGARO data from the final TTE dataset, stratified by exposure quartiles.

Next to the fit of the placebo data (grey), the finerenone treated subjects were divided in four exposure quartiles based on average concentration until (censored) event. The numbers indicate the ranges in µg/L. Thick lines indicate the observed KM curves and the ribbons indicate the 95% interval of the model predictions. In this plot, subjects who had a (censored) event prior to their first finerenone dose, and thus had no exposure to finerenone, were assigned to the placebo group.

The CHMP concluded that the final CV endpoint model is overall reasonable. The parameter estimates and associated parameter uncertainties of the final model are considered acceptable. Of note, CYP3A4 inhibitor use was implemented using 3 different parameters ("weak 0-50", "weak >50" and "any strong, moderate or unclassified"). CYP3A4 inhibitor use is already accounted for in the PK model used to predict drug concentrations and therefore, CYP3A4 was likely found to be significant due to association with the disease status of the subjects. This was discussed by the Applicant in the PopPK report and is not further pursued.

The observed KM curves of the subjects in the placebo group and with exposures in the lowest exposure quartile were close to the upper end of the 95% interval of the model prediction, whereas the observed KM curves of subjects with exposures in the two highest exposure quartiles, were beyond one year after randomization, close to the lower end of the 95% interval of the model prediction, which indicates that the treatment effect was overestimated.

The Assessor acknowledges that it is challenging to identify the true, underlying exposure-response relationship given the study design. The study design is not considered adequate to accurately predict exposure-response relationship given adaptive elements in the protocol, e.g. where subjects received a different starting dose depending on the baseline characteristics (eGFR) and dose titrations and/or interruptions were possible during the course of the study. However, considering that the model was not used to extrapolate efficacy data or to give dosing recommendations, the issue is not further pursed.

Renal endpoint

The base hazard model was described by an exponential model. A double Emax model was implemented in which a hazard increasing effect (ER1) was multiplied with a delayed hazard decreasing effect (ER2). The Emax of ER2 (Emax2) was parametrized as 1/Emax of ER1 (Emax1) as they could not be independently estimated with good precision. UACR, eGFR-EPI at baseline, race/ethnicity, likely Child-Pugh score, CYP3A4 inhibitor use and SGLT-2 inhibitor use were significant covariates on the base hazard. UACR was a significant covariate on EC50 for the delay hazard decreasing effect. The parameter estimates of the final model are shown in *Table 7*. A VPC stratified on exposure quantiles are shown in *Figure 10*.

Table 7 Parameter estimates and uncertanties of the final renal TTE model (final TTE dataset)

Parameter Name	Estimate	SE	RSE (%)	95% CI
Lambda (log scale, Weibull hazard)	-19.3	0.566	2.93	(-20.4, -18.2)
Alpha (Weibull hazard)	1.67	0.0575	3.43	(1.56, 1.79)
Log of Keff[a]	-2.76	0.202	7.33	(-3.16, -2.36)
E_{max_1}	1.04	0.0996	9.59	(0.844, 1.23)
EC_{50_1}	3.09	0.640	20.7	(1.83, 4.34)
$HILL_1$	1 FIX	-	-	-
E_{max_2}	-1 FIX	-	-	-
EC_{50_2} (set equal to EC_{50_1} for a subject with UACR of 308 mg/g)	-	-	-	-
$HILL_2$	1 FIX	-	-	-
UACR effect on EC_{50_2} (log-transformed)	-1.94	0.398	20.4	(-2.72, -1.17)
PFs on baseline hazard				
eGFR-EPI at baseline (log-transformed)	-0.785	0.125	15.9	(-1.03, -0.540)
UACR (log-transformed)	0.628	0.0426	6.78	(0.545, 0.712)
Likely / certain Child-Pugh B	1.74	0.413	23.7	(0.930, 2.55)
Weak CYP3A4 inhibitor use >0-<50% of at-risk period	1.08	0.298	27.6	(0.495, 1.66)
Weak CYP3A4 inhibitor use ≥50% of at-risk period	0.424	0.143	33.8	(0.143, 0.705)
Any Strong, Moderate or Unclassified CYP3A4 inhibitor use during at-risk period	0.403	0.204	50.6	(0.00342, 0.802)
SGLT-2 inhibitor use >0% of at-risk period	-0.293	0.0690	23.5	(-0.429, -0.158)
Black / African-American	0.558	0.281	50.3	(0.00789, 1.11)
All Asian ethnicities except Japanese	0.533	0.139	26.1	(0.261, 0.805)

[a]corresponds to a delay half-life of 11.0 h

RSE (%) is calculated as SE/Estimate×100; 95% CI is calculated as Estimate ± 1.96×SE

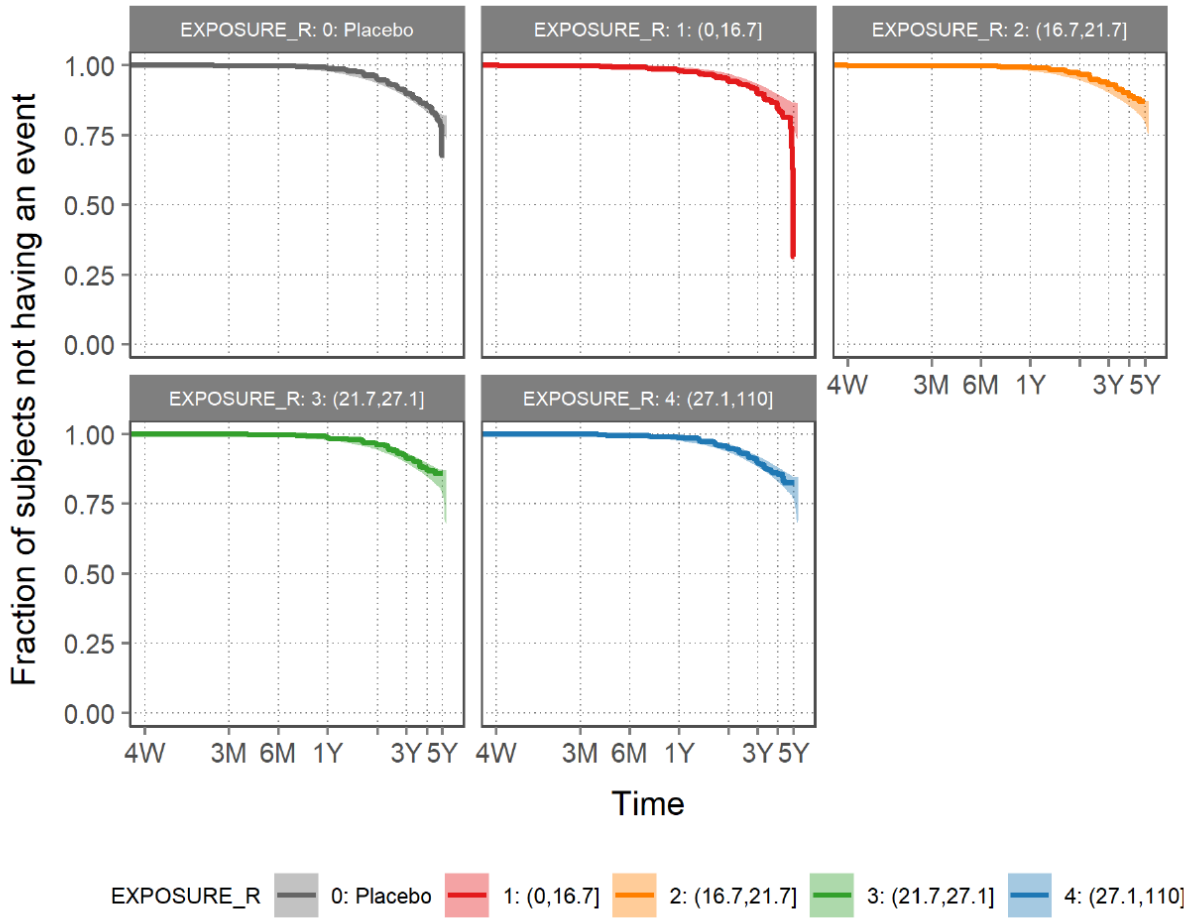


Figure 10 VPC of the final renal TTE model applied to FIGARO data from the final TTE dataset, stratified by exposure quartiles.

Next to the fit of the placebo data (grey), the finerenone treated subjects were divided in four exposure quartiles based on average concentration until (censored) event. The numbers indicate the ranges in µg/L. Thick lines indicate the observed KM curves, and the ribbons indicate the 95% interval of the model predictions. In this plot, subjects who had a (censored) event prior to their first finerenone dose, and thus had no exposure to finerenone, were assigned to the placebo group.

The parameter estimates and associated parameter uncertainties of the final model are considered acceptable and the VPCs describe the observed data overall well for placebo subjects and across the exposure quartiles. As outlined for the final CV model, it is considered challenging to identify exposure-response relationships given the study design, which should be considered if attempts are made to extrapolate these findings outside the context of the study design.

The EC50 in the typical patient is the same for both the immediate and delayed effect components, respectively. The absolute Emax values are similar between the immediate and delayed effect components, however, each component operate in different directions (increased and decreased hazard, respectively). Consequently, the 'net effect' on the hazard is near null in the typical patient, whereas a subject with high baseline UACR is noted to benefit from the treatment whereas a patient with low UACR is predicted to have increased risk following finerenone treatment. Based on these model-derived conclusions, it could mean that the subgroup of patients in FIGARO with the lowest UACR values have limited benefit from the treatment, as seen in the renal endpoint (this is outlined further in the clinical efficacy assessment). Of note, these trends can be seen also in the underlying observed data according to *Figure 8*.

d. MAH conclusion

The final CV TTE model captured the exposure-response relationship in the FIGARO population reasonably well. However, based on the VPCs, the treatment effect appears to be over-estimated to some extent, especially for subjects in the eGFR ≥60 mL/min/1.73 m2 at screening subgroup and an exposure in exposure quartile 3 or 4. Generally, patients in the eGFR <60 mL/min/1.73 m2 at screening subgroup with higher exposure benefited more from finerenone treatment in terms of reducing the risk for a CV event, compared to subjects with lower exposure in the same subgroup. The EC50 was estimated to be 9.69 µg/L and the maximum decrease of the hazard was fixed to 100% (Emax). Based on typical subject simulations, the simulated duration above the EC90 within a 24 h dose interval was 2.0 h after 20 mg finerenone OD at steady-state. PFs with the largest effect on the baseline hazard were: History of CV disease, Likely Child-Pugh Score and Weak CYP3A4 inhibitor use for >0-<50% of the at-risk period.

The final renal TTE model generally captured the exposure response relationship adequately. Two Emax functions were needed to separate the impact of two processes on the baseline hazard: one to capture the increase in baseline hazard representing the 'acute' effect of finerenone on eGFR and one to capture the decrease in baseline hazard representing finerenone's beneficial effect on disease progression. UACR was found to be an important prognostic factor on the EC50 of the hazard decreasing effect (EC502). Generally, patients with higher UACR and higher finerenone exposure benefited more from finerenone treatment in terms of reducing the risk for a renal event, compared to patients with lower UACR and lower finerenone exposure.

Exposure-response relationships were identified between finerenone exposure and prevention of cardiovascular and renal events. Exposure-response relationships identified between finerenone exposure and prevention of cardiovascular events seem not completely reliable, since at highest exposure quartiles the treatment effect was overestimated. Therefore, the model should not be used for extrapolations or dosing recommendation. For what concerns the renal events, UACR was identified as covariate, indicating patients with higher UACR baseline values benefit more from finerenone treatment, while patients with lower UACR baseline values seem to show even a detrimental effect from finerenone treatment. This evidence is further discussed in clinical efficacy assessment.

An important limitation is that the results for both endpoints may be influenced by some adaptive elements embedded in the study design and, as a consequence, the final models should generally not be used for extrapolations outside the setting that resembles the FIGARO study protocol. As the analysis is seen as supportive evidence considered to have rather low impact, the results are considered acceptable as is.

2.3.4.2. Potassium analysis

The main objectives of the potassium PKPD model were to:

- establish a PopPKPD model to describe serum potassium concentration data and frequency of crossing pre-defined safety thresholds (>5.5 mmol/L and >6.0 mmol/L) in FIGARO, and
- use simulations to assess the safety impact of switching to a serum potassium threshold of ≤5.0 mmol/L to determine eligibility for inclusion and up-titration of finerenone compared to the FIGARO threshold of ≤4.8 mmol/L.

The first objective is considered the most relevant for the current submission and the only objective covered by this assessment. No updates to the SmPC is sought for an updated 5 mmol/L threshold and

therefore, this objective was not considered crucial for the current submission. As a general comment and as outlined above, exposure-response is not considered crucial for the overall benefit-risk assessment and the analysis was not subject to a detailed assessment.

a. Data

The final PopPKPD dataset contained a total of 205121 serum potassium observations (87691 local laboratory and 117430 central laboratory data) from 13112 subjects (7352 from PMx FAS and 5760 from screening failure dataset). In the subset of patients in the PMx FAS, there were a total of 196604 serum potassium observations (87691 local laboratory, 108913 central laboratory), of which 189254 were post-baseline serum potassium observations. Of the 7352 subjects in the PMx FAS, 3666 were randomised to placebo, 1359 to finerenone 10 mg starting dose, and 2327 to finerenone 20 mg starting dose. There is a moderate to strong correlation between the local and central measurements (r=0.84).

The large size of the dataset is acknowledged. As the study design allowed dose discontinuations as well as (up and down) titration of the dose based on potassium measurements, the dataset is not considered optimal for identifying a “true” exposure-response, which should be acknowledged when assessing the resulting exposure-response model(s).

b. Methods

A starting point for the analysis was a base model that includes some of the key aspects of the previously developed FIDELIO PopPKPD potassium model (PKPD report R-13534). In this model, finerenone’s effect on serum potassium was characterized with a turnover model, with the drug effect being implemented on the hypothetical first order rate constant (kout), describing the loss of serum potassium, resulting in a finerenone concentration dependent increase in serum potassium (*Figure 11*).

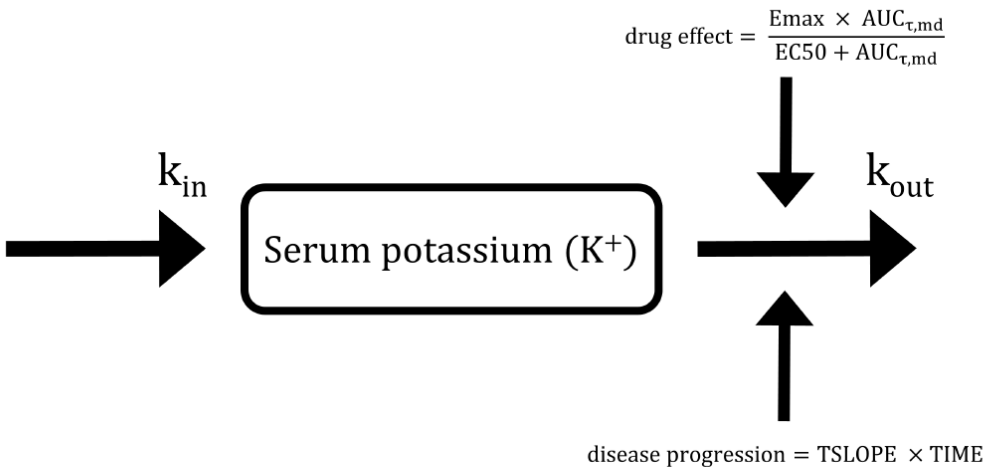


*Figure 11 Schematic display of the serum potassium base model structure. The first order dissipation rate constant in turnover model kout is calculated as kin*BSL. The chance in serum potassium over time is calculated with the differential equation:*

$$\frac{dK}{dt} = k_{in} + k_{out} \cdot K \cdot (1 - drug\ effect) \cdot (1 - disease\ progression)$$

$AUC_{T,md}$ was used as driver of effect, and this effect on kout was characterized with an Emax equation. Additionally, a t-distribution was used for the residual error. The development of the FIGARO serum PopPKPD potassium model was carried out in four phases:

1. Structural model development, using central laboratory data from the PMx FAS dataset (baseline visit and beyond)
2. Adding the local laboratory data from the PMx FAS dataset
3. Covariate exploration
4. Adding the screening failure data and the run-in/screening data from the PMx FAS dataset

A limited number of known risk factors for hyperkalemia were tested as potential covariates: age, baseline eGFR-EPI, baseline urine albumin-to-creatinine ratio (UACR), sex, CYP3A4 inhibitor use, SGLT-2 inhibitor use and Japanese ethnicity. The covariate exploration was performed on the dataset containing the local and central serum potassium observations from the PMx FAS dataset.

The predictive performance of the model was evaluated using VPCs. Simulated subjects were screened at the run-in and screening visits according to the FIGARO protocol, and removed from the simulated study if they did not meet the serum potassium inclusion criterion (≤4.8 mmol/L). To adequately reflect the FIGARO dosing algorithm, the simulations for the VPC include simulation of dose-titration decisions on the basis of simulated local laboratory serum potassium observations. Finally, the occurrence of serum potassium retests (which were planned in FIGARO +/-3 days after hyperkalemia observations) and up-titration visits (which were planned in FIGARO-DKD +/-4 weeks after up-titration) were also dependent on the simulated serum potassium observations and simulated up-titration decisions.

The applied model development and evaluations are considered acceptable. The Applicant made efforts to reflect the rather complicated dosing algorithm of the study protocol (including up- and down-titration) in the simulations which is endorsed. To our understanding, dose interruptions/dropout due to high serum potassium occurred in the observed data based on potassium measurements which does not seem to be reflected in the simulations. Since this exposure-response analysis has a supportive role for the submission, this is however considered overall acceptable and this issue is not further pursued.

c. Results

First, the starting model was re-estimated on the FIGARO data and baseline eGFR-EPI was evaluated and included as a covariate on the parameter describing the baseline potassium level (BSL, dOFV=-292). A proportional difference between central and local laboratory data characterized the difference between central and local laboratory data. The distribution of IIV on Emax was changed from a log-normal distribution to a proportional distribution, in which the individual posthoc estimate of Emax can in theory also become negative. A disease progression term TSLOPE that was dependent on BSL was added to the model. This was considered the base model.

The base model was used for covariate testing using SCM. The covariates included in the final model were baseline eGFR-EPI on BSL, baseline eGFR-EPI on Emax, age on Emax, CYP3A4 inhibitor use on BSL, SGLT-2 inhibitor use on BSL as well as Japanese ethnicity on . As a model finalization step, a Box-Cox transformation was included for IIV on BSL in the final model (*Table 8*). A VPC for the final model is shown in *Figure 12*.

Table 8 Parameter estimates and uncertainties of the final PopPKPD potassium model

Parameter Name	Estimate	SE	RSE (%)	95% CI
$\theta_{pop,BSL}$, BSL (mmol/L)	4.50	0.00537	0.119	(4.49, 4.51)
$\theta_{pop,local}$, Relative difference local lab versus central lab	0.0208	0.000414	1.99	(0.0200, 0.0216)
$\theta_{pop,kin}$, k_{in} (mmol/L*hr)	0.00579	0.000739	12.8	(0.00434, 0.00724)
$\theta_{pop,EMAX}$, E_{max}	0.0633	0.000844	1.33	(0.0616, 0.0649)
$\theta_{pop,EC50}$, EC50 (mg*hr/L)	0.350	0.0174	4.99	(0.316, 0.384)
$\theta_{pop,TSLOPE_{placebo}}$ TSLOPE in placebo arm (/year)	0.000117	0.0000102	8.68	(0.0000974, 0.000137)
$\theta_{pop,TSLOPE_{active}}$ TSLOPE in active treatment arm (/year)	-0.00242	0.000388	16.1	(-0.00318, -0.00165)
$\theta_{JAP,\sigma}$, Relative σ with Japanese ethnicity (%)	74.7	-	-	-
$\theta_{JAP,BSL}$, Relative difference in BSL with Japanese ethnicity (%)	-3.13	-	-	-
$\theta_{EGFR,BSL}$, Effect of EGFREPI0 on BSL	-0.0566	0.00210	3.71	(-0.0607, -0.0525)
$\theta_{BSL,TSLOPE}$, Effect of BSL on TSLOPE (L/mmol/year)	0.00778	0.00117	15.0	(0.00549, 0.0101)
$\theta_{UACR,TSLOPE}$, Effect of UACR0 on TSLOPE (g/mg/year)	0.00000371	0.000000406	10.9	(0.00000292, 0.00000451)
$\theta_{EGFR,EMAX}$, Effect of EGFREPI0 on Emax	-0.245	0.0334	13.7	(-0.310, -0.179)
$\theta_{AGE,EMAX}$, Effect of AGE on Emax	0.559	0.0813	14.6	(0.399, 0.718)
$\theta_{CYPINH,BSL}$, Effect of CYPINH on BSL	0.965	0.00147	0.153	(0.962, 0.968)
$\theta_{SGLT2,BSL}$, Effect of SGLT-2 on BSL	0.985	0.00193	0.196	(0.981, 0.988)
Variability	**Estimate**	**SE**	**RSE (%)**	**%CV**
ω^2 Exponential BSL	0.00557	0.000105	1.88	7.47
ω^2 Proportional E_{max}	1.40	0.0413	2.94	175
ω^2 Covariance BSL/E_{max}	-0.0313	0.00222	7.10	-0.239
Shape parameter Box-Cox transformation exponential IIV on BSL	-1.72	0.0796	4.62	-
Residual Error	**Estimate**	**SE**	**RSE (%)**	**stDev**
σ^2 - scalar of residual error	0.00412	0.0000304	0.736	0.0642
v - degrees of freedom of t-distributed residual error	6.98	0.0876	1.26	-

RSE (%) is calculated as SE/Estimate*100; 95% CI is calculated as Estimate +/- 1.96*SE; for back-transformed parameters 95% CI is back-transformed values of 95% CI; %CV is calculated as sqrt(exp(OM)-1)*100 in case of exponential variability or sqrt(OM)/TH*100 in case of additive variability, or presents the correlation coefficient (OMx,y / (sqrt(exp(OMx)-1) * sqrt(exp(OMy)-1))) for the covariance between parameters; StDev is calculated as sqrt(SIG), if SIG is defined already as StDev it will be the same as estimate

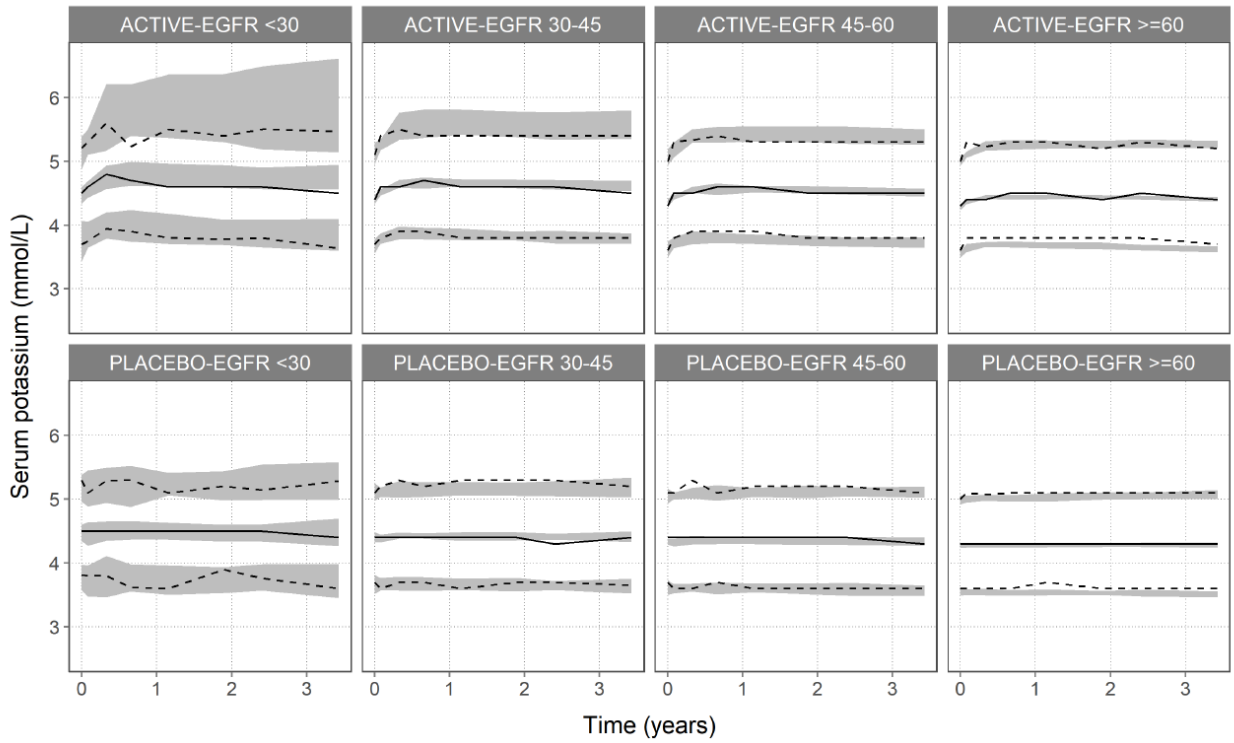


Figure 12 VPC of central laboratory serum potassium data over time, stratified by eGFR-EPI category. The black lines show the observed median (solid line) and 5th and 95th percentile (dashed lines), while the grey areas indicate the 99% interval of the same percentiles in the simulations, which include variability but not parameter uncertainty. Units of eGFR-EPI are mL/min/1.73 m2.

The final model parameters and RSEs are considered overall reasonable. However, it is unclear how well the estimated exposure-response parameters (Emax and EC50) reflects the "true" exposure-response, given limitations of the study design (see above). Since the results does not warrant any changes to the dose adaptations based on serum potassium as outlines in the SmPC, this issue is not further pursued. The final model described the observed data overall well, according to a VPC.

2.3.4.3. Exploratory ER analysis for safety endpoints

Graphical analysis for selected safety endpoints were provided. However, the visualizations should be interpreted in the light of the underlying complexity of correlations and interactions between the PD parameters as well as serum potassium- and eGFR-based dose titration.

eGFR: For eGFR, the change for baseline exposure-response analysis indicates an initial exposure-dependent eGFR decrease along with a longer-term benefit of slowed eGFR decline.

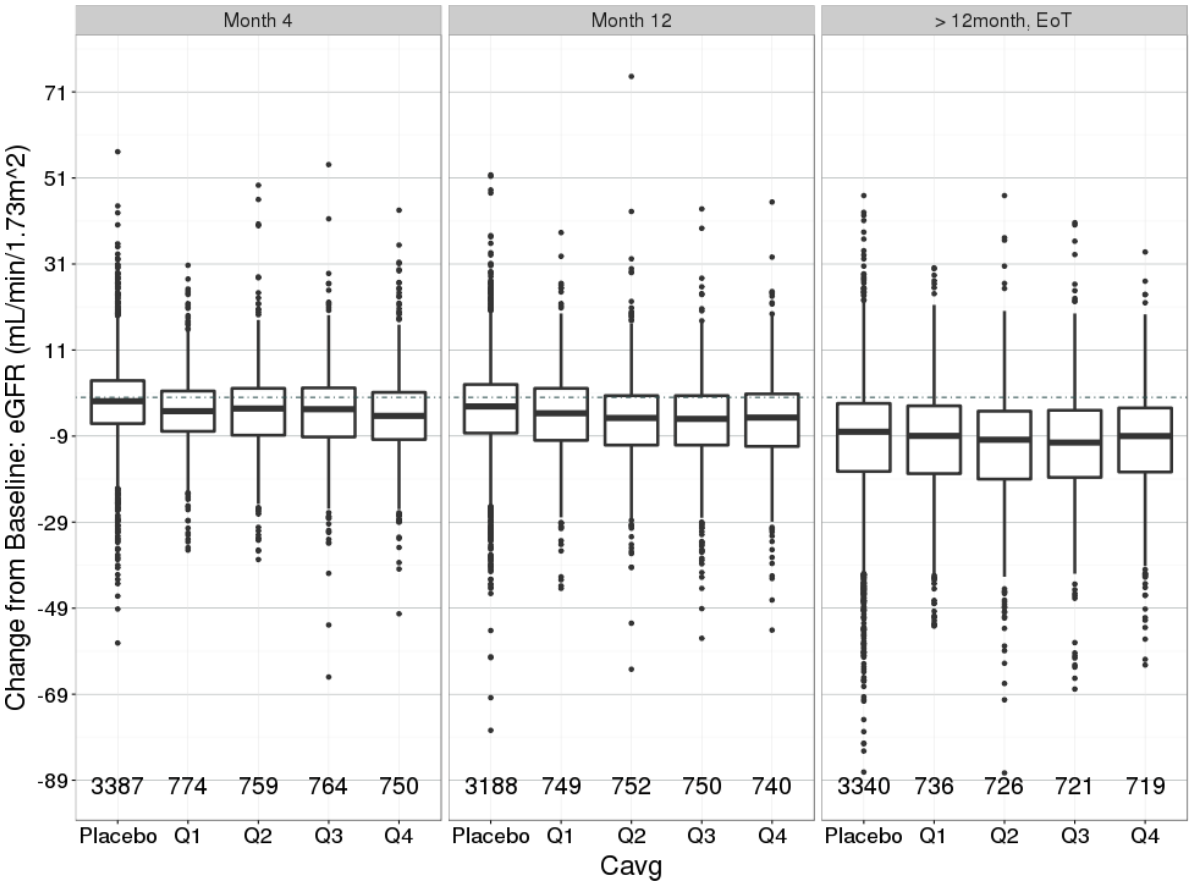


Figure 13 Change from baseline: Estimated glomerular filtration rate (eGFR) versus running average (from first drug administration) drug concentration (Cavg) exposure quartiles (Q1-Q4) boxplots at three representative timepoints. The line in the boxplots marks the median with the surrounding box from 25th to 75th percentiles, whisker extensions defined as 1.5 interquartile range (IQR) and outliners shown as points above and below. The quartiles are based on the exposure at the respective timepoint indicated at the top of the figure; the number in the lower part of the figure represents the number of subjects per quartile; EoT = End of Treatment.

Hemodynamic parameters: For blood pressure, the change from baseline indicates a

sustained slight exposure-dependent decrease. This decrease is smaller for diastolic bloop pressure (*Figure 15*) than for systolic blood pressure (*Figure 14*). There are no indications for an effect on heart rate.

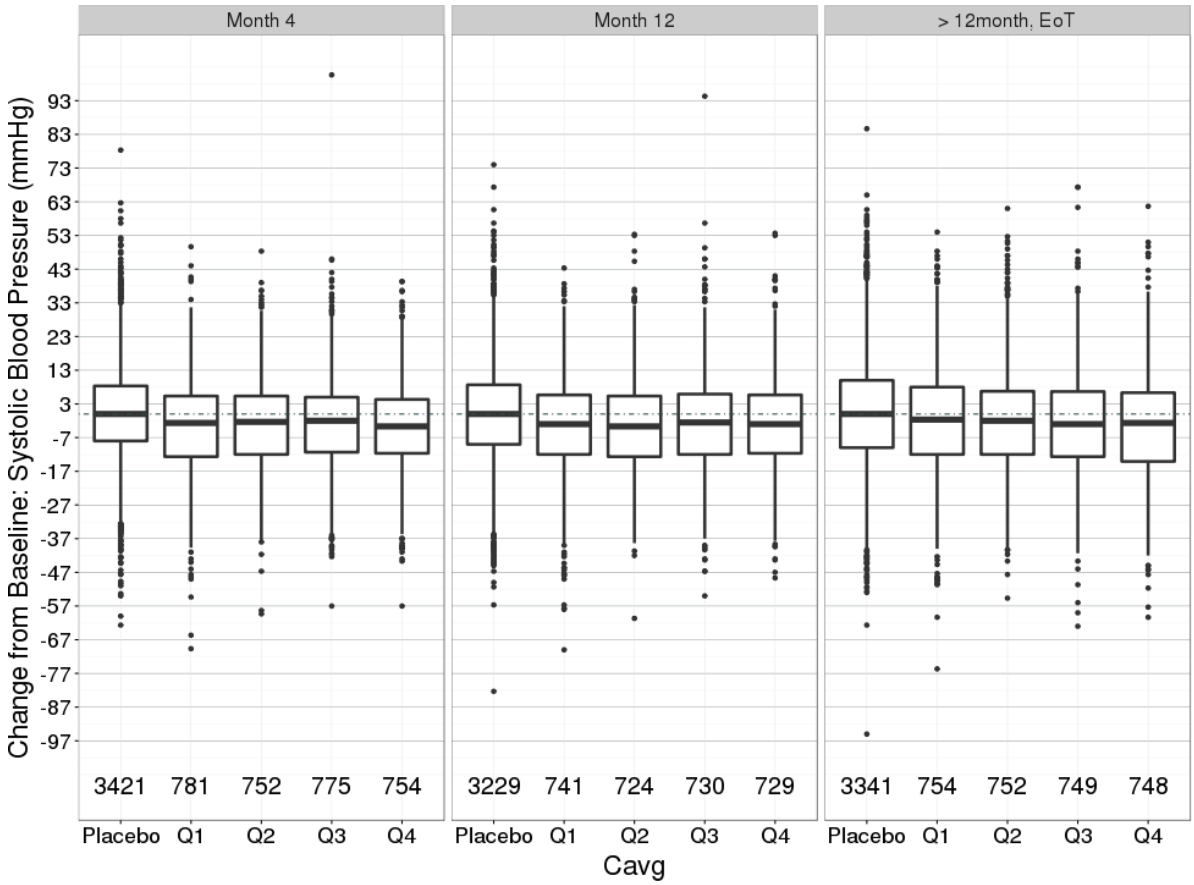


Figure 14 Change from baseline: Systolic Blood Pressure versus running average (from first drug administration) drug concentration (Cavg) exposure quartiles (Q1-Q4) boxplots at three representative timepoints. The line in the boxplots marks the median with the surrounding box from 25th to 75th percentiles, whisker extensions defined as 1.5 interquartile range (IQR) and outliners shown as points above and below. The quartiles are based on the exposure at the respective timepoint indicated at the top of the figure; the number in the lower part of the figure represents the number of subjects per quartile; EoT = End of Treatment.

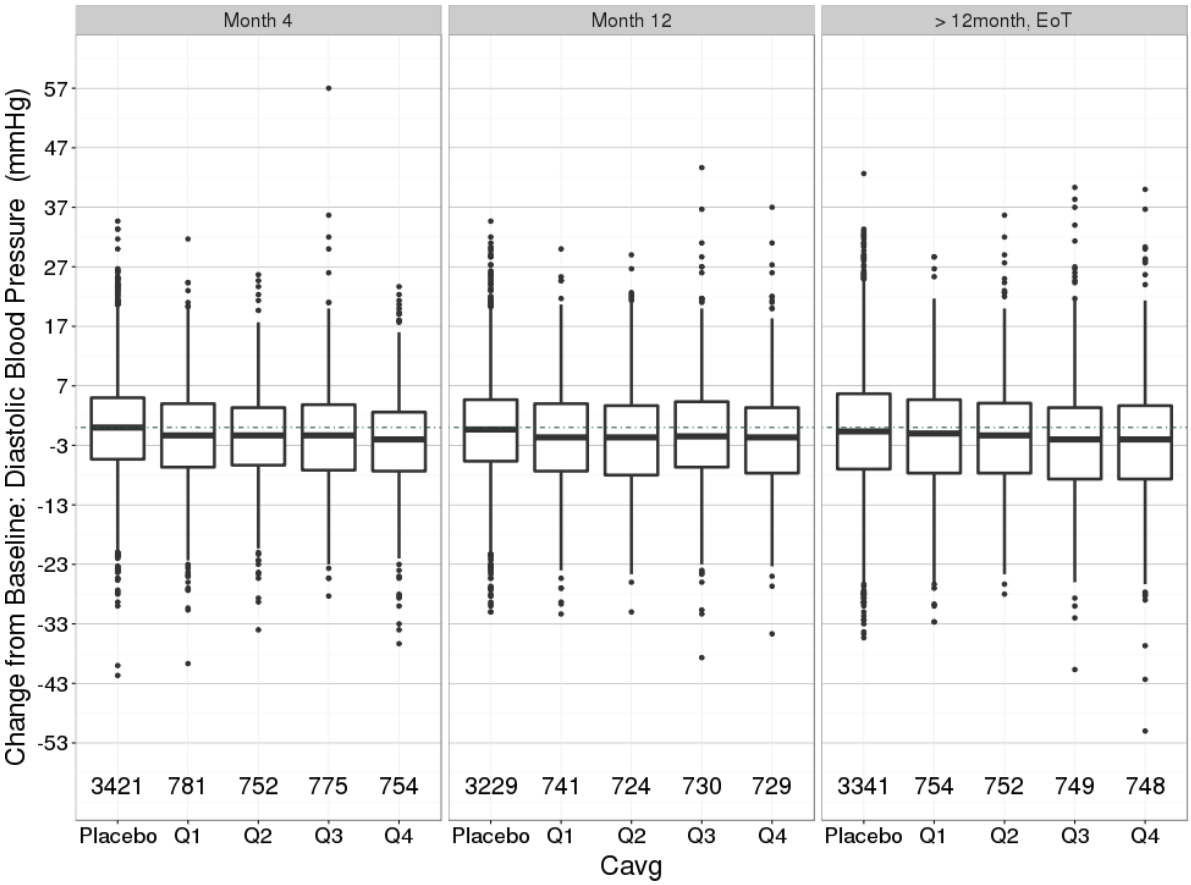


Figure 15 Change from baseline: Diastolic Blood Pressure versus running average (from first drug administration) drug concentration (Cavg) exposure quartiles (Q1-Q4) boxplots at three representative timepoints. The line in the boxplots marks the median with the surrounding box from 25th to 75th percentiles, whisker extensions defined as 1.5 interquartile range (IQR) and outliners shown as points above and below. The quartiles are based on the exposure at the respective timepoint indicated at the top of the figure; the number in the lower part of the figure represents the number of subjects per quartile; EoT = End of Treatment.

Sodium: For serum sodium, the initial change from baseline indicates that the treatment effect may be saturated for higher exposures and that the drug effect overall may decrease or cease over time (*Figure 16*).

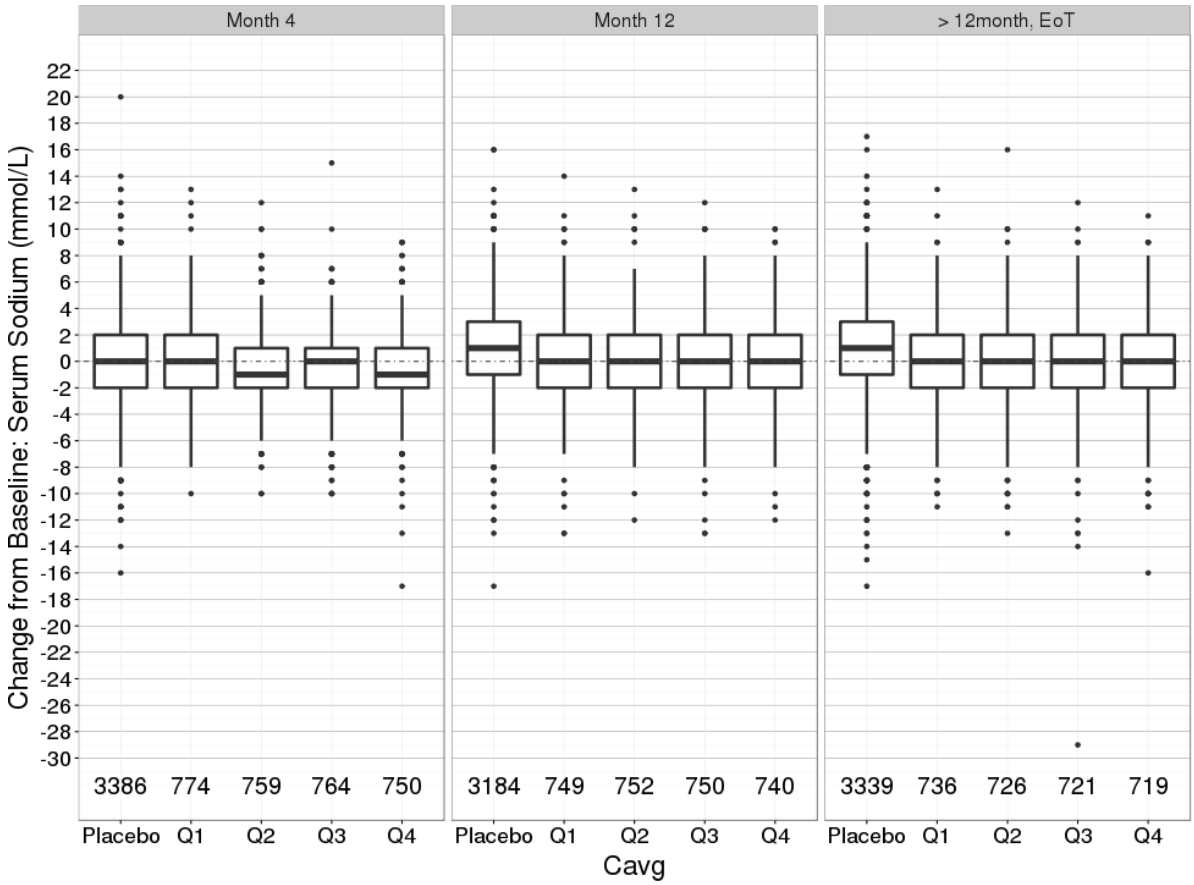


Figure 16 Change from baseline: Serum Sodium versus running average (from first drug administration) drug concentration (Cavg) exposure quartiles (Q1-Q4) boxplots at three representative timepoints. The line in the boxplots marks the median with the surrounding box from 25th to 75th percentiles, whisker extensions defined as 1.5 interquartile range (IQR) and outliners shown as points above and below. The quartiles are based on the exposure at the respective timepoint indicated at the top of the figure; the number in the lower part of the figure represents the number of subjects per quartile; EoT = End of Treatment.

No safety events have occurred in both the finerenone and placebo group together at an event rate greater than 10%. However, the analysis included all common safety events, except hyperuricaemia. The presented analysis display slight exposure-response trends for most endpoints, however no unexpected relationships were detected. Since the analysis has a purely descriptive purpose, no specific issues are identified.

2.3.5. Discussion on clinical pharmacology

A key addition to the finerenone clinical development program for the current submission is the FIGARO study. FIGARO study included sparse sampling for PK in addition to measurements of several biomarkers and clinical efficacy and safety. The finerenone PK and PKPD relationships for FIGARO was mainly evaluated using PopPK and PKPD approaches. The assessments of these aspects are discussed below. FIGARO is a Phase 3 study designed to evaluate finerenone clinical efficacy and safety and therefore, the the PopPK and PKPD characterizations were not considered pivotal for the submission.

Pharmacokinetics

A FIGARO population PK model was developed using a similar workflow as for FIDELIO (included in the initial MAA). The objectives for the FIGARO PopPK analysis were to characterize PK, identify covariate

effects and to provide individual exposures for subsequent exposure-response analyses. The data and methods used are considered overall acceptable. However, correlated covariates were explored during the covariate analysis. This could potentially lead to selection bias and the Applicant is strongly recommended to make pre-specified decisions to include only one of several correlated covariates in future submissions.

The final model included overall reasonable covariates, however, CYP inhibitor use was included on V and different body size descriptors were used for CL and V, which is not seen as optimal. The final model gave acceptable description of the observed data despite slight over- and underpredictions of the observed data at early and late time-points, respectively. These issues outlined for the PopPK model are not pursed, given the limited impact of PopPK for the current submission. The issues should however be considered in case the PopPK model is used in future applications, e.g. for extrapolations (e.g. exposure predictions in paediatric patients or patients with higher-than-observed weight).

FIGARO includes more CKD stages compared to FIDELIO (considerably more patients with CKD stages I and II). An increase of trough concentrations of ~60-70% were seen between moderate and severe groups compared to normal and mild groups which is considered reasonable given the study design and patient population.

Exposure-response

Finerenone exposure-response relationships were explored for several endpoints including cardiovascular events, renal events, serum potassium, eGFR, systolic blood pressure, diastolic blood pressure and serum sodium. As the exposure-response relationships were not deemed pivotal for the current submission, they are not subject to an in-depth assessment.

Time-to-event models were developed to describe exposure-response for the cardiovascular and renal events. The datasets used to develop the respective models and the model development workflows are considered overall acceptable and are comparable to the workflow used to develop corresponding models for FIDELIO. Finerenone exposure was found to reduce the risk of cardiovascular events using an Emax model with EC50 estimated at 9.69 ug/L. For the renal endpoint, a more complex exposure-response relationship was implemented. Baseline UACR was included as a covariate for the exposure-response and only subjects with high baseline UACR were predicted to have reduced risk of renal events. Subjects with low baseline UACR were predicted to have increased risk of renal events. This could mean that the subgroup of patients in FIGARO with the lowest UACR values have limited benefit from the treatment, as seen in the renal endpoint (for more details, see clinical efficacy assessment).

For serum potassium, a turn-over model was used to describe exposure-response where exposure was based on the individual AUC at steady state. An Emax model was used to describe the exposure-response relationship where serum potassium increased with finerenone exposure with the EC50 estimated to 0.350 mg*h/L. It is unclear how well the estimated exposure-response parameters (Emax and EC50) reflect the “true” exposure-response, given that the study design allowed dose discontinuations as well as (up and down) titration of the dose based on potassium measurements. Since the results does not warrant any changes to the dose adaptations based on serum potassium in the SmPC, this issue is not further pursued. The final model described the observed data overall well, according to a VPC.

2.3.6. Conclusions on clinical pharmacology

A population PK model and several exposure-response analyses were performed on data from FIGARO study. The population PK model as well as the exposure-response analyses are considered overall acceptable. Of note, limitations of the provided analyses are present. However, since the PopPK and exposure-response characterizations are not considered pivotal for the submission, the identified limitations are not further pursued. The application was considered acceptable from clinical pharmacology

point of view.

2.4. Clinical efficacy

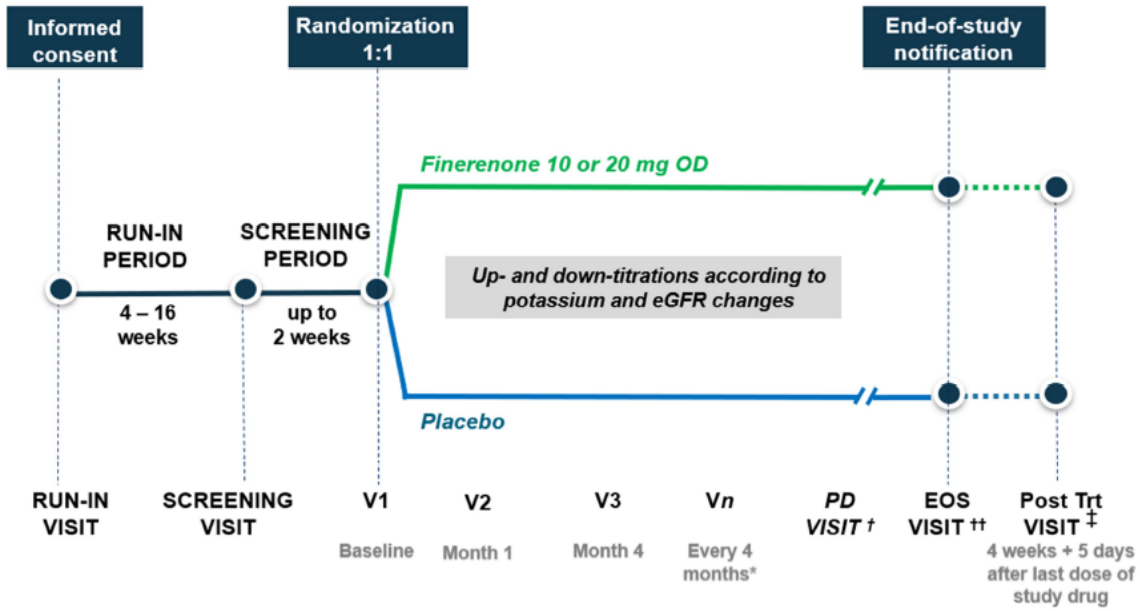
2.4.1. Main study

FIGARO-DKD (Study 17530)

FIGARO-DKD (FInerenone in reducinG cArdiovascular moRtality and mOrbidity in Diabetic Kidney Disease), is the pivotal phase III study in support for this application for variation.

Methods

The FIGARO-DKD Study 17530 was a randomised, double-blind, placebo controlled, parallel-group, multicentre, event-driven Phase 3 study in patients with T2D and CKD. A schematic description of the overall study design is given in *Figure 17*.



* Scheduled visits continued even if treatment with study drug was discontinued
† PD Visit conducted only after permanent withdrawal from treatment
†† EOS Visit conducted after notification of end-of-study by Bayer
‡ Post-treatment Visit for all subjects on study drug treatment at EOS

eGFR = estimated glomerular filtration rate, EOS = end-of-study, OD = once daily, PD = permanent discontinuation, Post Trt = post-treatment, V = visit

Figure 17. Overall study design of the FIGARO-DKD study.

Description of the study periods:

Run-in period (4 up to 16 weeks): Subjects with written informed consent who completed the Run-in Visit and met all eligibility criteria were enrolled into a mandatory Run-in Period, the purpose of which

was to ensure that the subject's standard of care therapy including treatment with ACEIs or ARBs was optimized and that all inclusion and exclusion criteria were met at the Screening Visit.

In the absence of documentation of diagnosis of high or very high albuminuria, the subject still could be enrolled into the study as albuminuria was measured at the Run-in Visit; in this case, the Run-in Period had to last for a minimum of 12 weeks and a maximum of 16 weeks.

Screening period (up to 2 weeks): At the end of the Run-in Period, a Screening Visit to confirm the subject's eligibility took place within ≤ 2 weeks prior to the planned randomization. At this visit, it was assessed whether the subject still met all eligibility criteria.

For those subjects without a prior documented diagnosis of high or very high albuminuria, the Screening Visit had to be performed at least 12 weeks after the Run-in Visit, and albuminuria then had to be re-evaluated. If the subject still suffered from high or very high albuminuria whilst on standard of care treatment, and fulfilled all other eligibility criteria, she/he could be randomized into the study.

Treatment period: Eligible subjects were randomized to receive once daily oral doses of finerenone (10 mg or 20 mg, see below) or placebo in addition to their standard of care therapy.

There were up to 4 planned visits (including randomization at Visit 1) in the first 4 months; thereafter visits took place every 4 months until the end of the study. Study drug dose could be up-titrated from Visit 2 (Month 1) onwards or down-titrated at any point (even between scheduled visits). At the discretion of the investigator, subjects could be seen throughout the study in addition to scheduled visits.

It was planned that all randomized subjects remained in the trial until either:

a) the projected number of subjects with a primary endpoints was reached, or

b) the trial was terminated prematurely at the recommendation of the independent DMC.

It was planned that all randomized subjects, including any subject who experienced a prespecified endpoint event, should continue to receive study drug until the trial was completed provided there were no safety grounds for discontinuing treatment.

Discontinuation of study drug (for any reason) did not constitute the subject's withdrawal from the study, unless the investigator believed that it was in the best interest of the subject or if the subject withdrew consent.

Follow-up: The period between the subject's last intake of study drug and last visit in the study is referred to as the 'Follow-up Period'.

For a subject who withdrew from study drug permanently but did not withdraw from the study, the Follow-up Period was the period between the PD visit (as soon as possible following permanent discontinuation of study drug) and the EOS Visit. For a subject who discontinued treatment at the EOS Visit, the Follow-up Period was the period between the EOS and Post-treatment Visits. All subjects who withdrew consent were followed up for vital status if they did not sign the 'Declaration of Objection' form. In addition, vital status could be obtained by the investigator from publicly available data sources. The collection of vital status had to be obtained within the timelines provided by Bayer.

The CHMP considered that the overall study design was adequate, in line with the scientific advice provided by the EMA.

All randomized subjects, including subjects who experienced a health event considered for the pre-specified endpoints, continued to receive study drug until the trial was completed (provided there were no safety grounds for discontinuing treatment).

Study participants

Key inclusion criteria

The study enrolled patients with T2D and a clinical diagnosis of DKD treated with the individual maximum tolerated labelled dose of either an ACEI or an ARB (but not both).

The main criteria for inclusion were:

- Men or women aged 18 years and older.
- Subjects with T2DM as defined by the American Diabetes Association 2013.
- Diagnosis of DKD based on either of the following criteria at the Run-in and Screening Visits:
- Persistent high albuminuria defined as UACR of ≥ 30 mg/g (≥ 3.4 mg/mmol) but < 300 mg/g (< 33.9 mg/mmol) in 2 out of 3 first morning void samples and eGFR ≥ 25 but ≤ 90 mL/min/1.73 m^2

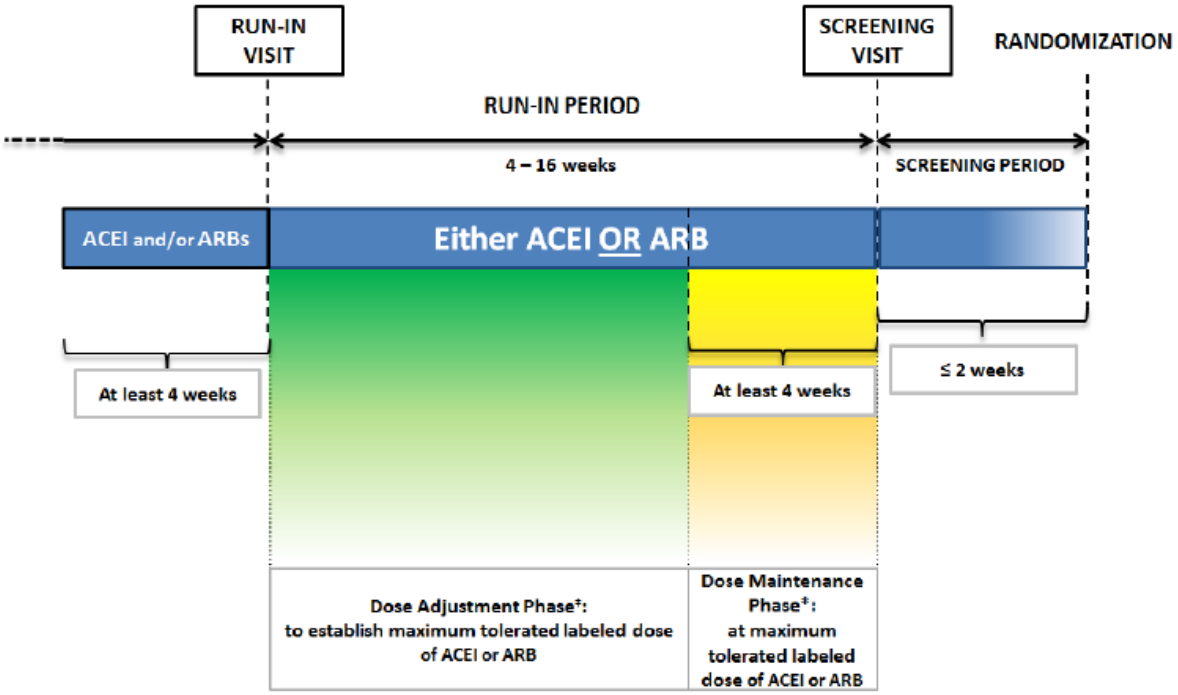
OR

- Persistent very high albuminuria defined as UACR of ≥300 mg/g (≥33.9 mg/mmol) in 2 out of 3 first morning void samples and eGFR ≥60 mL/min/1.73 m^2
- Prior treatment with ACEIs and ARBs as follows:
- For at least 4 weeks prior to the Run-in Visit, subject was treated with either an ACEI or ARB, or both
- Starting with the Run-in Visit, subject was treated with only an ACEI or an ARB
- For at least 4 weeks prior to the Screening Visit, subject was treated with the maximum tolerated labelled dose (but not below the minimal labelled dose) of only an ACEI or an ARB (not both) preferably without any adjustments to dose or choice of agent or to any other antihypertensive or antiglycaemic treatment (*Figure 18*)
- Serum potassium ≤ 4.8 mmol/L at both the Run-in and the Screening Visits

Key exclusion criteria

- Known significant non-diabetic renal disease, including clinically relevant renal artery stenosis
- UACR >5000 mg/g (>565 mg/mmol) at the Run-in Visit or Screening Visit
- HbA1c >12% (>108 mmol/mol) at the Run-in Visit or Screening Visit
- Uncontrolled arterial hypertension with mean sitting SBP ≥170 mmHg (or mean sitting DBP ≥110 mmHg at the Run-in Visit or mean sitting SBP ≥160 mmHg or mean sitting DBP ≥100 mmHg at the Screening Visit)
- Clinical diagnosis of chronic heart failure with reduced ejection fraction and persistent symptoms (NYHA class II to IV) at the Run-in Visit (class 1A recommendation for MRAs)

- Stroke, transient ischemic cerebral attack, acute coronary syndrome, or hospitalization for worsening heart failure, in the last 30 days prior to the Screening Visit
- Dialysis for acute renal failure within 12 weeks prior to the Run-in Visit
- Renal allograft in place or a scheduled kidney transplant within the next 12 months from the Run-in Visit
- Concomitant therapy with eplerenone, spironolactone, any renin inhibitor, or potassium-sparing diuretic which could not be discontinued at least 4 weeks prior to the Screening Visit
- Concomitant therapy with both ACEI and ARBs which could not be discontinued for the purpose of the study



Note: Before the Run-in Visit, subjects were treated with ACEI and/or ARBs.
Starting with the Run-in Visit, subjects were treated with only an ACEI or an ARB.
‡ If applicable
* During the maintenance phase, preferably there was no adjustment to dose of ACEI or ARB or to any other antihypertensive or anti-glycemic treatment
ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker, RAS = renin angiotensin system

Figure 18. FIGARO-DKD: Background therapy with RAS blockade

Compared with the previous FIDELIO-DKD, study, FIGARO-DKD enrolled patients with a less advanced DKD still associated with high or very high albuminuria in order to enrich the population for CV rather than renal events. Patients in the FIDELIO-DKD trial with 'high' albuminuria (but not the 'very high' albuminuria patients) were required to have diabetic retinopathy, which was not required in the present study. In the previous FIDELIO-DKD study, the number of subjects with 'high' albuminuria and presence of diabetic retinopathy in the medical history was capped at approximately 10% of the total population at screening, thus, the study primarily enrolled patients with 'very high albuminuria'.

The inclusion and exclusion criteria were otherwise in overall similar in the two studies and in line with the EMA Scientific Advice. However, at the time the CHMP concluded the scientific advice, a confirmed risk factor for CV disease or at least 1 additional risk factor for CV disease was an inclusion criteria, which was omitted in the final study design.

Treatments

The starting dose of finerenone depended on the eGFR value at the Screening Visit (*Table 9*). Thus, at randomization, in addition to standard of care subjects with an eGFR between 25 to <60 mL/min/1.73 m² at the Screening Visit (central laboratory results) were assigned to the lower dose of finerenone (10 mg) or placebo, whilst subjects with an eGFR ≥60 mL/min/1.73 m² were assigned to the higher dose of finerenone (20 mg) or placebo.

Table 9. Dosage of study drug for administration.

eGFR value at the Screening Visit, based on central laboratory results:	**25 to < 60 mL/min/1.73m²**		**≥ 60 mL/min/1.73m²**	
Subject randomized to group: Receives	**Finerenone** 10 mg finerenone OD + SoC	**Placebo** Placebo OD + SoC	**Finerenone** 20 mg finerenone OD + SoC	**Placebo** Placebo OD + SoC
Study drug intake	One tablet of SD once daily, preferably in the morning at approximately the same time each day.			
Missed intake	• If >8 hours before the next scheduled dose, the subject should take one tablet of SD as soon as possible. • If ≤8 hours of the next scheduled dose, the subject should wait and take the next tablet of SD at the usual time.			
Up-titration of dose Allowed from Visit 2 (Month 1) onwards provided that: • Potassium is ≤4.8 mmol/L [a] • eGFR decrease is less than 30% below the value measured at the last scheduled visit [a] • Must be documented in eCRF	20 mg finerenone OD, maintain SoC	Sham-titrate, maintain SoC	Not applicable	Not applicable
Down-titration of dose • Only for safety reasons (for guidance, see Section 9.7.1) • Allowed any time during the study (e.g. between scheduled visits) • Must be documented in eCRF • An unscheduled safety visit is performed within an adequate timeframe proposed by the investigator	• If at higher dose of SD, down-titrate to lower dose of SD, maintain SoC • If at lower dose of SD, interrupt SD, maintain SoC			

Abbreviations: eGFR = estimated glomerular filtration rate; SD = study drug; SoC = standard of care
[a] Potassium and eGFR according to local laboratory values

The dosage in study FIGARO-DKD was the same as the dosage in FIDELIO-DKD study and in line with the currently approved SmPC for Kerendia.

Objectives / endpoints

Primary objective	Primary endpoint

Demonstrate whether, in addition to standard of care, finerenone is superior to placebo in delaying the time to first occurrence of CV mortality and morbidity in subjects with T2D and the clinical diagnosis of DKD.	Time to the first occurrence of the composite endpoint of CV death or non-fatal MI, non-fatal stroke, or hospitalization for heart failure (abbreviated as CV composite endpoint).
Secondary objective To determine whether, in addition to standard of care, finerenone compared to placebo:	Secondary endpoint
Delayed the progression of kidney disease in subjects with T2D and the clinical diagnosis of DKD	Time to the first occurrence of the renal composite endpoint of onset of kidney failure, a sustained decrease of eGFR ≥40% from baseline over at least 4 weeks, or renal death (abbreviated as 40% renal composite endpoint).
Delayed the time to all-cause hospitalization	Time to all-cause hospitalization
Delayed the time to all-cause mortality	Time to all-cause mortality
Reduced UACR from baseline to Month 4	Change in UACR from baseline to Month 4
Delayed the time to first occurrence of the following composite endpoint (abbreviated as 57% renal composite endpoint): onset of kidney failure, a sustained decrease in eGFR of ≥57% from baseline over at least 4 weeks or renal death.	Time to first occurrence of the 57% renal composite endpoint of onset of kidney failure, a sustained decrease in eGFR of ≥57% from baseline over at least 4 weeks or renal death.

Endpoints of the study were in line with CHMP SA. The first secondary endpoint in the FIGARO-DKD study was the primary endpoint in the FIDELIO-DKD study and vice versa, otherwise the endpoints in both studies were the same with the exception of time to all-cause hospitalization and all-cause mortality shifted place in the hierarchical order.

Sample size

This was an event-driven study. Initially, it was planned that a total of 960 primary efficacy endpoint events were to achieve 90% power to demonstrate superiority of finerenone to placebo using a log rank test at a two-sided significance level of 5%, assuming a 20% relative risk reduction, i.e. a true hazard ratio of 0.80 (the hazard ratio that will be observed in the study will be different, i.e. closer to 1 due to treatment discontinuations).

With an assumed study duration of 36 months (recruitment period: 18 months, equal recruitment pattern, maximum treatment period of the last subject recruited: 18 months), the planned total number of subjects to be randomised was estimated to be 6210 subjects, assuming an annual placebo event rate of 8%, a common annual lost to follow-up rate of 0.7% in both treatment groups, an annual finerenone discontinuation rate of 5% and assuming that placebo discontinuation was not to change the hazard. A total of 6400 subjects were planned to be randomised taking a certain ramp-up during recruitment into account. Assuming a screening failure rate of 50%, 12800 subjects were planned to be screened.

Due to the minimal effect of the interim analysis on the overall power of the study, an adjustment of sample size would be negligible.

The assumption of the annual placebo event rate of 8% was based on the results from the MICRO-HOPE, RENAAL, IDNT, ALTITUDE and SAVOR-TIMI 53 trials. Event rates were obtained from the respective studies in the arms where treatment would more closely resemble that in the placebo population of the CV-DKD study who were to be on standard of care treatment for DKD. Annual event rates for the composite CV endpoint range from 7-10% for older studies and 5-6% for more recent studies. As the anticipated study population was to be enriched for CV outcomes, an annual placebo event rate of 8% was assumed to be appropriate. The calculations of the required total number of events and subjects to be randomized were performed using PASS 11.

The study was event driven. A total of 6210 subjects were initially planned to be randomised in order to detect 960 primary efficacy endpoint events (CV death or non-fatal MI, non-fatal stroke, or hospitalization for heart failure) across both treatment arms during the assumed treatment duration of 36 months. For the calculations, an 8% annual event rate for the primary endpoint in the placebo group was assumed based on data from previous clinical studies.

The sample size calculation was revised with protocol amendment 3 (May 2017). According to the description changes were implemented to account for a lower-than-expected recruitment rate. With this amendment, the number of primary efficacy endpoint events was slightly increased (from 960 to between 970 and 976) in order to achieve 90% power, the assumed treatment/study duration was increased from 36 to 44-48 months and the planned total number of subjects increased from 6210 to 6212-6286. In addition, the number of sites required worldwide were increased.

Due to a lower-than-expected event rate, a further increase in the sample size was subsequently made. This did not lead to a change in the CSP which the applicant justified based on that this had no impact on the original planning assumptions, but the new expected sample size was added in the SAP (SAP version 2.0, dated 29 MAY 2019.). For transparency and GCP compliance it had been expected that the final planned sample size had been correctly reproduced also in the CSP. The sample size increase by approximately 1000 subjects implied that the required number of randomised subjects was expected to be approximately 7400. In the end, 7437 subjects were randomised.

Similar changes for the same reasons were implemented also in the FIDELIO-DKD study submitted in support for the initial market authorisation application.

Randomisation

Eligible subjects were randomised 1:1 at baseline (visit 1) to receive finerenone (10 mg or 20 mg) or placebo in addition to their SoC therapy.

The finerenone starting dose depended on the screening eGFR value; at randomisation, subjects with an eGFR between 25 to < 60 mL/min/1.73m² (central laboratory results) were assigned to finerenone 10 mg or placebo, whilst subjects with an eGFR ≥ 60 mL/min/1.73m² were assigned to finerenone 20 mg or placebo.

Randomisation was to occur within ≤ 2 weeks after the screening visit and was stratified by region (North America, Europe, Asia, Latin America and others), type of albuminuria at screening (high or very high albuminuria), eGFR at screening (25 to <45, 45 to <60, ≥ 60 mL/min/1.73m²) and history of cardiovascular disease (present, absent; for definition of CV disease see table below).

The number of subjects with high albuminuria and eGFR ≥ 60 mL/min/1.73 m2 was to be capped at approximately 10% of the total population with high albuminuria at screening. The number of subjects with high albuminuria and without a history of CVD was to be capped at approximately 40% of the total population with high albuminuria at screening.

Table 10. Definition of cardiovascular disease for stratification purposes.

Coronary Artery Disease: • Previous Myocardial Infarction (MI) • History of coronary revascularization (percutaneous coronary intervention or coronary artery bypass graft) • Angiographically proven stenosis ≥ 50% in at least one major epicardial coronary artery
Cerebrovascular Disease: • Previous ischemic stroke [transient ischemic attack (TIA) alone not sufficient to fulfill this criterion]
Peripheral Arterial Disease: • Previous non-traumatic leg amputation • History of lower-limb revascularization (either surgical or percutaneous) • History of intermittent claudication with ankle brachial pressure index (ABPI) of ≤ 0.80 in at least one side • Previous carotid endarterectomy or carotid stenting

The CHMP concluded that the randomisation procedure appears to have been appropriate. FIGARO-DKD and FIDELIO-DKD shared the same stratification factors except that in this study, patients were also stratified based on CV disease history.

Blinding (masking)

Finerenone IR tablets (10 mg and 20 mg) and placebo tablets were identical in appearance (size, shape, colour). The packaging and labelling were designed to maintain the blinding of the investigator's team and the subjects. The study data remained blinded until database lock and authorization of data release according to standard operating procedures. Furthermore, measures were taken to maintain blinding of the study team while bioanalysis of PK and biomarker samples was ongoing.

Clinical Event Committee (CEC)

The independent CEC was blinded to study drug assignment and adjudicated all potential CV and renal endpoint events, as well as all fatal events and hospitalizations that occurred from the day of randomisation (Visit 1) onwards until the respective EOS visit for each subject performed following the study termination notification. To adjudicate eGFR endpoints, results of central laboratory assessments were available. Roles and responsibilities and details on the adjudication process were defined in the CEC charter.

The CHMP concluded that the blinding procedure appear to have been adequate. As in the FIDELIO-DKD study, for subjects starting on the lower finerenone dose, up-titration was allowed from visit 2 (month 1) onwards; for subjects in the placebo arm there was a sham up-titration.

During the study and as reported in the CSR, there were 43 subjects who had their randomisation codes broken by the sponsor's pharmacovigilance department for the purpose of regulatory reporting (finerenone: 14 subjects, placebo: 29 subjects). None of the subjects who were unblinded were excluded from FAS or SAF. According to the applicant there were no unblinding events reported by the investigators.

Statistical methods

The approved SAP version 1.0 was dated 03 AUG 2016 (same date as for FIDELIO-DKD). Following version 1.0, the SAP history and document changes have been described with the latest version of the SAP being version 6.0, dated 15 Feb 2021.

Analysis populations

For the statistical analysis, the following populations were defined:

- Safety analysis set. The SAF comprised all randomised subjects who took at least 1 dose of study drug (except those with critical GCP violations).
- Full analysis set. The FAS comprised all randomised subjects (except those with critical GCP violations)
- Per-protocol set. The PPS comprised all subjects of the FAS without any of the prespecified validity findings.

For analyses based on FAS, all subjects were analysed according to the planned treatment group. For safety analyses (SAF), all subjects were analysed according to the actual treatment received.

Primary efficacy variable: primary analysis

The primary efficacy variable was the time to first occurrence of the composite endpoint of CV death or non-fatal CV event (myocardial infarction, stroke, or hospitalization for HF). All events classifying for the primary endpoint had to be adjudicated positively by the independent adjudication committee (CEC).

The primary analysis of the primary efficacy variable was performed in the FAS based on all randomised subjects except in case of critical GCP violations (added with amendment X).

Events for inclusion in the primary analysis were counted from the day of randomisation onwards until the EOS visit following the study termination decision, or until the date of EOS notification + 4 weeks if the EOS visit has not been performed. In the event of premature discontinuation from the study with no subsequent follow-up information, events were counted up to the day of withdrawal from the study or non-CV death. Randomised subjects without an event of the primary composite endpoint at the time of analysis were censored at the date of their last contact up to and including the EOS visit or date of non-CV death. Subjects without any information about the primary composite endpoint after baseline were censored at Day 1.

Superiority for finerenone versus placebo was tested using a stratified log-rank test. In order to provide a point estimate of the hazard ratio and a corresponding two-sided 95% confidence interval, a stratified Cox proportional hazard regression model was used. In addition, Kaplan Meier curves were provided for the cumulative incidence risk of outcome events by treatment groups.

The primary analysis of the primary efficacy variable was repeated in the PPS as a supportive analysis. For the PPS analysis, the censoring rules for the primary analysis was restricted to events occurring up to 30 days after last study drug intake.

Secondary efficacy variables: primary analysis

The primary analysis of the secondary time-to-event endpoints was conducted analogously to the primary analysis of the primary composite endpoint, with modifications to the censoring rules as the events differed.

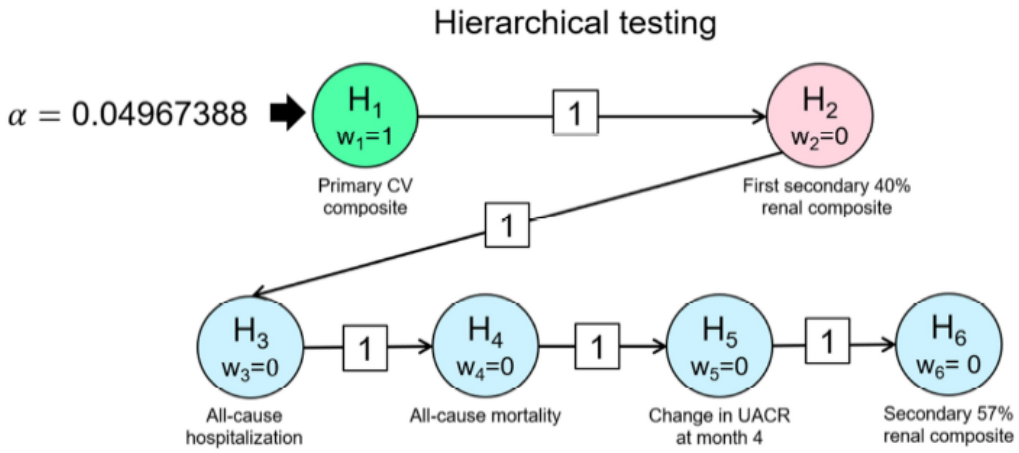
Testing procedure and multiplicity adjustment

One formal interim analysis was planned when 2/3 of the required total number of primary efficacy endpoint events had been observed. The testing procedure and multiplicity adjustment were pre-defined covering both the situation where a decision could be made to stop the study early for success and the situation where a decision was made not to stop the study early for success.

On 17 JAN 2020, the DMC communicated the decision to continue the study as planned without changes to the CSP.

Since the study could not be stopped early for success, the final primary analyses were pre-planned as follows:

- A group sequential design with a single interim analysis when 2/3 of the information was available with a stopping rule of two-sided p <0.00270 required a small adjustment to the significance level of the final analysis (α = 0.04967388) to maintain the overall significance level at 5%.
- A hierarchical testing procedure was used for the primary and secondary efficacy variables in the order below with each variable being tested at the adjusted two-sided significance level of 0.04967388.
- Primary CV composite endpoint
- 40% renal composite endpoint
- Remaining secondary efficacy endpoints in the order shown in the figure below.



CV = Cardiovascular, UACR = Urinary albumin-to-creatinine ratio
H_x refers to the null hypothesis of no treatment effect for each endpoint, and w_x denotes the weight allocated to the test of H_x which in case of rejection is passed on to the next test as indicated by the arrows.

Figure 19. Scheme of the testing strategy

If the testing strategy stopped at one point due to a non-significant result, the testing of the remaining secondary efficacy variables was performed in an explorative manner.

Subgroup analyses

Exploratory subgroup analyses were performed for primary and secondary efficacy variables. These subgroup analyses included the randomization stratification factors. Analyses included descriptive statistics, graphical display of estimated treatment effects with 95% CIs in a Forest plot and a statistical test for interaction.

Stratification factors:

- Region (North America, Latin America, Europe, Asia, Others)

- eGFR category at screening (eGFR 25 to <45, 45 to <60 and ≥60 mL/min/1.73 m2)
- Type of albuminuria at screening (high albuminuria, very high albuminuria
- History of CVD (present, absent)

Key subgroups in addition to stratification factors:

- Sex (male, female)
- Race (white, black, Asian, other)
- Age at run-in visit (<65, ≥65 years)
- eGFR category at baseline (eGFR <25, 25 to <45, 45 to <60 and ≥60 mL/min/1.73m2)
- Type of albuminuria at baseline (normalbuminuria (UACR <30 mg/g), high albuminuria, very high albuminuria)
- Baseline serum potassium value (≤ median and > median in the FAS)
- UACR at baseline (≤ median and > median in the FAS)
- Systolic blood pressure at baseline (≤ median and > median in the FAS)
- Baseline BMI (<30, ≥30 kg/m2)
- Haemoglobin A1c (≤7.5% / >7.5%)
- SGLT-2 inhibitors treatment at baseline (yes, no)
- GLP-1 receptor agonists treatment at baseline (yes, no)

Supportive efficacy analyses to account for the COVID-19 pandemic

Supportive analyses to evaluate the impact of the COVID-19 pandemic on the primary analysis were to be conducted for primary and secondary time-to-event endpoints.

Post-hoc analyses

Post-hoc analyses for demographics and efficacy were described in a separate SAP (version 1.0, 28 May 2021). All analyses were to be conducted on the full analysis set (FAS) unless otherwise specified. In subgroup analyses for albuminuria categories at baseline, patients with missing baseline UACR or normalbuminuria were to be excluded.

Efficacy

Subgroup analyses of eGFR for baseline albuminuria (30-<300/≥300 mg/g), high albuminuria at baseline (30-<150, 150-<300mg/g, i.e. excluding ≥300 mg/g) and baseline potassium (≤/>4.5 mmol/L):

o Mixed model of eGFR by <subgroup>(FAS)

o Line plot for least square means of eGFR absolute changes from baseline by visit and <subgroup>(FAS)

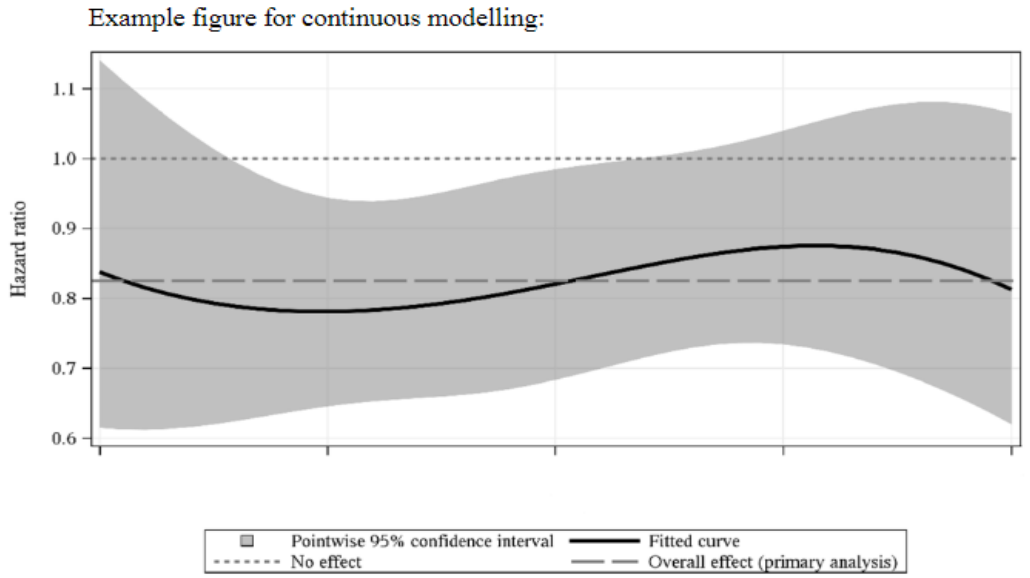
o Summary statistics for acute and chronic eGFR slopes by <subgroup>(FAS)

o Analysis of covariance for eGFR slopes (full analysis set) by <subgroup>(FAS)

Continuous modelling of baseline UACR and potassium for 40% and 57% renal composites

o Hazard ratio for time to onset of kidney failure, a sustained decrease of eGFR ≥ 40% (or ≥57%) from baseline over at least 4 weeks, or renal death by continuous baseline UACR (FAS)

o Hazard ratio for time to onset of kidney failure, a sustained decrease of eGFR ≥ 40% (or ≥57%) from baseline over at least 4 weeks, or renal death by continuous baseline serum potassium (FAS)



The FIGARO-DKD study shared a number of design and analysis features with the FIDELIO-DKD study. In that respect it is acknowledged that besides the different endpoint order, the two studies had slightly differently defined multiple testing procedures (MTPs). The MTP as planned for and used in the FIDELIO-DKD study implied a weighted Bonferroni-Holm procedure for the primary and key secondary endpoint. However, as in the current study, only if both the primary and most important secondary endpoint achieved formal statistical significance, were the remaining secondary endpoints to be tested. As already commented on above; the first secondary endpoint in the FIGARO-DKD study was the primary endpoint in FIDELIO-DKD study and vice versa, otherwise same endpoints but time to all-cause hospitalization and all-cause mortality shifted place in the hierarchical order.

FIGARO-DKD completed on 02 Feb 2021. The latest version of the submitted SAP was version 6.0, dated 15 Feb 2021. Final release of the clinical database occurred 19 April 2021. FIDELIO-DKD completed on 14 Apr 2020. The changes made to the FIGARO-DKD study has thoroughly been accounted for in the SAP. Some were major, however none that raise any serious concern, and none that appears to have been inspired by the analysis of the FIDELIO-DKD study.

Supportive analyses to account for the COVID-19 pandemic for primary and secondary time-to-event efficacy endpoints were planned (SAP version 5, 05 Nov 20202) and have been presented considering four different versions for the COVID-19 onset date (country-specific, global, individual pandemic related disruption date, individual COVID-19 AE date). The supportive analyses took only events that occurred before the COVID-19 onset date into account and implied exclusion of what appear to be proportionally not that dissimilar number of events in the two treatment arms. For the primary endpoint, the impact on the estimates were small but the p-values for the difference changed to being less favourable or no longer <0.05 depending on onset date definition where global and country-specific had a larger impact compared with any individual onset date explained by the difference in number of excluded events. Based on the supportive analyses performed on the primary endpoint, the impact of the COVID-19 pandemic appears to have been limited.

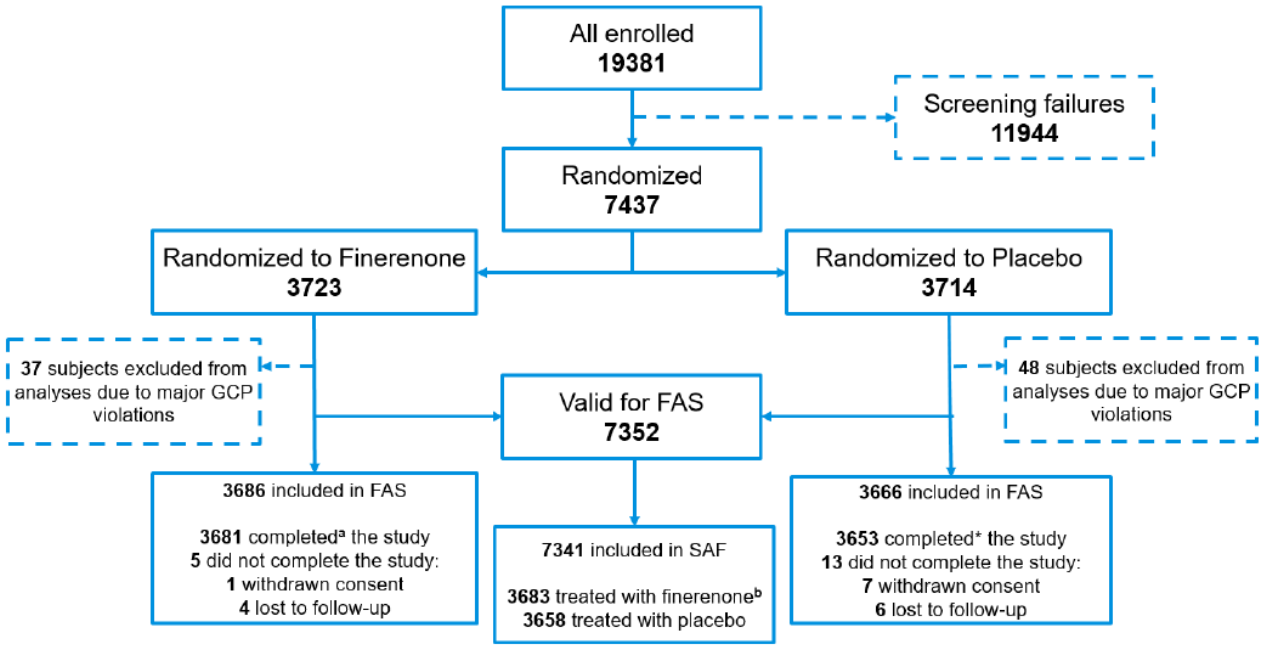
In addition, a number of post-hoc analyses have been performed for further assessments after subgroup analyses revealed treatment interactions ($p<0.05$) concerning baseline factors correlating with stage of kidney disease (this is further discussed below). In that respect, post-hoc analyses are appreciated. These post-hoc analyses were only briefly described in a separate SAP (version 1.0, 28 May 2021). Although the value of pre-definition is inherently less when it comes to analyses that by nature are data-driven, the SAP lacked details. This concerned for example continuous modelling of baseline UACR and potassium for renal composite endpoints. Different models to characterise non-linear effects of continuous covariates exist. Hence, the applicant was requested to clarify how and why a cubic B-spline was decided to best fit the data and also to justify number of knots that have been noted to differ depending on baseline covariate and analysis (at least in pooled analyses of both studies). Recognising the exploratory objective, the brief description presented was accepted although did not add the details that were thought to be missing in the provided SAP. It is supported that candidates for knots were not only data-driven but also based on medical judgement while the selection of a cubic B-spline function was considered as a compromise between smoothness of the curves and overfitting the data.

Further, the applicant will be requested to clarify where to find the SAP for the pre-planned pooled analyses of FIGARO-DKD and FIDELIO-DKD. The Applicant has confirmed that the SAP for the pooled analysis of FIGARO-DKD and FIDELIO-DKD was part of report submitted with the application. This SAP was dated 24 FEB 2021 (version 3.0).

Results

Participant flow

The FIGARO-DKD study was conducted in 1019 sites across 48 countries and enrolled 19381 patients. Screening failures occurred either during run-in or during the actual ⩽2-week screening period. With a total of 11944 screening failures, the screening failure rate was higher than anticipated (50% assumed vs actual 61.6%). The remaining 7437 subjects were randomized, 3723 subjects to finerenone and 3714 subjects to placebo. 85 subject IDs were prospectively excluded from the analyses because of critical GCP violations, resulting in a FAS population of 7352 subjects, with 3686 subjects in the finerenone arm and 3666 subjects in the placebo arm *Figure 20*).



a The subject is considered as having completed the study if there is a contact with the subject after the End of Study notification (15 NOV 2020) or if the subject died.
b One subject was randomized to placebo but received finerenone for the entire treatment duration.
FAS = full analysis set, GCP = good clinical practice, SAF = safety analysis set
Source: Module 5.3.5.1, PH-39747, Table 14.1.1/8

Figure 20. Subject disposition flow (FIGARO-DKD)

Treatment duration (from first to last intake of study drug) was similar between the finerenone and placebo arms. Mean and median duration of treatment in the FAS were 35.2 and 35.9 months in the finerenone arm and 35.3 and 35.9 months in the placebo arm, respectively.

A total of 81.1% of subjects in the finerenone arm and 80.7% of subjects in the placebo arm took the study medication for at least 24 months. Approximately half of the subjects took the study medication for at least 36 months (49.7% in finerenone, 49.9% in placebo) and approximately 30% of subjects took the study drug for at least 44 months (32.1% in finerenone, 31.8% in placebo)

The total exposure of subjects to study drug was 21593 patient-years, with 10802 patient years

in the finerenone arm and 10791 patient-years in the placebo arm.

The screening failure rate was higher than expected (50% assumed vs actual 61.6%). The applicant is requested to provide data on reasons for screening failure and discuss possible impact on the intended target population. It was clarified that the relatively high screening failure rate was related to an appropriate selection of patients within the target population.

Out of the 7437 patients that were randomised, a similar and low number of patients were excluded from analysis in the two treatment arms. Thus, the percentage of randomized subjects that completed the study was high (98.9% finerenone; 98.4% placebo). Over 80% of the participants took the medication for over 24 months.

Recruitment

The FIGARO-DKD study was conducted in 1019 sites across 48 countries.

First subject, first visit: 17 SEP 2015

Last subject, last visit: 02 FEB 2021

Conduct of the study

Amendments

The original study protocol was amended twice globally (Amendment 3 and 4). In addition, two local amendments were made, only affecting sites in Japan and Turkey.

Amendment 3, was a global amendment of the CSP dated 02 MAY 2017

1) To account for the lower than expected recruitment rate, the duration of study and the number of sites required worldwide were increased.

2) To allow re-screening at an earlier stage and even if the reason for initial screen failure was an elevated blood potassium value, the re-screening rules were amended.

3) To allow randomization of patients with a recent CVD episode (i.e. those suffering from stroke, transient ischemic cerebral attack, acute coronary syndrome or hospitalization for worsening heart failure in the last 30 days prior to the Screening visit), the respective Exclusion criterion (#7) was modified.

4) In order to allow up-titration of study drug at any time during the study (from Visit 2 onwards), the instructions for up-titration were modified. Additionally, a requirement to specify the reason for not dispensing the 20 mg dose in the eCRF was added.

5) The recommended blood pressure targets after randomization were updated according to the most recent literature.

6) Definitions of the endpoint “kidney failure” and the definitions of cardiovascular disease history for stratification purposes were added.

Amendment 4, was a global amendment of the CSP dated 12 MAR 2019

1) To perform the Post-treatment Visit as a telephone contact for all subjects except those participating in the iohexol clearance sub-study instead of an on-site visit to minimize the burden on subjects, sites, and the sponsor. This change neither compromised subject safety nor scientific value.

2) To specify baseline values to clarify the handling of subjects who did not immediately start with study drug treatment at randomization.

3) To increase the time window after last study drug administration from 3 to 30 days for on-treatment efficacy analyses to better reflect the more protracted nature of the development and diagnosis of clinical outcome events of interest in relation to treatment exposure.

4) To provide a more precise wording about the type of discontinuation. It is the impact of permanent discontinuation of the study drug that is of particular interest.

5) To specify the definition of TEAEs to account for permitted study drug interruptions (i.e. temporary discontinuations) which might have occurred over extended periods

6) To specify interruption of study treatment in a similar manner as done for the AE presentation when analysing laboratory parameters

7) To delete some laboratory analyses (absolute value of serum potassium >5.0 mmol/L, relative decrease from baseline in eGFR of ≥25%, and increase from baseline in serum creatinine >0.3 mg/dL and >0.5 mg/dL) that do not provide additional clinically relevant information.

Baseline data

Demographic data and baseline characteristics are provided in *Table 11* and *Table 12* whereas the number of subjects with pre-specified medical history findings of interest is summarized in *Table 13*. New concomitant medication of interest during the study are presented in *Table 14*.

Overall, 69.4% of subjects were male. Most subjects were White (71.8%) or Asian (19.8%). A total of 47.7% of subjects were from Europe, 22.1% were from Asia, 15.1% from North America and 11.4% from Latin America.

The mean age was 64.13 years. The largest proportion of subjects (44.3%) was between 45 and 64 years of age. The mean BMI was 31.43 kg/m^2 (SD 5.99 kg/m^2) and 24.0% of the subjects had a BMI of ≥35 kg/m^2. Mean SBP at baseline was 135.75 mmHg (SD 14.01 mmHg).

The mean eGFR value at baseline was 67.80 mL/min/1.73 m^2 (SD 21.69 mL/min/1.73 m^2). The median value of UACR at baseline was 308.18 mg/g (Q1-Q3 108.09-739.86 mg/g). Similar numbers of subjects were categorized as having high albuminuria (30 mg/g to <300 mg/g: 46.4%) and very high albuminuria (≥300 mg/g: 50.7%). Due to inherent intra-individual variability, a shift in eGFR and UACR categories between screening and baseline was seen.

The mean serum potassium value at baseline was 4.33 mmol/L (SD 0.43 mmol/L) and 28.5% of subjects had serum potassium values of >4.5 mmol/L, 5.8% had >4.8 to 5 mmol/L, and 4.6% had >5 mmol/L at baseline.

At baseline, approximately half of the subjects (45.3%) had a history of CV disease. The mean duration of diabetes was 14.49 years (SD 8.52 years) and mean HbA1c value was 7.72% (SD 1.37%). 97.9% of the subjects took anti-diabetic treatments at baseline, mostly biguanides (68.9%) and insulins and analogues (54.3%). The most frequently used non-antidiabetic treatments at baseline were RAS inhibitors (ARBs: 57.3%; ACEIs: 42.7%) and statins (70.5%).

Table 11. Demographic data (FAS, FIGARO-DKD).

	Finerenone N=3686 (100%)	Placebo N=3666 (100%)
Sex: Male	2528 (68.6%)	2577 (70.3%)
Female	1158 (31.4%)	1089 (29.7%)
Race		
WHITE	2672 (72.5%)	2605 (71.1%)
BLACK OR AFRICAN AMERICAN	113 (3.1%)	145 (4.0%)
ASIAN	715 (19.4%)	739 (20.2%)
AMERICAN INDIAN OR ALASKA NATIVE	73 (2.0%)	70 (1.9%)
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	17 (0.5%)	14 (0.4%)
NOT REPORTED	9 (0.2%)	7 (0.2%)
MULTIPLE	87 (2.4%)	86 (2.3%)
Ethnicity		
NOT HISPANIC OR LATINO	3058 (83.0%)	3057 (83.4%)
HISPANIC OR LATINO	618 (16.8%)	603 (16.4%)
NOT REPORTED	10 (0.3%)	6 (0.2%)
Region		
Europe	1754 (47.6%)	1750 (47.7%)
North America	559 (15.2%)	548 (14.9%)
Asia	810 (22.0%)	815 (22.2%)
Latin America	424 (11.5%)	417 (11.4%)
Others	139 (3.8%)	136 (3.7%)
Age (years)		
n	3686	3666
Mean (SD)	64.13 (9.67)	64.13 (10.00)
Median	65.00	65.00
Q1, Q3	58.00, 71.00	58.00, 71.00
Age group (years) category		
18 - 44 years	127 (3.4%)	123 (3.4%)
45 - 64 years	1626 (44.1%)	1634 (44.6%)
65 - 74 years	1438 (39.0%)	1383 (37.7%)
≥ 75 years	495 (13.4%)	526 (14.3%)
Baseline BMI (kg/m^2)		
n	3675	3659
Mean (SD)	31.46 (6.04)	31.40 (5.93)
Median	30.70	30.60
Q1, Q3	27.30, 34.70	27.10, 34.80
Baseline BMI (kg/m^2) category, missing	11 (0.3%)	7 (0.2%)
< 20 kg/m^2	26 (0.7%)	26 (0.7%)
≥ 20 - < 25 kg/m^2	400 (10.9%)	406 (11.1%)
≥ 25 - < 30 kg/m^2	1202 (32.6%)	1217 (33.2%)
≥ 30 - < 35 kg/m^2	1160 (31.5%)	1130 (30.8%)
≥ 35 kg/m^2	887 (24.1%)	880 (24.0%)
Baseline waist-hip ratio		
n	3668	3652
Mean (SD)	1.00 (0.11)	1.00 (0.11)
Median	0.99	0.99
Q1, Q3	0.94, 1.05	0.94, 1.04
Smoking History		
Never	1760 (47.7%)	1684 (45.9%)
Former	1275 (34.6%)	1346 (36.7%)
Current	651 (17.7%)	636 (17.3%)
Alcohol Use, missing	3 (<0.1%)	0
Abstinent	2197 (59.6%)	2134 (58.2%)
Light	1253 (34.0%)	1278 (34.9%)
Moderate	216 (5.9%)	239 (6.5%)
Heavy	17 (0.5%)	15 (0.4%)

Race "Multiple": Subjects who reported that they belong to more than one race. Region "Others": New Zealand, South Africa, Australia
BMI = body mass index, FAS = full analysis set, N = number of subjects, n = number of subjects in category, Q = quartile, SD = standard deviation
Source: Module 5.3.5.1, PH-39747, Table 14.1.2/1

Table 12. Baseline characteristics (FAS, FIGARO-DKD)

	Finerenone N=3686 (100%)	Placebo N=3666 (100%)
Baseline serum potassium (mmol/L)		
n	3686	3664
Arithm.Mean (Arithm.SD)	4.33 (0.43)	4.33 (0.43)
Median	4.30	4.30
Q1, Q3	4.10, 4.60	4.10, 4.60
Baseline serum potassium (mmol/L) category		
Missing	0	2 (<0.1%)
≤4.5 mmol/L	2643 (71.7%)	2612 (71.2%)
>4.5 mmol/L	1043 (28.3%)	1052 (28.7%)
Baseline serum potassium (mmol/L) category		
Missing	0	2 (<0.1%)
≤4.8 mmol/L	3295 (89.4%)	3288 (89.7%)
>4.8 to 5.0 mmol/L	223 (6.0%)	204 (5.6%)
>5.0 mmol/L	168 (4.6%)	172 (4.7%)
Baseline systolic blood pressure (mmHg)		
n	3686	3666
Arithm.Mean (Arithm.SD)	135.81 (13.96)	135.70 (14.06)
Median	135.67	136.00
Q1, Q3	126.67, 145.33	126.33, 145.67
Baseline systolic blood pressure (mmHg) category		
<130 mmHg	1187 (32.2%)	1197 (32.7%)
≥130 -<160 mmHg	2392 (64.9%)	2355 (64.2%)
≥160 mmHg	107 (2.9%)	114 (3.1%)
Baseline eGFR (mL/min/1.73 m^2)		
n	3686	3665
Arithm. Mean (Arithm.SD)	67.62 (21.65)	67.99 (21.74)
Median	67.35	67.80
Q1, Q3	50.40, 84.60	51.00, 84.60
Baseline eGFR (mL/min/1.73 m^2) category		
Missing	0	1 (<0.1%)
<25 mL/min/1.73 m^2	15 (0.4%)	12 (0.3%)
25 - <45 mL/min/1.73 m^2	641 (17.4%)	610 (16.6%)
45 -<60 mL/min/1.73 m^2	745 (20.2%)	789 (21.5%)
≥60 mL/min/1.73 m^2	2285 (62.0%)	2254 (61.5%)
Baseline albuminuria (mg/g) category		
missing	0	2 (<0.1%)
Normalbuminuria (UACR <30 mg/g)	109 (3.0%)	98 (2.7%)
High albuminuria (≥30 - <300 mg/g)	1726 (46.8%)	1688 (46.0%)
Very high albuminuria (≥300 mg/g)	1851 (50.2%)	1878 (51.2%)
Baseline UACR (mg/g)		
n	3686	3664
Geom.Mean (Geom.SD)	284.33 (3.58)	288.87 (3.53)
Median	302.36	315.06
Q1, Q3	105.47, 749.05	111.24, 731.01
UACR at baseline (below median and above median in the FAS)		
Missing	0	2 (<0.1%)
≤308.2mg/g (median in FAS)	1861 (50.5%)	1814 (49.5%)
>308.2mg/g (median in FAS)	1825 (49.5%)	1850 (50.5%)
Baseline Hemoglobin A1c (%)		
n	3681	3660
Arithm.Mean (Arithm.SD)	7.74 (1.39)	7.69 (1.35)
Median	7.50	7.50
Q1, Q3	6.70, 8.60	6.70, 8.50
Use of the following at baseline:		
ARB	2108 (57.2%)	2104 (57.4%)
ACEI	1576 (42.8%)	1561 (42.6%)
Beta-blocker	1774 (48.1%)	1762 (48.1%)
Diuretic	1748 (47.4%)	1748 (47.7%)
Statin	2552 (69.2%)	2632 (71.8%)
Anti-diabetic treatment	3607 (97.9%)	3589 (97.9%)
Insulins and analogues	2023 (54.9%)	1970 (53.7%)
Dipeptidyl peptidase 4 inhibitors	896 (24.3%)	860 (23.5%)
GLP-1 agonists	308 (8.4%)	242 (6.6%)
SGLT-2 inhibitors use	314 (8.5%)	304 (8.3%)
Biguanides	2561 (69.5%)	2506 (68.4%)
Sulfonamides	1037 (28.1%)	1025 (28.0%)
Alpha glucosidase inhibitors	160 (4.3%)	172 (4.7%)
Meglitinides	105 (2.8%)	103 (2.8%)
Thiazolidinediones	144 (3.9%)	144 (3.9%)
Potassium supplement	111 (3.0%)	104 (2.8%)
Potassium lowering agent (including binders)	24 (0.7%)	22 (0.6%)
History of CV disease, present	1676 (45.5%)	1654 (45.1%)
Duration of diabetes (in years)		
n	3682	3663
Arithm. Mean (Arithm. SD)	14.53 (8.60)	14.44 (8.44)
Median	13.18	13.90
Q1, Q3	8.14, 20.11	8.15, 19.27

ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker, Arithm = arithmetic, CV = cardiovascular, eGFR = estimated glomerular filtration rate, FAS = full analysis set, Geom = geometric, GLP-1 agonist = glucagon-like peptide-1 receptor agonist, N = number of subjects, n = number of subjects in category, Q = quartile, SD = standard deviation, SGLT-2 = sodium-glucose co-transporter-2, UACR = urinary albumin-to-creatinine ratio
Source: Module 5.3.5.1, PH-39747, Table 14.1.4/1

Table 13. Medical history findings of interest (FAS, FIGARO-DKD).

	Finerenone N =3686 (100%)	Placebo N= 3666 (100%)
Type 2 diabetes mellitus [a]	3686 (100.0%)	3666 (100.0%)
Chronic kidney disease [a]	3686 (100.0%)	3666 (100.0%)
Hypertension [b]	3544 (96.1%)	3517 (95.9%)
Hyperlipidemia [b]	1515 (41.1%)	1550 (42.3%)
Diabetic retinopathy [a]	1193 (32.4%)	1098 (30.0%)
Coronary artery disease [a]	1148 (31.1%)	1147 (31.3%)
Diabetic neuropathy [c]	1046 (28.4%)	990 (27.0%)
Myocardial infarction [a]	640 (17.4%)	616 (16.8%)
Peripheral arterial occlusive disease [a]	587 (15.9%)	575 (15.7%)
Ischaemic stroke [a]	442 (12.0%)	425 (11.6%)
Atrial fibrillation and atrial flutter [c]	328 (8.9%)	317 (8.6%)
Cardiac failure [b]	290 (7.9%)	281 (7.7%)
Percutaneous coronary intervention [c]	217 (5.9%)	198 (5.4%)
Coronary artery bypass graft [c]	207 (5.6%)	199 (5.4%)
Periodontal disease [a]	195 (5.3%)	174 (4.7%)
Carotid endarterectomy [a]	43 (1.2%)	50 (1.4%)

a selected MedDRA preferred terms
b Bayer MedDRA Labeling Groupings
c Product-specific Bayer MedDRA queries
FAS = full analysis set, MedDRA = Medical Dictionary for Regulatory Activities, N = number of subjects
Source: Module 5.3.5.1, PH-39747, Table 14.1.6/5, Table 14.1.6/9, Table 14.1.6/13

Table 14. New concomitant medication of interest (FAS, FIGARO-DKD).

	Finerenone 3686 (100%)	Placebo 3666 (100%)
Number (%) of subjects with at least one new non anti-diabetic concomitant medication of interest	2796 (75.9%)	2834 (77.3%)
ACEI	531 (14.4%)	567 (15.5%)
ARB	850 (23.1%)	889 (24.2%)
RAS-inhibitors	1257 (34.1%)	1312 (35.8%)
Beta-blocker	895 (24.3%)	920 (25.1%)
Diuretics	1243 (33.7%)	1325 (36.1%)
Loop diuretics	783 (21.2%)	866 (23.6%)
Thiazide diuretics	363 (9.8%)	423 (11.5%)
Potassium supplements	245 (6.6%)	298 (8.1%)
Potassium lowering agents (including binders)	167 (4.5%)	101 (2.8%)
Alpha blocking agents	895 (24.3%)	926 (25.3%)
Calcium channel blockers	1015 (27.5%)	1132 (30.9%)
Centrally acting antihypertensives	159 (4.3%)	187 (5.1%)
CYP3A4 inhibitors		
Strong	186 (5.0%)	186 (5.1%)
Moderate	497 (13.5%)	497 (13.6%)
Weak	1339 (36.3%)	1355 (37.0%)
Unclassified	166 (4.5%)	171 (4.7%)
CYP3A4 inducers		
Strong	48 (1.3%)	50 (1.4%)
Moderate	269 (7.3%)	275 (7.5%)
Weak	245 (6.6%)	240 (6.5%)
Unclassified	146 (4.0%)	138 (3.8%)
Oral anticoagulants	324 (8.8%)	322 (8.8%)
Acetylsalicylic acid and its salts	572 (15.5%)	582 (15.9%)
Statins	1058 (28.7%)	1010 (27.6%)
Erythropoeitin stimulating agents	58 (1.6%)	53 (1.4%)
NSAIDs (excluding acetylsalicylic acid)	1125 (30.5%)	1106 (30.2%)
ARNIs	7 (0.2%)	6 (0.2%)
Potassium-sparing diuretics	199 (5.4%)	225 (6.1%)
Platelet aggregation inhibitors (excluding heparin)	858 (23.3%)	846 (23.1%)
Trimethoprim and derivatives	114 (3.1%)	108 (2.9%)
Number (%) of subjects with at least one new anti-diabetic medication of interest	2259 (61.3%)	2302 (62.8%)
Insulins and analogues	1527 (41.4%)	1509 (41.2%)
Dipeptidyl peptidase 4 inhibitors	603 (16.4%)	570 (15.5%)
Glucagon-like peptide-1 agonists	419 (11.4%)	413 (11.3%)
SGLT-2 inhibitors	580 (15.7%)	578 (15.8%)
Biguanides	969 (26.3%)	944 (25.8%)
Sulfonylureas	479 (13.0%)	480 (13.1%)
Alpha glucosidase inhibitors	137 (3.7%)	123 (3.4%)
Meglitinides	100 (2.7%)	95 (2.6%)
Thiazolidinediones	118 (3.2%)	115 (3.1%)

Medications that began after the start of study drug, and those that were started after end of study drug, are included in this table. Multiple drug groups per drug are possible. Therefore, the same drug may be counted in more than one category for the same subject.
ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker, ARNIs = angiotensin receptor neprilysin inhibitors, CYP3A4 = cytochrome P450 isoenzyme 3A4, FAS = full analysis set, NSAIDs =non-steroidal anti-inflammatory drug, RAS = renin angiotensin system, SGLT-2 = sodium-glucose co-transporter-2
Source: Module 5.3.5.1, PH-39747, Table 14.1.7/15, Table 14.1.7/17

Baseline characteristics were similar in the two treatment arms and was comparable to the previous FIDELIO-DKD study, except that mean eGFR was higher and UACR lower in the present study due to different inclusion criteria. Also, the occurrence of diabetic retinopathy was less frequent in the present study compared to the FIDELIO-DKD (App. 30% compared to 45%). Almost all patients had hypertension. Approximately 40% of patients had hyperlipidaemia, 30% coronary artery disease and 30% diabetic neuropathy. Although inclusion of patients with HbA1c up to 12% was allowed, mean values were app. 7.7% in both groups. Unlike the FIDELIO-DKD study, the FIGARO trial included patients with Stage 1 and 2 (i.e. eGFR≥60 ml/min/m^2) that constituted the prevailing subgroup (around 60% of the

total population), while Stage 3 and 4 (i.e. eGFR<60ml/min/m^2) were also included but contributed to 40% of the total population. According to the inclusion criteria, patients with eGFR ≥60 were required to have “very high albuminuria” (UACR ≥300 mg/g), while “high albuminuria” (UACR 30-300 mg/g) was required for the lower eGFR ranges (i.e. Stage 3 and 4).

The number of participants with previous medical history of cardiac failure was 7.9% vs. 7.7% in the finerenone and placebo groups. The applicant was requested to provide details on the degree of heart failure for these patients. Also, given that the study was amended to allow inclusion of patients with a recent CVD episode, data on number of patients with hospitalization for worsening heart failure in the last 30 days prior to the Screening visit should be provided. The applicant clarified that the FIGARO-DKD study excluded patients with HFrEF with symptomatic heart failure (NYHA II-IV) whereas patients with HFpEF and patients with mid-range EF could be enrolled. No further information appears to be available on these patients and the issue is not further pursued. In addition, the study was amended to include patients with a recent CVD episode. Only a very small and balanced number of patients had a medical history of HF within days prior to the screening visit (4 and 5 subjects, respectively, in the finerenone and the placebo group).

Approximately 45% of participants were from Europe, ~70% were White, ~20% Asian and ~4% Black.

All patients were on either ARB or ACEI. In addition, ~50% of patients received beta-blockers and diuretics and ~70% statins. 98% of patients were treated with anti-diabetic agents, ~8% of patients received SGLT2 inhibitors. Slightly more patients received GLP-1 agonists in the finerenone arm compared to placebo at baseline (8.4% vs. 6.6%).

Among new concomitant medications during the study, slightly lower numbers are noted for diuretics and blood pressure lowering agents in the finerenone group than placebo, which may be expected given the mechanism of action for finerenone. For other medications, similar numbers are noted.

Compliance and titration

With mean values of 91.478% (finerenone) and 92.883% (placebo), treatment compliance was high in both treatment arms (Table 14.1.8/34). Compliance values of 80% to 120% were achieved by 87.6% of all FAS subjects in the finerenone arm and 89.8% subjects in the placebo arm.

The mean average daily dose was 17.514 mg (SD 3.751 mg) in the finerenone arm and 18.156 mg (SD 3.203 mg) in the placebo arm (*Table 15*). The mean average daily doses by eGFR category at screening were similar between the finerenone and placebo arms. The extent of exposure increases with higher eGFR at screening, with the subgroup of subjects with eGFR ≥60 mL/min/1.73m^2 at screening reporting the highest exposure in both treatment arms.

Table 15. Extent of exposure (SAF).

		Finerenone N= 3683 (100%)	Placebo N= 3658 (100%)
Extent of exposure (overall, mg)			
n		3682[a]	3658
Mean (SD)		19115.554 (9265.921)	19874.882 (9091.498)
Median		19165.000	20090.000
Min-Max		20.00-69520.00	10.00-37360.00
Mean daily dose (mg)			
n		3682[a]	3658
Mean (SD)		17.514 (3.751)	18.156 (3.203)
Median		19.665	19.775
Min-Max		0.80-39.98	1.93-22.86
Mean daily dose (mg) by eGFR category at screening			
eGFR 25 -<45 mL/min/1.73m^2	n	637	627
	Mean (SD)	14.793 (4.399)	15.950 (4.234)
	Median	15.977	18.029
	Min-Max	0.80-19.86	2.87-22.86
eGFR 45 -<60 mL/min/1.73m^2	n	720	729
	Mean (SD)	15.968 (4.230)	17.159 (3.594)
	Median	18.055	18.867
	Min-Max	3.99-20.64	2.87-21.40
eGFR ≥60mL/min/1.73m^2	n	2325	2302
	Mean (SD)	18.737 (2.680)	19.073 (2.205)
	Median	20.000	20.000
	Min-Max	3.04-39.98	1.93-20.40

eGFR = estimated glomerular filtration rate, Max = maximum, Min = minimum, N = number of subjects in the SAF, n = number of subjects in category, SAF = safety analysis set, SD = standard deviation

a For 1 subject (Subject 17530141267050) only 1 period of 20 mg exposure is recorded, with no end date on study drug intake. Thus, exposure could not be calculated for this subject (Listing 16.2.5/4)

Source: Table 14.1.8/27, Table 14.1.8/30, Table 14.1.8/33

Table 16 summarizes the titration status by starting dose, the overall reasons for not dispensing the 20 mg dose, and the overall reasons for down-titration or temporary interruption of study drug for the SAF.

In total, 1371 subjects (37.2%, calculated manually) in the finerenone arm and 1366 subjects 37.3%, calculated manually) in the placebo arm started study drug at 10 mg OD. 2312 subjects (62.8%, calculated manually) in the finerenone arm and 2292 subjects (62.7%, calculated manually) in the placebo arm started study drug at 20 mg OD.

On Day 1, approximately 60% of all subjects in both treatment arms started on the 20 mg dose. By Month 1, 70% of subjects were on the 20 mg dose. Starting with Month 4, approximately 80% or more of the subjects were on the 20 mg dose, which was stable for the entire course of the study thereafter. From Month 4 onwards a higher proportion of subjects in the placebo arm were on the 20 mg dose than in the finerenone arm (approximate difference of 5%). Only a very low number of subjects interrupted treatment (i.e., 0 mg) at any time during the study (approximately 2-3% both treatment arms).

Overall, more subjects in the finerenone arm (50.9%) compared with the placebo arm (46.4%) were not dispensed the 20 mg dose in at least 1 visit. The most frequently reported reason for not dispensing the 20 mg dose was ”other” (31.6% in finerenone, 29.2% in placebo), followed by local potassium >4.8 mmol/L (23.7% in finerenone, 15.5% in placebo). Down titration to 10 mg study drug (4.8% in finerenone, 3.4% in placebo) and study drug interrupted (10.2% in finerenone, 8.8% in placebo) were more common in the finerenone arm than in the placebo arm. An eGFR decrease ≥30% since the previous visit, symptomatic hypotension and other adverse or outcome event as reasons not to dispense the 20 mg dose were balanced between finerenone and placebo.

Table 16. Titration status (SAF).

		Finerenone (N=3683)	Placebo (N=3658)
Titration status by starting dose [a,b]		**3683 (100%)**	**3658 (100%)**
Starting dose	Titration Status		
10 mg	n	1371 (100.0%)	1366 (100.0%)
	Never up-titrated	311 (22.7%)	211 (15.4%)
	Up-titrated once	760 (55.4%)	835 (61.1%)
	Up-titrated more than once	300 (21.9%)	320 (23.4%)
	Up-titrated at least once	1060 (77.3%)	1155 (84.6%)
20 mg	n	2312 (100.0%)	2292 (100.0%)
	Never down-titrated	1189 (51.4%)	1242 (54.2%)
	Down-titrated once	854 (36.9%)	796 (34.7%)
	Down-titrated more than once	269 (11.6%)	254 (11.1%)
	Down-titrated at least once	1123 (48.6%)	1050 (45.8%)
Subjects with main reasons for not dispensing finerenone 20 mg OD – overall [c]		**3683 (100%)**	**3658 (100%)**
Number of subjects not dispensed with finerenone 20 mg		1874 (50.9%)	1699 (46.4%)
Local potassium > 4.8 mmol/l		874 (23.7%)	567 (15.5%)
Symptomatic hypotension		44 (1.2%)	25 (0.7%)
Other adverse event / outcome event		161 (4.4%)	149 (4.1%)
Down-titrated to 10 mg study drug		176 (4.8%)	125 (3.4%)
Study drug interrupted		376 (10.2%)	321 (8.8%)
Restarted with lower study drug dose		384 (10.4%)	333 (9.1%)
Site error		35 (1.0%)	55 (1.5%)
Other		1162 (31.6%)	1069 (29.2%)
eGFR decrease ≥ 30% since previous Visit		120 3.3%)	99 (2.7%)
Number of subjects with main reason for down-titration or temporary interruption of study drug [d]		**3683 (100%)**	**3658 (100%)**
Resulting dose	Main reason if study drug is down-titrated or temporarily interrupted		
10 mg [e]	Number of subjects ever down-titrated	280 (7.6%)	251 (6.9%)
	Blood potassium level	62 (1.7%)	47 (1.3%)
	Change in eGFR level	88 (2.4%)	61 (1.7%)
	Low blood pressure	4 (0.1%)	6 (0.2%)
	Adverse Event / Outcome Event	69 (1.9%)	66 (1.8%)
	Other safety concerns	32 (0.9%)	22 (0.6%)
	Other reason (non-safety related)	37 (1.0%)	62 (1.7%)
	Logistical reason: COVID-19 pandemic related	0	1 (<0.1%)
0 mg [e]	Number of subjects ever down-titrated	1853 (50.3%)	1735 (47.4%)
	Blood potassium level	456 (12.4%)	244 (6.7%)
	Change in eGFR level	51 (1.4%)	55 (1.5%)
	Clinical condition of subject	1 (<0.1%)	1 (<0.1%)
	Low blood pressure	2 (<0.1%)	0
	Adverse event / outcome event	844 (22.9%)	780 (21.3%)
	Other safety concerns	108 (2.9%)	109 (3.0%)
	Other reason (non-safety related)	536 (14.6%)	538 (14.7%)
	Subject decision: COVID-19 pandemic related	88 (2.4%)	102 (2.8%)
	Physician decision: COVID-19 pandemic related	36 1.0%)	42 (1.1%)
	Logistical reason: COVID-19 pandemic related	339 (9.2%)	332 (9.1%)

The titration status includes sham titration.

a The overall summary (never up-titrated or never down-titrated) includes subjects discontinued which have not reached the respective visits.

b Up-titration = Yes, if local potassium value ≤4.8 mmol/L at the respective visit and eGFR decrease (local laboratory value) is less than 30% below the value measured at the last regular visit.

c The number of subjects not dispensed with 20 mg overall are the number of subjects not treated with 20 mg in at least 1 visit. One subject can have different reasons for not up-titrating to 20 mg and can thus be counted under different reasons.

d A subject could be down-titrated more than once or have a temporary interruption more than once during the study. In case of multiple down-titrations or interruptions for the same subject, it is possible that the subject had different reasons on the multiple occasions so that the subject was counted under each reason.

e Dose resulting from down-titration or study drug interruption.

COVID-19 = coronavirus disease 2019, eGFR = estimated glomerular filtration rate, N = number of subjects in the SAF, n = number of subjects in category, OD = once daily, SAF = safety analysis set

Source: Table 14.1.8/39, Table 14.1.8/45, 14.1.8/48

The CHMP concluded that the compliance was high and similar (~92%) in both study groups. Approximately 60% of patients in both groups started at the 20 mg dose and after month 4, approximately 80% of patients were on the 20 mg dose. Of patients starting with the 10 mg dose, slightly more patients in the finerenone group than in the placebo group were never up-titrated (22.7% vs. 15.4%). A serum potassium level exceeding 4.8 mmol/L was an important reason for not up-titrating (23.7% vs. 15.5% in finerenone vs. placebo) and also an important reason for temporary interruptions of the study drug (12.4% vs. 6.7%).

Numbers analysed

Table 17. Analysis sets (all randomized subjects) in FIGARO-DKD.

Validity finding category	Finerenone[a] 3723 (100%)	Placebo[a] 3714 (100%)
Subjects valid for FAS[a]	**3686 (99.0%)**	**3666 (98.7%)**
Excluded from FAS	37 (1.0%)	48 (1.3%)
V8.2 Exclude subject from all analysis datasets on account of critical GCP and protocol violations, causing unreliable data.	37 (1.0%)	48 (1.3%)
Subjects valid for SAF[a]	**3682 (98.9%)**	**3659 (98.5%)**
Excluded from safety analysis	41 (1.1%)	55 (1.5%)
V7.1 Subject was randomized but never received any study medication	4 (0.1%)	7 (0.2%)
Subjects valid for per protocol analysis	**3157 (84.8%)**	**3199 (86.1%)**
Excluded from per protocol analysis [a]	566 (15.2%)	515 (13.9%)
V1.4 Subject with no clinical diagnosis of DKD (no persistent high/very high albuminuria at run-in or screening visit (UACR<30mg/g (3.4 mg/mmol).	10 (0.3%)	9 (0.2%)
V1.5 Subject with clinical diagnosis of DKD and persistent high albuminuria, but eGFR < 25 mL/min/1.73 m^2 or > 90 mL/min/1.73 m^2 or missing at run-in or screening visit.	8 (0.2%)	10 (0.3%)
V1.6 Subject with clinical diagnosis of DKD and persistent very high albuminuria, but eGFR < 60 mL/min/1.73 m^2 or missing at run-in or screening visit.	53 (1.4%)	52 (1.4%)
V1.10 UACR >5000 mg/g (565 mg/mmol) or missing in any of the urinary first morning void samples at the run-in visit or screening visit.	6 (0.2%)	9 (0.2%)
V1.12 Subject was not treated with any ACE inhibitor or ARB starting from run-in visit.	2 (<0.1%)	0
V1.13 Participation in another clinical study or treatment with another investigational product 30 days prior to randomization (except for the run-in and screening of the Study 16244.)	2 (<0.1%)	1 (<0.1%)
V1.15 Known significant non-diabetic renal disease, including clinically relevant renal artery stenosis.	0	1 (<0.1%)
V2.1 Subject should have been withdrawn but was not (investigational drug other than the study drug is used).	4 (0.1%)	4 (0.1%)
V3.1 An ACE inhibitor and an ARB OR more than 1 ACE inhibitor OR more than 1 ARB were used in combination during study drug treatment for more than 30 days.	14 (0.4%)	13 (0.4%)
V3.2 Eplerenone, spironolactone, any renin inhibitor, or potassium sparing diuretic were used during study drug treatment for more than 30 days.	35 (0.9%)	48 (1.3%)
V3.2 Eplerenone, spironolactone, any renin inhibitor, or potassium sparing diuretic were used during study drug treatment for more than 30 days.	35 (0.9%)	48 (1.3%)
V3.3 Potent CYP3A4 inducers were taken for more than 30 days during study drug treatment.	18 (0.5%)	23 (0.6%)
V4.1 Wrong study medication (incorrect treatment (placebo vs. verum) was dispensed to subject.	9 (0.2%)	17 (0.5%)
V5.1 The subject is not compliant (<80%).	389 (10.4%)	291 (7.8%)
V5.2 The subject is not compliant (>120%).	1 (<0.1%)	4 (0.1%)
Subjects valid for pharmacokinetics	**3417 (91.8%)**	**0**
Excluded from pharmacokinetics	306 (8.2%)	3714 (100.0%)
V9.1 None of the PK samples available for a subject assigned to Finerenone is valid.	275 (7.4%)	3714 (100.0%)

a One subject was randomized to placebo but received finerenone treatment during the entire course of the study (Subject 17530200447001, Listings 16.2.2/1 and 16.2.2/2). Thus, 3683 were treated with finerenone and 3658 received placebo.

ACE = angiotensin-converting enzyme, ARB = angiotensin receptor blocker, CYP = cytochrome P450, DKD = diabetic kidney disease, eGFR = estimated glomerular filtration rate, FAS = full analysis set, GCP = good clinical practice, PK = pharmacokinetics, SAF = safety analysis set, UACR = urinary albumin-to-creatinine ratio

Source: Table 14.1.1/7, Table 14.1.1/22

The primary efficacy analysis was based on the full analysis set (all randomized subjects without critical GCP violations) that encompassed 99.0% and 98.7% of patients in the finerenone and placebo groups, respectively. For the per protocol analysis, 84.8 and 86.1% of the patients were included. Non-compliance was the main reason for exclusion from the per protocol analysis (10.4% and 7.8% in finerenone and placebo groups, respectively).

Outcomes and estimation

Primary and secondary efficacy endpoints were included in a hierarchical testing strategy to account for multiple testing (see previous sections). The primary CV composite endpoint showed a statistically significant result (*Table 18*), meeting the primary objective of the study to delay the time to first occurrence of CV mortality and morbidity. With a p-value of 0.0689, the secondary 40% renal composite endpoint did however not meet the pre-planned criterion for significance (*Table 18*). Therefore, the remaining secondary endpoints all-cause hospitalization, all-cause mortality, change of UACR from baseline to Month 4 and the 57% renal composite endpoint were not tested formally, but in an exploratory manner.

Table 18. Summary on treatment effect estimates and test decisions for primary and secondary efficacy endpoints (FAS, FIGARO-DKD)

	Comparison of Finerenone vs placebo			Pre-specified local significance level[a]	Statistical significance achieved
	Treatment effect		p-value		
Primary efficacy endpoint:					
CV composite endpoint of CV death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for heart failure	HR (95% CI)	0.87 (0.76; 0.98)	0.0264	0.04967388	Yes
Secondary efficacy endpoints					
40% renal composite endpoint of onset of kidney failure, sustained decrease of eGFR ≥40% from baseline over at least 4 weeks, or renal death	HR (95% CI)	0.87 (0.76; 1.01)	0.0689	0.04967388	No
All-cause hospitalization	HR (95% CI)	0.97 (0.90;1.04)	0.3558	Not applicable	-
All-cause mortality	HR (95% CI)	0.89 (0.77;1.04)	0.1337	Not applicable	-
Change in UACR from baseline to Month 4	Ratio of LS means (95% CI)	0.676 (0.650;0.704])	<0.0001	Not applicable	-
57% renal composite endpoint of onset of kidney failure, sustained decrease of eGFR ≥57% from baseline over at least 4 weeks, or renal death	HR (95% CI)	0.77 (0.60;0.99)	0.0406	Not applicable	-

p-value: For the endpoint "Change in UACR from baseline to Month 4", the p-value from ANCOVA F-test is presented. For all other endpoints, the two-sided p-value from logrank test is presented.
a A hierarchical testing procedure was used for the primary and secondary efficacy variables with each variable being tested at the adjusted two-sided significance level of 0.04967388.
ANCOVA = analysis of covariance, CI = confidence interval, CV = cardiovascular, eGFR = estimated glomerular filtration rate, FAS = full analysis set, HR = hazard ratio, LS = least squares, UACR = urinary albumin-to-creatinine ratio
Source: Module 5.3.5.1, PH-39747, Table 14.2.1/8, Table 14.2.2.1/8, Table 14.2.2.2/8, Table 14.2.2.3/7, Table 14.2.2.4/2, Table 14.2.2.5/8

Primary endpoint

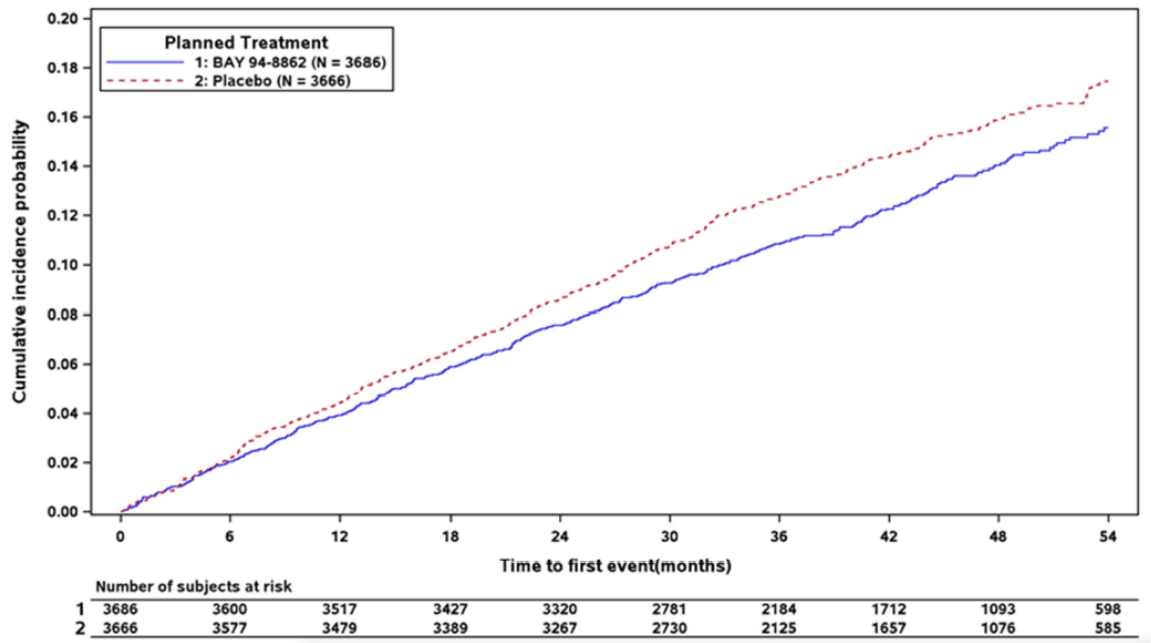
Treatment with finerenone reduced the risk of the primary CV composite endpoint of CV death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for heart failure when compared with placebo as shown by a HR of 0.87 (95% CI 0.76; 0.98, logrank test p=0.0264) (*Table 19*). The CV composite endpoint occurred in 458 subjects (12.4%) in the finerenone arm and 519 subjects (14.2%) in the placebo arm. The incidence rate for the CV composite endpoint was lower in the finerenone arm (3.87/100 patient-years) than in the placebo arm (4.45/100 patient-years).

Table 19. Summary of results for the adjudicated CV composite endpoint and its components (FAS, FIGARO-DKD)

	Finerenone N = 3686 n (%)	Placebo N = 3666 n (%)	Finerenone n/100 p-yrs (95% CI)	Placebo n/100 p-yrs (95% CI)	HR (95% CI)	p-value
CV composite	**458 (12.4%)**	**519 (14.2%)**	**3.87 (3.52;4.23)**	**4.45 (4.08;4.84)**	**0.87 [0.76; 0.98]**	**0.0264**
Components:						
CV death	194 (5.3%)	214 (5.8%)	1.56 (1.35; 1.79)	1.74 (1.52;1.98)	0.90 [0.74; 1.09]	0.2742
Non-fatal MI	103 (2.8%)	102 (2.8%)	0.85 (0.69; 1.02)	0.85 (0.69;1.02)	0.99 [0.76; 1.31]	0.9628
Non-fatal stroke	108 (2.9%)	111 (3.0%)	0.89 (0.73; 1.06)	0.92 (0.76;1.10)	0.97 [0.74; 1.26]	0.7932
Hospitalization due to heart failure	117 (3.2%)	163 (4.4%)	0.96 (0.80; 1.14)	1.36 (1.16;1.57)	0.71 [0.56; 0.90]	0.0043

Events were adjudicated by an independent adjudication committee and considered from randomization up until the end-of-study visit. For composite outcomes and each component, the first event after randomization is considered. Subsequent events of the same type are not shown.
The incidence rate is estimated as the number of subjects with incidence events divided by the cumulative at-risk time in the reference population, where a subject was no longer at risk once an incident event occurred.
p-value: two-sided p-value from logrank test, stratified
CI = confidence interval, CV = cardiovascular, CV composite = CV death, non-fatal MI, non-fatal stroke, or hospitalization for heart failure, FAS = full analysis set, HR = hazard ratio for the comparison of finerenone versus placebo, MI = myocardial infarction, N = number of subjects, n = number of subjects with event, n/100 p-yrs = incidence rate, p-yrs = patient years
Source: Module 5.3.5.1, Report PH-39747, Table 14.2.1/1, Table 14.2.1/8, Table 14.2.3.1/31, Table 14.2.3.1/34 to Table 14.2.3.1/36

Kaplan-Meier curves for finerenone and placebo diverge from Month 6 with a consistent course up until Month 42; thereafter the curves remain stable (*Figure 21*). The absolute risk reduction based on Kaplan-Meier cumulative incidences for the primary CV endpoint was 2.0% at Month 36 and 2.1% at Month 42, corresponding to NNTs to prevent one primary endpoint event of 51 and 47 subjects, respectively (*Table 20*).



CV = cardiovascular, CV composite endpoint = CV death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for heart failure, FAS = full analysis set, N = number of subjects
Source: Module 5.3.5.1, Report PH-39747, Figure 14.2.1/1

Figure 21. Kaplan-Meier curves for time to first occurrence of the CV composite endpoint (FAS, FIGARO-DKD)

Table 20. Kaplan-Meier cumulative incidence probability, risk difference and NNT by time point for the CV composite endpoint (FAS, FIGARO-DKD)

By time point	Cumulative incidence probability [95% CI]		Risk difference [95% CI]	NNT [a]
	Finerenone	Placebo	Finerenone minus Placebo	(95% CI)
At Month 12	0.039 [0.033;0.045]	0.044 [0.038;0.051]	-0.005 [-0.014;0.004]	194
At Month 18	0.059 [0.051;0.067]	0.065 [0.057;0.073]	-0.006 [-0.017;0.005]	164
At Month 24	0.076 [0.067;0.084]	0.086 [0.077;0.095]	-0.010 [-0.023;0.002]	97
At Month 30	0.093 [0.083;0.102]	0.108 [0.098;0.118]	-0.016 [-0.029;-0.002]	64 [33;614]
At Month 36	0.108 [0.098;0.119]	0.128 [0.117;0.139]	-0.020 [-0.035;-0.004]	51 [28;237]
At Month 42	0.123 [0.111;0.134]	0.144 [0.132;0.156]	-0.021 [-0.038;-0.004]	47 [26;226]
At Month 48	0.141 [0.128;0.153]	0.159 [0.145;0.172]	-0.018 [-0.037;0.000]	55

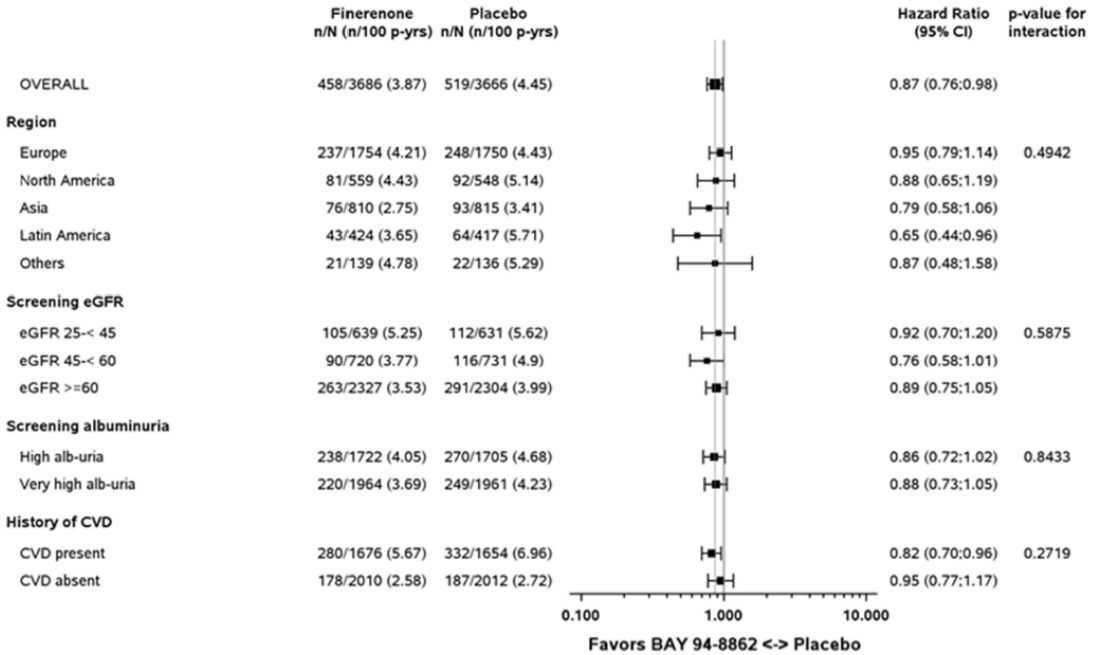
NNT = 1/(difference of Kaplan-Meier estimates), rounded to integer.
a CIs for NNT are only calculated if the CI for the difference of Kaplan-Meier estimates did not encompass zero.
CI = confidence interval, CV = cardiovascular, CV composite endpoint = CV death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for heart failure, FAS = full analysis set, NNT = number needed to treat
Source: Module 5.3.5.1, Report PH-39747, Table 14.2.1/3

Treatment with finerenone resulted in a 13% relative risk reduction compared with placebo for the CV composite endpoint of CV death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for heart failure (HR 0.87 [95% CI 0.76; 0.98]; p=0.0264). The primary endpoint of the study was thus met. The Kaplan-Meier curves did separate starting 6 months after treatment initiation, which indicates a sustained effect.

The effect is driven by hospitalizations due to heart failure (HR 0.71 [95% CI 0.56; 0.90]; p=0.0043). The components non-fatal stroke and non-fatal MI were unchanged by the treatment whereas CV death was numerically slightly lower in the finerenone compared to the placebo arm (194/3686 vs. 214/3666 cases; HR 0.90 [95% CI 0.74; 1.09]; p=ns).

Subgroup analyses of the primary endpoint

Forest plots for the results by the stratification factors region, eGFR at screening, UACR at screening and CV disease history are summarized in Figure 22. A forest plot of other key subgroups is summarized in Table 21. An additional forest plot of the primary CV endpoint by GFR subgroups according to KDIGO categories is provided in Figure 23. The point estimates of the HRs in the various subgroups were generally consistent with the result of the primary CV composite. No treatment interaction p-values <0.05 were observed.



Hazard ratios /95% CIs are based on stratified Cox proportional hazards models with treatment as fixed effect (primary analysis model) whereas interaction p-values (two-sided) are based on stratified Cox proportional hazards models including treatment, subgroup and a subgroup by treatment interaction term as fixed effects. The size of the square for the point estimate reflects the size of the (sub)group.
alb-uria = albuminuria, CI = confidence interval, CV(D) = cardiovascular (disease), eGFR = estimated glomerular filtration rate, FAS = full analysis set, N = number of subjects, n = number of subjects with event, p-yrs = patient-years
Source: Figure 14.2.4/1

Figure 22. Forest plot for the primary efficacy CV composite endpoint of CV death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for heart failure by stratification factors (FAS).

Table 21. Forest plot for the primary efficacy CV composite endpoint of CV death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for heart failure by key subgroups (FAS)

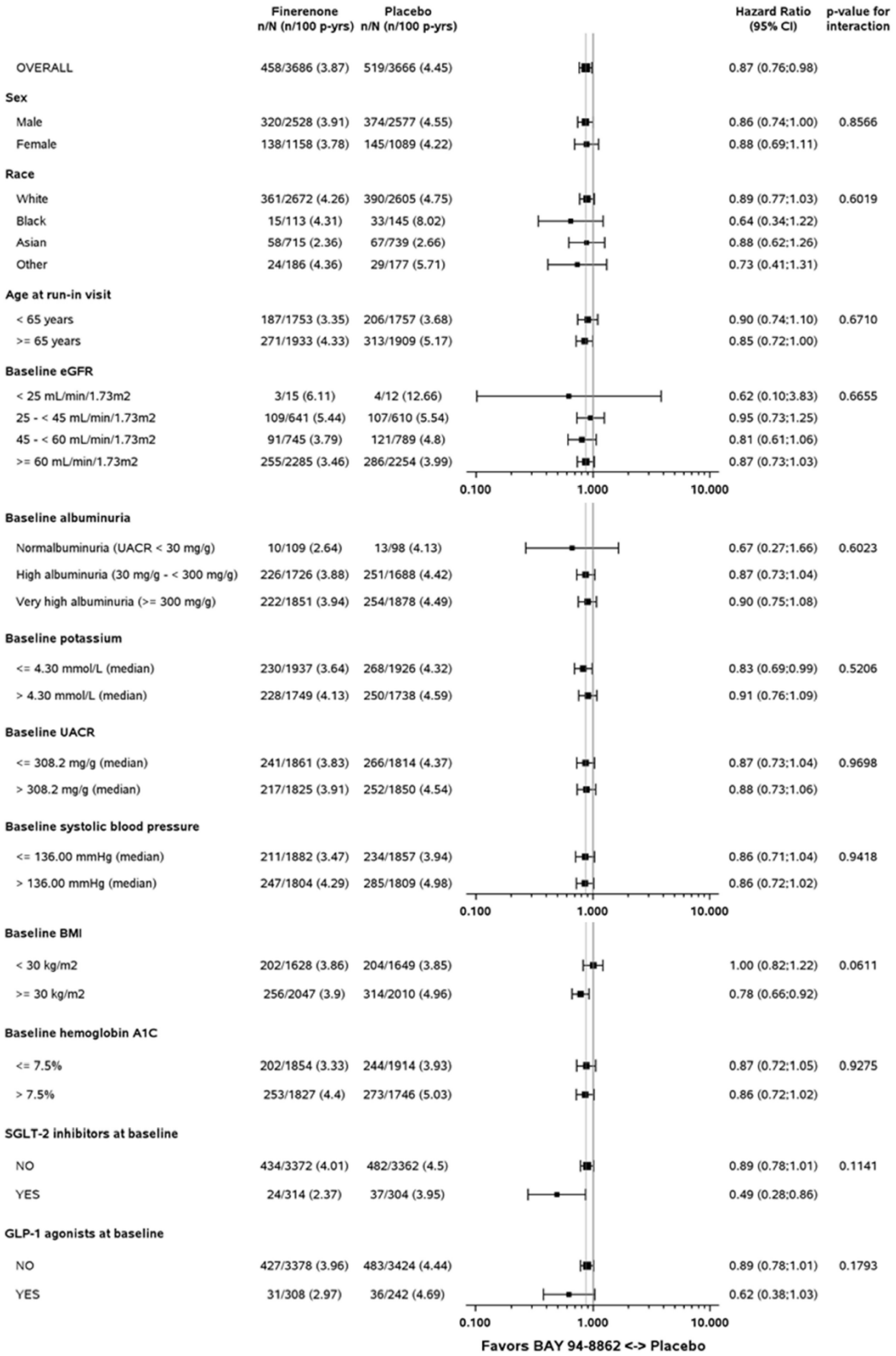
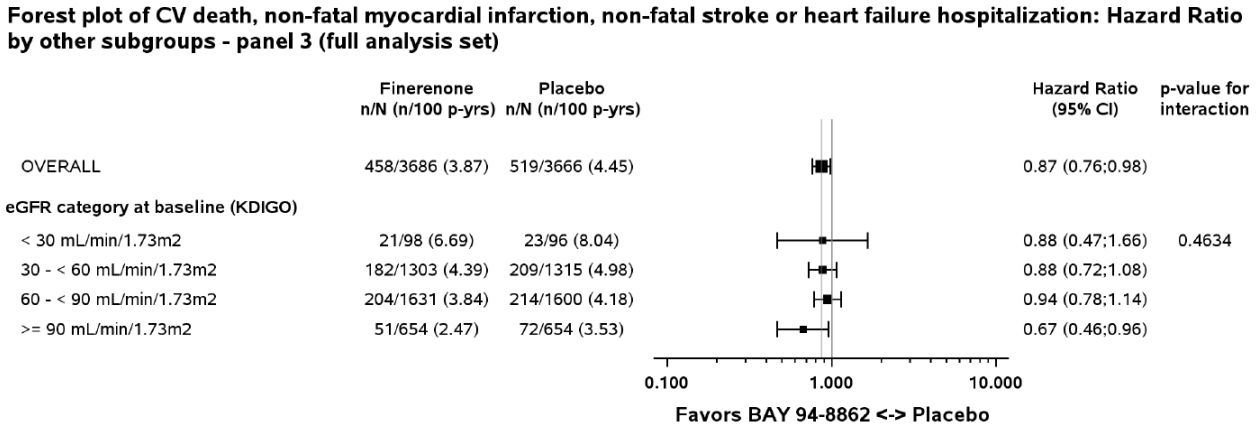


Figure 23. Forest plot for the primary efficacy CV composite endpoint of CV death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for heart failure by KDIGO eGFR category at baseline (FAS)



Hazard ratios (95% confidence interval) are based on the stratified Cox proportional hazards model with treatment as fixed effect (primary analysis model) whereas interaction p-values (two-sided) are based on the stratified Cox proportional hazards models including treatment, subgroup and a subgroup by treatment interaction term as fixed effects.

For the primary CV endpoint, the treatment effect appears in general consistent across subgroups, including eGFR categories, and there were no statistically significant interactions for the stratification factors or other key subgroups.

For the stratification factor region, the treatment effect however appears slightly less pronounced in Europe (HR=0.95) than in the other regions. However, in the previous FIDELIO-DKD study, the effect on this endpoint was comparable to that in other regions, indicating a that the present discrepancy is a chance finding. For the pooled analyses of the studies (see below) no differences between region were found.

For history of CVD, the effect appears less pronounced in those with an absent CVD history (HR=0.95 [95% CI 0.77;1.17] than those with CVD history present (HR=0.82 [95% CI 0.70; 0.96]). However, the baseline frequency for the primary endpoint is lower in individuals without CVD history making the point estimate less reliable. Furthermore, in the previous FIDELIO-DKD study, no difference between these subgroups was found for this endpoint.

The treatment effect appears reduced in subjects with low BMI (HR = 1 [95% CI 0.82; 1.22] vs HR = 0.78 [95% CI 0.66; 0.92]). The interaction was however not significant and in the previous FIDELIO-DKD study, there was instead a tendency for a more pronounced effect in these subjects.

Secondary endpoints

First secondary 40% renal composite

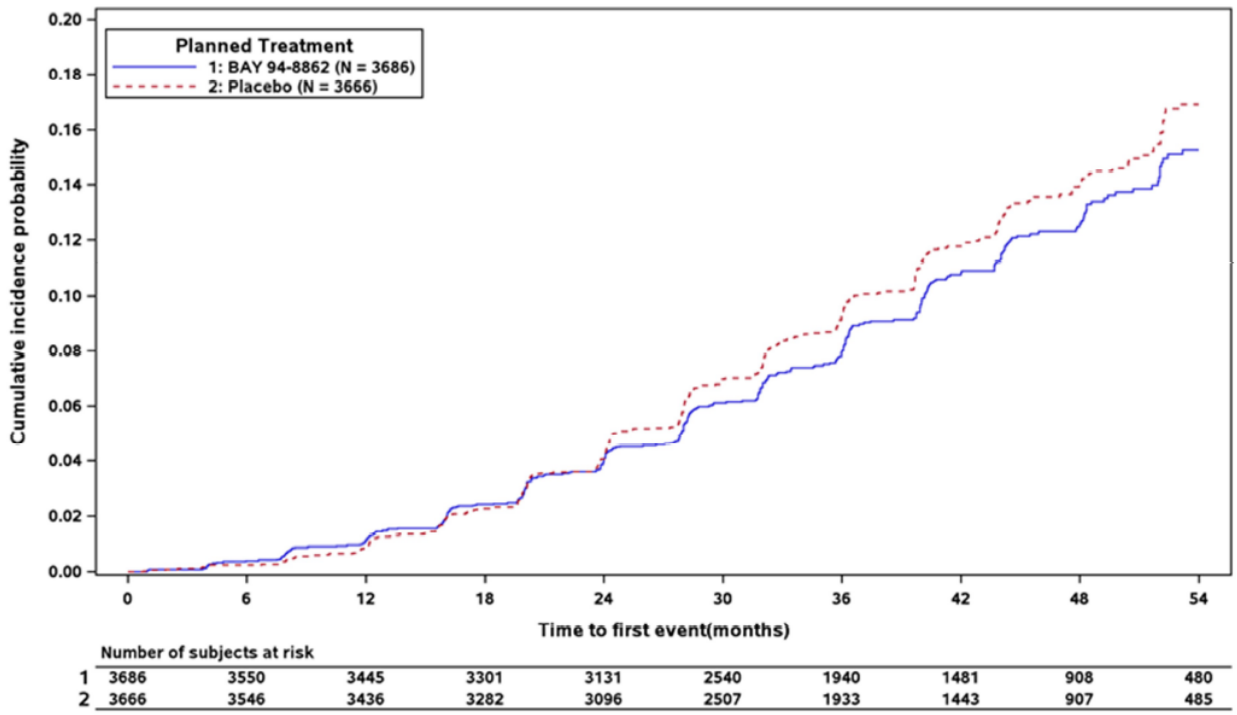
Treatment with finerenone led to a lower incidence rate for the secondary 40% renal composite endpoint when compared with placebo as shown by a HR of 0.87 (95% CI 0.76;1.01) (Table 22). The RRR of 13% in the 40% renal composite endpoint did not meet the pre-specified threshold for statistical significance (logrank test p=0.0689). Kaplan-Meier curves are provided in Figure 24.

The 40% renal composite endpoint occurred in 350 subjects (9.5%) in the finerenone arm and 395 subjects (10.8%) in the placebo arm. Incidence rates for the 40% renal composite endpoint were 3.15/100 patient-years in the finerenone arm and 3.58/100 patient years in the placebo arm.

Table 22. Summary of results for the adjudicated secondary 40% renal composite endpoint and its components (FAS)

	Finerenone N = 3686 n (%)	Placebo N = 3666 n (%)	Finerenone n/100 p-yrs (95% CI)	Placebo n/100 p-yrs (95% CI)	HR (95% CI)	p-value
Number of subjects with a 40% renal composite endpoint	**350 (9.5%)**	**395 (10.8%)**	**3.15 (2.83;3.49)**	**3.58 (3.23;3.94)**	**0.87 [0.76; 1.01]**	**0.0689**
Components:						
Kidney failure	46 (1.2%)	62 (1.7%)	0.40 (0.29;0.52)	0.54 (0.42;0.69)	0.72 [0.49; 1.05]	0.0889
ESRD	32 (0.9%)	49 (1.3%)	0.26 (0.18;0.36)	0.40 (0.30;0.52)	0.64 [0.41; 1.00]	0.0458
Sustained decrease in eGFR to <15 mL/min/1.73m^2	28 (0.8%)	38 (1.0%)	0.24 (0.16;0.34)	0.33 (0.24;0.45)	0.71 [0.43; 1.16]	0.1711
Sustained decrease in eGFR ≥40% (relative to baseline)	338 (9.2%)	385 (10.5%)	3.04 (2.73;3.38)	3.49 (3.15;3.84)	0.87 [0.75; 1.00]	0.0526
Renal death	0	2 (<0.1%)	-	-	-	-

Events were adjudicated by an independent adjudication committee and considered from randomization up until the end-of-study visit. Events based on a sustained decrease in eGFR are considered from randomization up until 5 months after the last eGFR was recorded at a clinic visit. For composite outcomes and each component, the first event after randomization is considered. Subsequent events of the same type are not shown.
The incidence rate is estimated as the number of subjects with incidence events divided by the cumulative at-risk time in the reference population, where a subject was no longer at risk once an incident event occurred.
Incidence rates, HRs and p-values were only calculated for pre-defined efficacy endpoints.
p-value: two-sided p-value from logrank test, stratified
CI = confidence interval, eGFR = estimated glomerular filtration rate, ESRD = end-stage renal disease, FAS = full analysis set, HR = hazard ratio for the comparison of finerenone versus placebo, N = number of subjects, n = number of subjects with event, n/100 p-yrs = incidence rate, p-yrs = patient years, 40% renal composite endpoint = onset of kidney failure, sustained decrease of eGFR ≥40% from baseline over at least 4 weeks, or renal death
Source: Table 14.2.2.1/1, Table 14.2.2.1/8, Table 14.2.3.1/26 to Table 14.2.3.1/29



eGFR = estimated glomerular filtration rate, FAS = full analysis set, 40% renal composite endpoint = kidney failure, sustained decrease of eGFR ≥40% from baseline over at least 4 weeks, or renal death, N = number of subjects
Source: Module 5.3.5.1, Report PH-39747, Figure 14.2.2.1/1

Figure 24. Kaplan-Meier curves for time to first occurrence of the secondary 40% renal composite endpoint (FAS, FIGARO-DKD)

Treatment with finerenone resulted in a 13% relative hazard reduction compared with placebo of the first secondary 40% renal composite endpoint (HR 0.87 [95% CI 0.76; 1.01] p=0.0689]) but the result did however not reach statistical significance. When analysing the components, directionally consistent changes in kidney failure and sustained decrease in eGFR ≥40% (relative to baseline) were observed. For renal death, too few cases occurred (2 in the placebo group) to draw any conclusions. The Kaplan-Meier curves did separate after 24 months and indicate a sustained effect after this timepoint.

In the previous FIDELIO-DKD study, a sustained effect was also noted, but with an earlier curve separation at 12 months.

Given that the secondary 40% renal composite endpoint did not meet the pre-planned criterion for significance, the remaining secondary endpoints were not tested formally, but in an exploratory manner.

All-cause hospitalization

For all-cause hospitalization, the comparison of finerenone with placebo showed a HR of 0.97 (95% CI 0.90;1.04, logrank test nominal p=0.3558) (*Table 23*). Statistical testing was performed in an exploratory manner. Further information on the components is presented in *Table 24*.

Table 23. Summary of results for adjudicated all-cause hospitalization (FAS, FIGARO-DKD).

	Finerenone N = 3686 n (%)	Placebo N = 3666 n (%)	Finerenone n/100 p-yrs (95% CI)	Placebo n/100 p-yrs (95% CI)	HR (95% CI)	p-value
All-cause hospitalization	**1573 (42.7%)**	**1605 (43.8%)**	**16.91 (16.09;17.76)**	**17.52 (16.68;18.39)**	**0.97 [0.90; 1.04]**	**0.3558**
Component[a]:						
CV hospitalization	689 (18.7%)	718 (19.6%)	6.15 (5.70; 6.62)	6.52 (6.05; 7.01)	0.94 [0.84; 1.04]	0.2290
Hospitalization due to heart failure	117 (3.2%)	163 (4.4%)	0.96 (0.80; 1.14)	1.36 (1.16; 1.57)	0.71 [0.56; 0.90]	0.0043

Events were adjudicated by an independent adjudication committee and considered from randomization up until the end-of-study visit. For composite outcomes and each component, the first event after randomization is considered. Subsequent events of the same type are not shown.
The incidence rate is estimated as the number of subjects with incidence events divided by the cumulative at-risk time in the reference population, where a subject was no longer at risk once an incident event occurred.
p-value: two-sided p-value from logrank test, stratified
a Results of the component "other hospitalization" is in Module 5.3.5.1, Report PH-39747, Table 14.2.2.2/1.
CI = confidence interval, CV = cardiovascular, FAS = full analysis set, HR = hazard ratio for the comparison of finerenone versus placebo, N = number of subjects, n = number of subjects with event, n/100 p-yrs = incidence rate, p-yrs = patient years
Source: Module 5.3.5.1, Report PH-39747, Table 14.2.2.2/1, Table 14.2.2.2/8, Table 14.2.3.1/33, Table 14.2.3.1/34

Table 24. Summary of results for adjudicated all-cause hospitalization (FAS, FIGARO-DKD)

	BAY 94-8862 n (%) N=3686 (100%)	BAY 94-8862 n/100 p-yrs (95% CI)	Placebo n (%) N=3666 (100%)	Placebo n/100 p-yrs (95% CI)
ALL-CAUSE HOSPITALIZATION	1573 (42.7%)	16.91 (16.09; 17.76)	1605 (43.8%)	17.52 (16.68; 18.39)
CARDIOVASCULAR HOSPITALIZATION	689 (18.7%)	6.15 (5.70; 6.62)	718 (19.6%)	6.52 (6.05; 7.01)
CARDIOVASCULAR DEATH	67 (1.8%)		74 (2.0%)	
NON-FATAL MYOCARDIAL INFARCTION	99 (2.7%)		92 (2.5%)	
NON-FATAL STROKE	102 (2.8%)		100 (2.7%)	
NEW ONSET ATRIAL FIBRILLATION/FLUTTER	31 (0.8%)		33 (0.9%)	
TRANSIENT ISCHEMIC ATTACK	20 (0.5%)		19 (0.5%)	
HEART FAILURE - HOSPITALIZATION DUE TO HEART FAILURE	117 (3.2%)	0.96 (0.80; 1.14)	163 (4.4%)	1.36 (1.16; 1.57)
OTHER CARDIOVASCULAR HOSPITALIZATION	396 (10.7%)		400 (10.9%)	
OTHER HOSPITALIZATION	1246 (33.8%)		1242 (33.9%)	

Events were adjudicated by an independent adjudication committee and considered from randomization up until the End of Study visit.
For composite outcomes and each component, the first event after randomization is considered. Subsequent events of the same type are not shown.
n/100 p-yrs: incidence rate estimated as number of subjects with incident events divided by the cumulative at-risk time in the reference population, where a subject is no longer at risk once an incident event occurred.
Incidence rates are only calculated for pre-defined primary, secondary or exploratory efficacy endpoints.
CV = Cardiovascular.

All-cause mortality

For all-cause mortality, the comparison of finerenone with placebo showed a HR of 0.89 (95% CI 0.77;1.04, logrank test p=0.1337). There were 333 subjects (9.0%) in the finerenone arm and 370 subjects (10.1%) in the placebo arm who died (Table 25). The incidence rates for all-cause mortality were 2.68/100 patient-years (finerenone) and 3.01/100 patient-years (placebo).

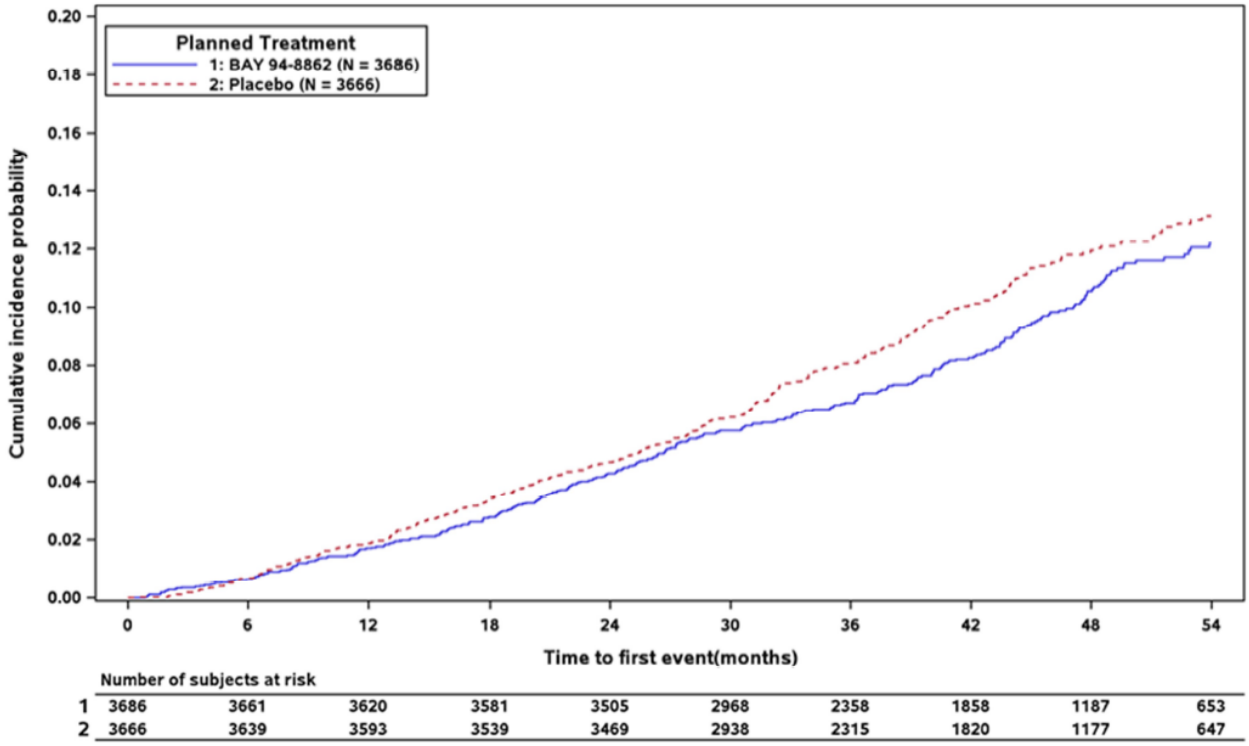
For all-cause mortality Kaplan-Meier curves for finerenone and placebo start to diverge at Month 12 (Figure 25). The absolute risk reduction was 1.3% at Month 36 and 1.8% at Month 42, corresponding to NNTs to prevent one death of 75 and 55 subjects, respectively.

Follow-up information for all-cause mortality was complete for almost all subjects (96.9% in the finerenone arm, 97.3% in the placebo arm).

Table 25. Summary of results for adjudicated all-cause mortality (FAS, FIGARO-DKD).

	Finerenone N = 3686 n (%)	**Placebo** N = 3666 n (%)	**Finerenone** n/100 p-yrs (95% CI)	**Placebo** n/100 p-yrs (95% CI)	**HR** (95% CI)	**p-value**
Number of subjects who died	**333 (9.0%)**	**370 (10.1%)**	**2.68 (2.40;2.98)**	**3.01 (2.71;3.33)**	**0.89 [0.77; 1.04]**	**0.1337**
Components:						
CV death	194 (5.3%)	214 (5.8%)	1.56 (1.35;1.79)	1.74 (1.52;1.98)	0.90 [0.74; 1.09]	0.2742
Renal death	0	2 (<0.1%)				
Fatal, non-CV/non-renal	139 (3.8%)	154 (4.2%)	1.12 (0.94;1.31)	1.25 (1.06;1.46)	0.90 [0.71; 1.13]	0.3592

Events were adjudicated by an independent adjudication committee and considered from randomization up until the end-of-study visit. For composite outcomes and each component, the first event after randomization is considered. Subsequent events of the same type are not shown.
The incidence rate is estimated as the number of subjects with incidence events divided by the cumulative at-risk time in the reference population, where a subject was no longer at risk once an incident event occurred.
Incidence rates, HRs and p-values were only calculated for pre-defined efficacy endpoints.
p-value: two-sided p-value from logrank test, stratified
CI = confidence interval, CV = cardiovascular, FAS = full analysis set, HR = hazard ratio for the comparison of finerenone versus placebo, N = number of subjects, n = number of subjects with event, n/100 p-yrs = incidence rate, p-yrs = patient years
Source: Module 5.3.5.1, Report PH-39747, Table 14.2.2.3/1, Table 14.2.2.3/7, Table 14.2.3.1/31, Table 14.2.3.1/32



FAS = full analysis set, N = number of subjects
Source: Module 5.3.5.1, Report PH-39747, Figure 14.2.2.3/1

Figure 25. Kaplan-Meier curves for time to all-cause mortality (FAS, FIGARO-DKD).

Change in UACR from baseline to Month 4

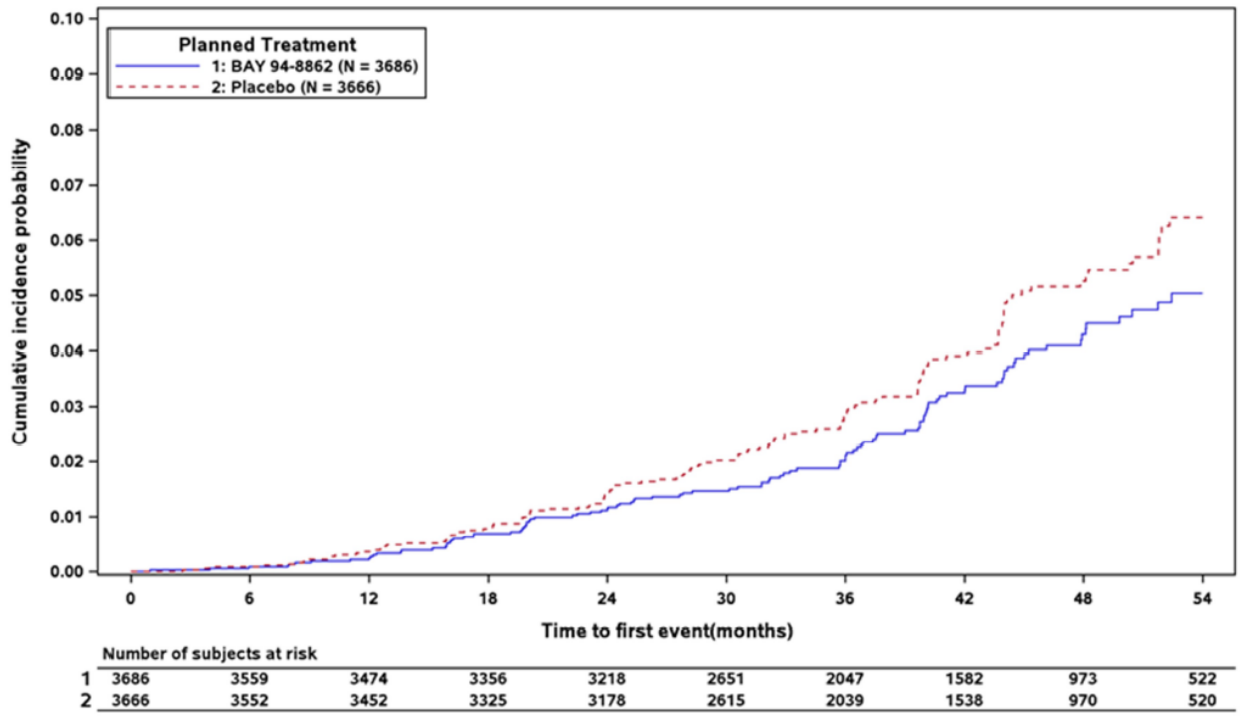
Finerenone led to a larger UACR reduction from baseline to Month 4 than placebo. At Month 4, the geometric mean of the ratio to baseline was 0.624 (geometric SD 2.462) in the finerenone arm compared to 0.922 (geometric SD 2.362) in the placebo arm.

For the change in UACR from baseline to Month 4 (closest visit), the comparison of finerenone versus placebo by ANCOVA resulted in a ratio of LS-means of 0.676 (95% CI 0.650, 0.704, nominal p-value of F-test <0.0001).

Secondary 57% renal composite

The 57% renal composite endpoint was defined as time to onset of kidney failure, a sustained decrease of eGFR ⩾57% from baseline over at least 4 weeks, or renal death. Compared to the secondary 40% renal composite endpoint, the 57% renal composite endpoint considered a greater sustained decrease in eGFR of 57%, which is equivalent to a doubling of serum creatinine.

For the 57% composite endpoint the comparison of finerenone with placebo showed a HR of 0.77 (95% CI 0.60;0.99, logrank test p=0.0406). Statistical testing was performed in an explorative manner.



eGFR = estimated glomerular filtration rate, eGFR = estimated glomerular filtration rate, FAS = full analysis set, 57% renal composite endpoint = kidney failure, sustained decrease of eGFR ≥57% from baseline over at least 4 weeks, or renal death, N = number of subjects
Source: Figure 14.2.2.5/1

Figure 26. Kaplan-Meier curves for time to first occurrence of the 57% renal composite endpoint (FAS).

Given that the secondary 40% renal composite endpoint did not meet the pre-planned criterion for significance, the remaining secondary endpoints were not tested formally, but in an exploratory manner.

Finerenone had no effect on all-cause hospitalisation (HR = 0.97 [95% CI 0.90;1.04]; logrank test nominal p=0.3558) but had an effect on the component hospitalization due to heart failure, as previously discussed in relation to the primary composite endpoint. Of note, numerically, non-heart failure related CV hospitalisations were slightly higher in the finerenone compared to the placebo group.

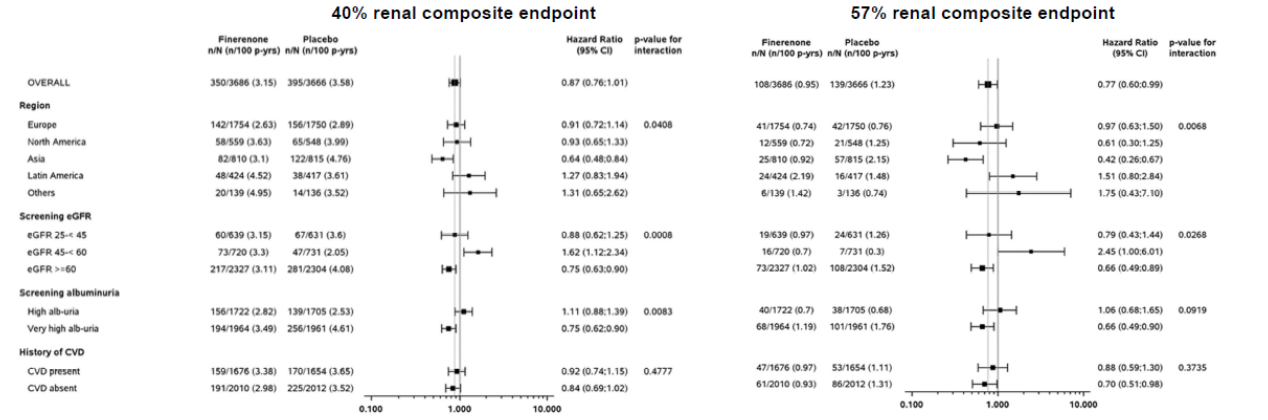
For all-cause mortality, finerenone treatment resulted in a 11% relative risk reduction compared to placebo, however the difference was not significant (HR = 0.89 [95% CI 0.77;1.04]; logrank test nominal p=0.1337) but indicates no general detrimental effect of the treatment, in line with previous findings from the FIDELIO-DKD study.

UACR from baseline to month 4 was reduced in the finerenone group compared to placebo (ratio of LS-means=0.676 [95% CI 0.650; 0.704]; nominal p-value of F-test <0.0001) which is in line with the treatment effect observed in the previous FIDELIO-DKD study and supports the renoprotective mode of action.

The secondary 57% renal composite defined a more pronounced eGFR decrease that corresponds to a doubling of serum creatinine, compared to the primary endpoint that involved a ≥40% reduction. Treatment with finerenone resulted in a 23% relative hazard reduction compared with placebo (HR 0.77 [95% CI 0.60;0.99]; logrank test nominal p=0.0406) i.e. a similar risk reduction as seen in the previous FIDELIO-DKD study, providing support for renoprotection.

Subgroup analyses of the secondary 40 % and 57 % renal composite endpoints

As the renal composite endpoints differed only in the laboratory component sustained decrease of eGFR ⩾40% or ⩾57% from baseline over at least 4 weeks, their subgroup results are described together to facilitate the interpretation. A forest plot by stratification factors is provided in *Figure 27*.



Hazard ratios /95% CIs are based on stratified Cox proportional hazards models with treatment as fixed effect (primary analysis model) whereas interaction p-values (two-sided) are based on stratified Cox proportional hazards models including treatment, subgroup and a subgroup by treatment interaction term as fixed effects. The size of the square for the point estimate reflects the size of the (sub)group.
alb-uria = albuminuria, CI = confidence interval, CVD = cardiovascular disease, eGFR = estimated glomerular filtration rate, FAS = full analysis set, N = number of subjects, n = number of subjects with event, p-yrs = patient-years
Source: Figure 14.2.4/11, Figure 14.2.4/41

Figure 27. Forest plots for the secondary efficacy renal composite endpoints of onset of kidney failure, sustained decrease of eGFR ⩾40% (or ⩾57%) from baseline over at least 4 weeks, or renal death by stratification factors (FAS).

Treatment interaction p-values <0.05 only for one but not the other renal composite endpoint and/or inconsistent courses of the HRs were not considered a relevant heterogeneity by the applicant. This applies to the subgroup factors waist circumference at baseline, ACEI use (or no ARB use) and quartiles of baseline HbA1c.

Based on treatment interaction p-values <0.05 for both renal composite endpoints, a potential heterogeneity in finerenone's treatment effect was indicated for subgroup factors by albuminuria, eGFR, serum potassium at baseline, region and race.

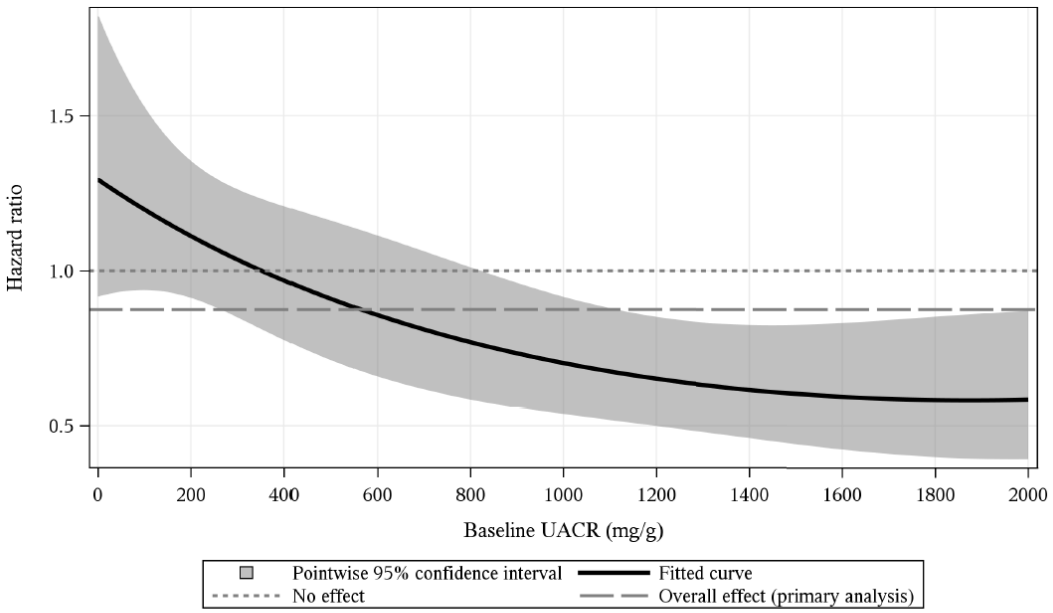
In FIGARO-DKD, due to the inclusion criteria there was a distinct relationship between albuminuria and eGFR at screening: the subgroup of high albuminuria corresponded to subjects with lower range of eGFR of ≥25 to ≤90 mL/min/1.73 m^2 whereas the subgroup of very high albuminuria corresponded to subjects with higher eGFR of ≥60 mL/min/1.73 m^2.

To explore a potential heterogeneity of the treatment effect that was indicated for eGFR and albuminuria by the main subgroup analyses of both renal composite endpoints in relation to the above-mentioned inclusion criteria, post-hoc subgroup analyses by eGFR were conducted separately for the discrete subgroups high and very high albuminuria at baseline. Since there may be further correlations, subgroup analyses split by albuminuria categories were also conducted for serum potassium at baseline, region and race subgroups and in short showed the following results:

By high vs very high albuminuria: Heterogeneity of treatment effects for albuminuria was observed in subgroups of the 40% and the 57% renal composite endpoints (Figure 27). Irrespective of categories of eGFR, baseline potassium, region and race, the treatment effect of finerenone was stronger (i.e. a lower HR) in the 'very high' albuminuria subgroup than the 'high' albuminuria subgroups. In addition, continuous modelling was done using a stratified Cox proportional hazards model with covariates treatment, a cubic B-spline of baseline UACR and its interaction with treatment. For the 40% renal composite the fitted curve indicates HRs <1.0 for baseline UACR values >400 mg/g (Figure 28). For the

57% renal composite endpoint, HRs <1.0 are already seen for baseline UACR values >200 mg/g (Figure 29). The confidence intervals for lower UACR values included unity for both renal composite endpoints; for the 57% renal composite endpoint also the overall treatment effect of HR 0.77 of the primary analysis was included.

Comparable with the overall population, analyses of eGFR decrease over time show an acute reduction in eGFR for subjects in the high and very high albuminuria categories, which is most pronounced at Month 1 and ameliorates from Month 4 onwards (Figure 30). While a stronger finerenone treatment effect on the total eGFR slope was observed earlier (as shown by a crossover of the curves at Month 24) for subjects in the very high albuminuria subgroup compared to those with high albuminuria (no crossover up until Month 48), a preservation of the chronic eGFR slope decline (from Month 4 onwards) was observed for all subjects as judged by positive values for chronic slope differences.



A stratified Cox proportional hazards model is fitted with covariates treatment, a cubic B-spline of baseline UACR with 3 equally spaced knots and its interaction with treatment.
Stratification factors: region, albuminuria at screening, eGFR at screening and history of CVD
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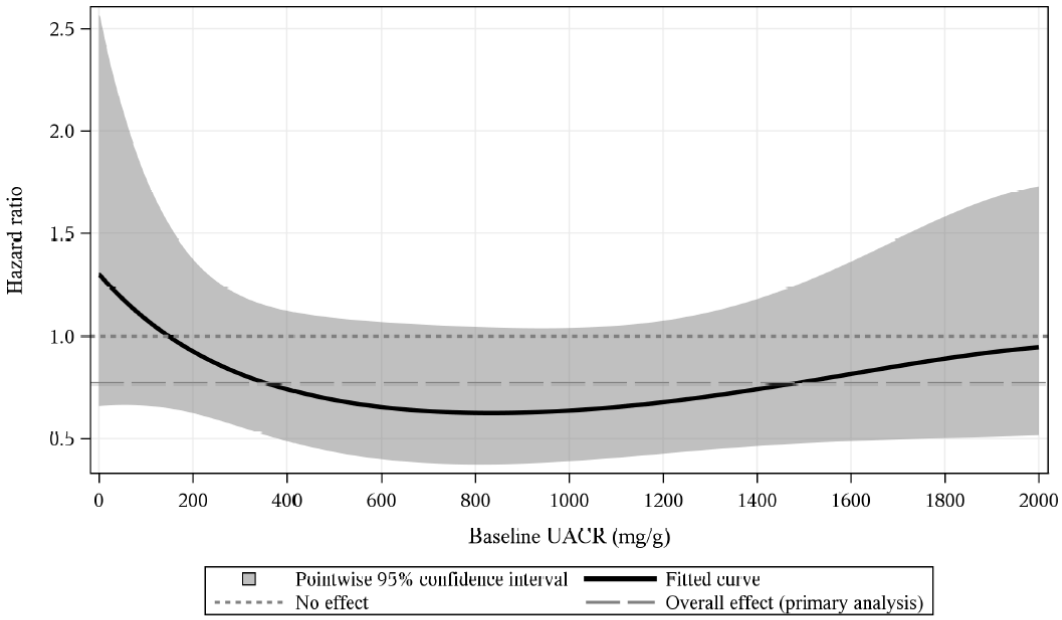
Figure 28. Hazard ratio for time to onset of kidney failure, a sustained decrease of eGFR>=40% from baseline over at least 4 weeks, or renal death by baseline UACR (FIGARO-DKD, full analysis set)



A stratified Cox proportional hazards model is fitted with covariates treatment, a cubic B-spline of baseline UACR with 3 equally spaced knots and its interaction with treatment.
Stratification factors: region, albuminuria at screening, eGFR at screening and history of CVD
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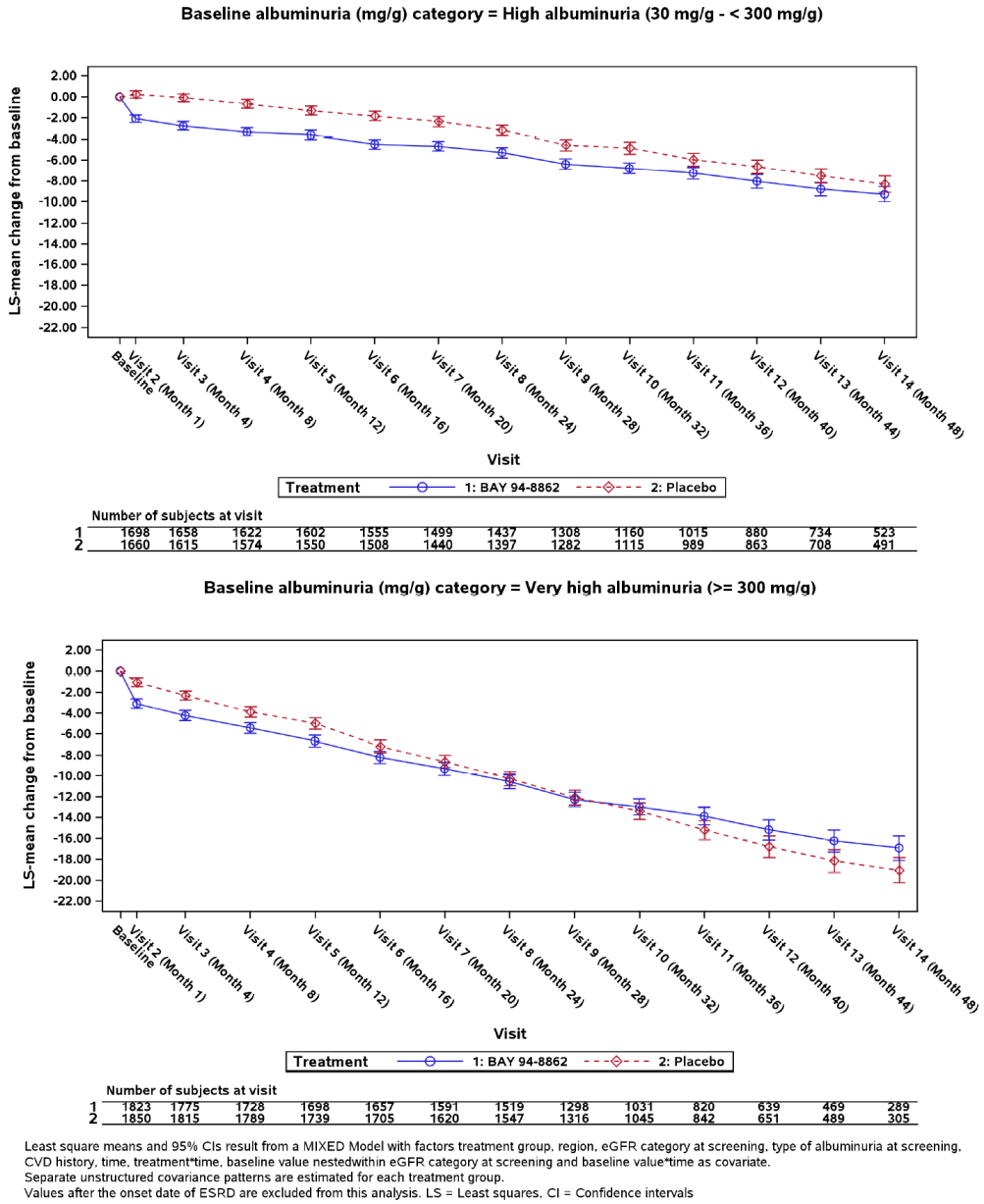
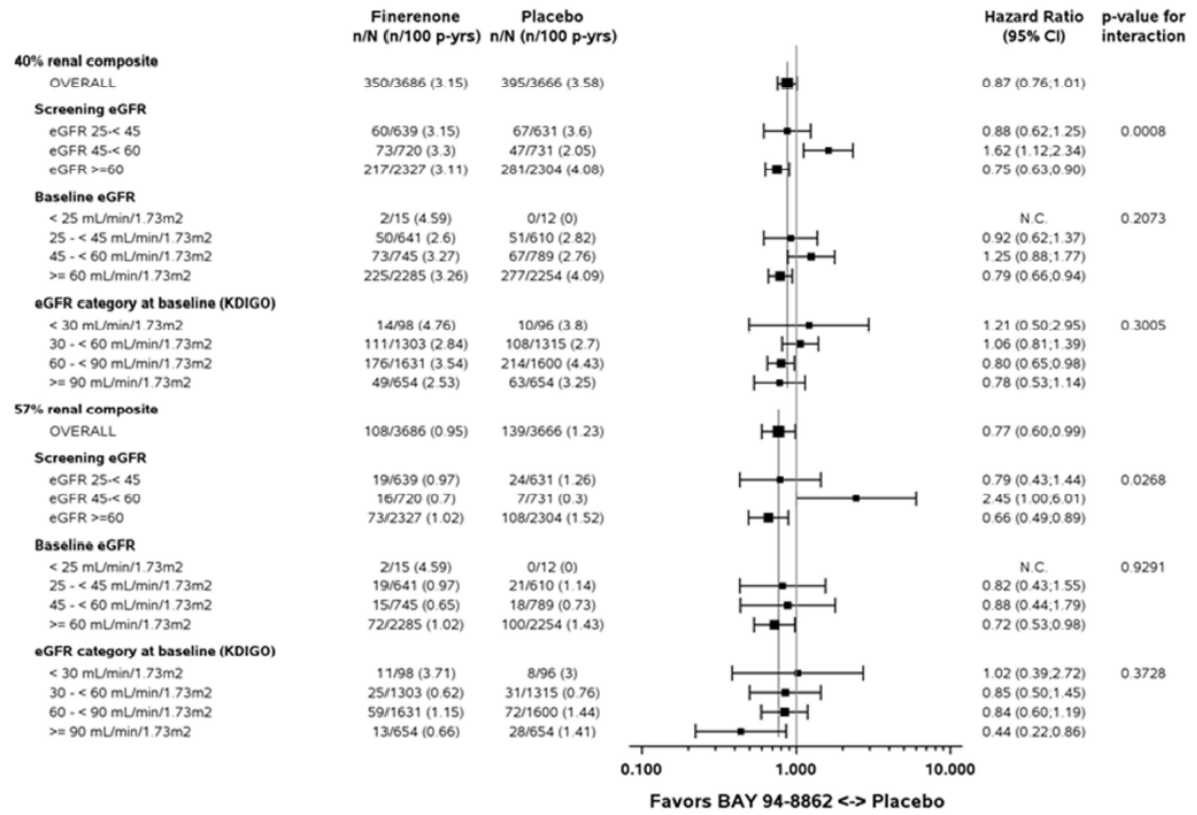
Figure 29. Hazard ratio for time to onset of kidney failure, a sustained decrease of eGFR>=57% from baseline over at least 4 weeks, or renal death by baseline UACR (FIGARO-DKD, full analysis set)



Least square means and 95% CIs result from a MIXED Model with factors treatment group, region, eGFR category at screening, type of albuminuria at screening, CVD history, time, treatment*time, baseline value nestedwithin eGFR category at screening and baseline value*time as covariate.
Separate unstructured covariance patterns are estimated for each treatment group.
Values after the onset date of ESRD are excluded from this analysis. LS = Least squares, CI = Confidence intervals

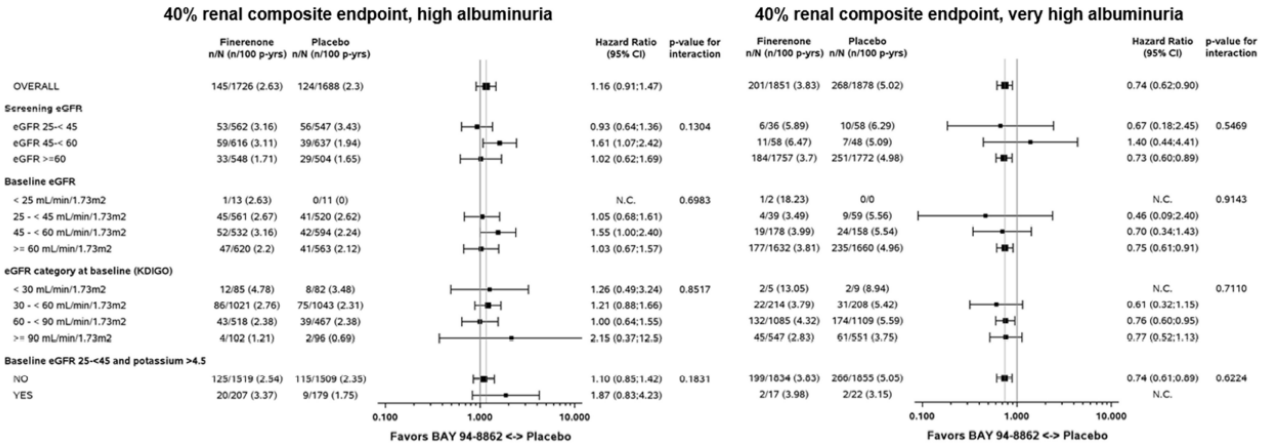
Figure 30. Line plot for least square means of eGFR absolute changes from baseline by visit and Baseline albuminuria (mg/g) category (FIGARO-DKD, full analysis set) (Modified by the Assessor)

Various eGFR categories: Subgroup analysis indicate a heterogeneity in the response regarding screening eGFR for both the 40% and 57% renal endpoints (reduced treatment effect in the 45-60 mL/min group) (see Figure 31 for an overview of GFR by different subgroups at screening/baseline). However, according to the applicant, results of the post-hoc analyses do not support the potential treatment effect heterogeneity for eGFR that was indicated by the main subgroup analysis. Within the 'high' and the 'very high' albuminuria subgroups there was no interaction of baseline eGFR with the treatment effect (as shown by treatment interaction p-values >0.05 for both renal composite endpoints, Figure 32). This suggests that finerenone delays progression of kidney disease consistently across the studied range of eGFR and that the observed heterogeneity in the treatment effect is likely to be attributed to albuminuria.



eGFR = estimated glomerular filtration rate, FAS = full analysis set, N = number of subjects, n = number of subjects with event, p-yrs = patient-years, 40% (or 57%) renal composite endpoint = onset of kidney failure, sustained decrease of eGFR ≥40% (or 57%) from baseline over at least 4 weeks, or renal death
Source: Figure 14.2.4/11, Figure 14.2.4/12, Figure 14.2.4/17, Figure 14.2.4/41, Figure 14.2.4/42, Figure 14.2.4/47

Figure 31. Forest plots for the secondary efficacy 40% and 57% renal composite endpoints by eGFR (FIGARO-DKD, FAS)

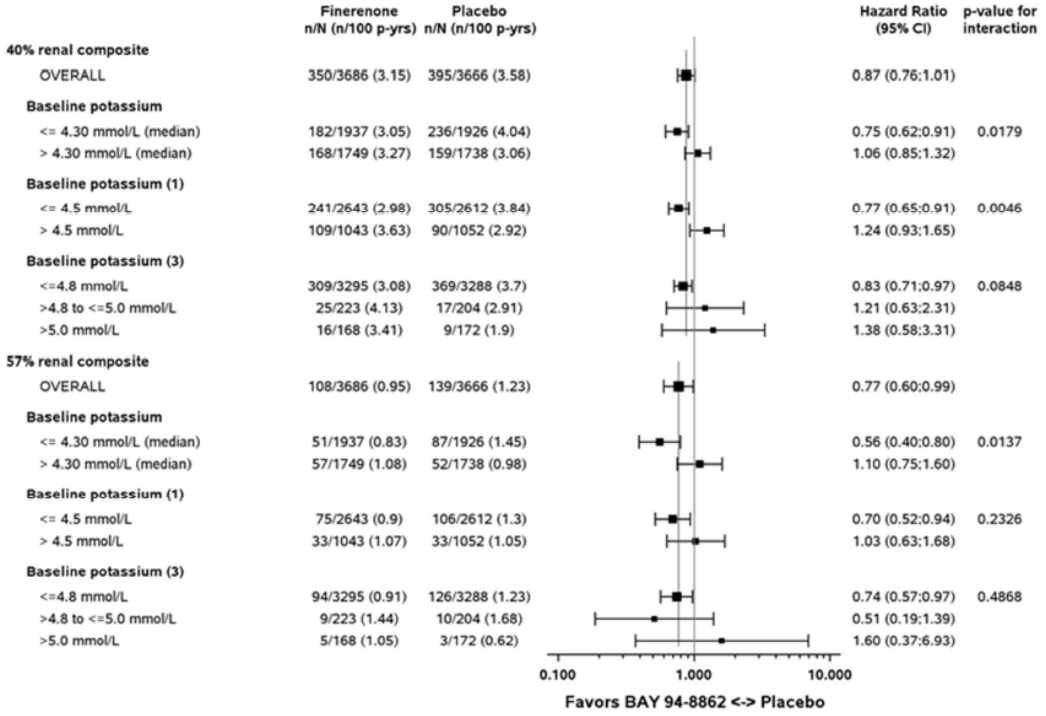


CI = confidence interval, eGFR = estimated glomerular filtration rate, FAS = full analysis set, N = number of subjects, n = number of subjects with event, N.C. = not calculated, p-yrs = patient-years, 40% renal composite endpoint = onset of kidney failure, sustained decrease of eGFR ≥40% from baseline over at least 4 weeks, or renal death
Source: Post-hoc analyses, Figure 16.4.1.1/2, Figure 16.4.1.1/8

Figure 32. Forest plots for the secondary 40% renal composite endpoint by eGFR (FIGARO-DKD, FAS subjects with high albuminuria and very high albuminuria at baseline).

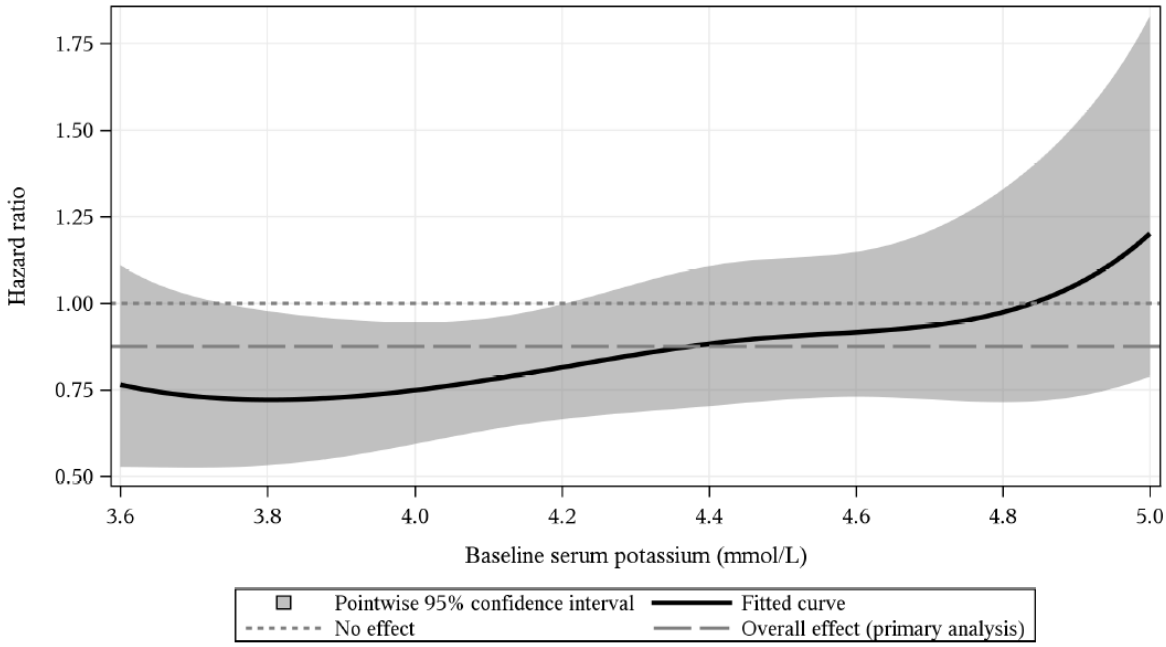
Serum potassium categories at baseline: The treatment effect heterogeneity observed for serum potassium (Figure 33) cannot primarily be explained by albuminuria. In general, lower HR values were associated with lower potassium categories. A stratified Cox proportional hazards model was fitted with covariates treatment, a cubic B-spline of baseline serum potassium and its interaction with treatment. For the 40% renal composite, the fitted curve indicates HRs <1.0 for all but baseline serum potassium values >4.8 mmol/L (Figure 34). For the 57% renal composite, HRs <1.0 are seen for all baseline serum

potassium values, including those >4.8 mmol/L (Figure 35). For higher baseline serum potassium values, the confidence intervals included the respective overall treatment effect of the primary analysis of HR 0.87 and HR 0.77 for the 40% and 57% renal composite endpoint, respectively.



CI = confidence interval, eGFR = estimated glomerular filtration rate, FAS = full analysis set, N = number of subjects, n = number of subjects with event, p-yrs = patient-years, 40% (or 57%) renal composite endpoint = onset of kidney failure, sustained decrease of eGFR ≥40% (or 57%) from baseline over at least 4 weeks, or renal death
Source: Figure 14.2.4/13, Figure 14.2.4/15, Figure 14.2.4/43, Figure 14.2.4/45

Figure 33. Forest plots for the secondary efficacy 40% and 57% renal composite endpoints by serum potassium (FIGARO-DKD, FAS)



A stratified Cox proportional hazards model is fitted with covariates treatment, a cubic B-spline of baseline serum potassium with 3 equally spaced knots and its interaction with treatment.
Stratification factors: region, albuminuria at screening, eGFR at screening and history of CVD
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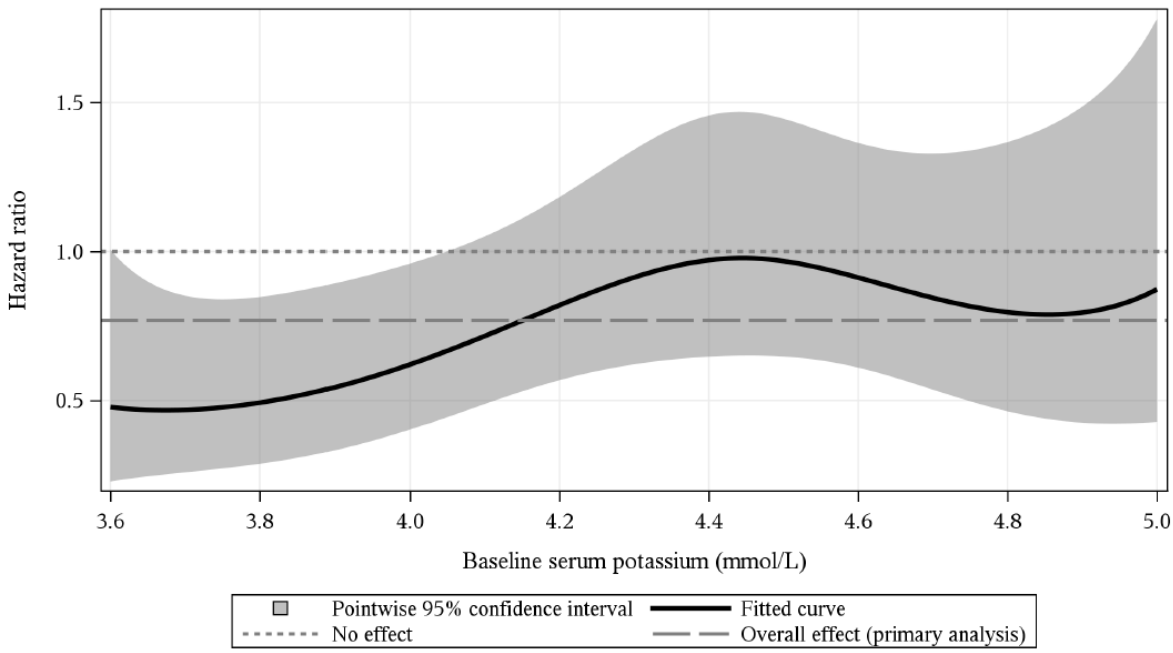
Figure 34. Hazard ratio for time to onset of kidney failure, a sustained decrease of eGFR>=40% from baseline over at least 4 weeks, or renal death by baseline serum potassium (FIGARO-DKD, full analysis set).



A stratified Cox proportional hazards model is fitted with covariates treatment, a cubic B-spline of baseline serum potassium with 3 equally spaced knots and its interaction with treatment.
Stratification factors: region, albuminuria at screening, eGFR at screening and history of CVD
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Figure 35. Hazard ratio for time to onset of kidney failure, a sustained decrease of eGFR>=57% from baseline over at least 4 weeks, or renal death by baseline serum potassium (FIGARO-DKD, full analysis set).

Region and race: The trend for a more expressed treatment effect of finerenone in the region Asia and in Asian subjects seen in the main subgroup analysis was also seen in the subgroup analyses of both renal endpoints by high or very high albuminuria. The proportion of very high albuminuria was only slightly higher in Asia (53.4%) than in the overall population (50.7%), indicating that the treatment heterogeneity cannot be primarily attributed to albuminuria, but also to region and race.

The CHMP assessment of the secondary endpoints

For screening eGFR, given the inclusion criteria, most patients were in the ≥60 mL/min/1.73m^2 group. A positive treatment effect was shown in this group as well as the 25-45 group. However, finerenone treated patients in the 45-60 group displayed an increased HR (1.62 [95% CI 1.12; 2.34]) for both the 40% and the 57% endpoints compared to the other GFR categories. Given that most patients in this GFR subgroup had 'high' albuminuria, the increased HR may be related to the degree of albuminuria rather than GFR. This is supported by data from the FIDELIO-DKD trial that showed no heterogeneity with regards to GFR. However, given that the applicant proposes an extended indication to encompass all stages of CKD, further justification was requested for the renoprotective effect for all GFR categories.

The overall HR for the 40% renal composite was 0.87 (95% CI 0.76; 1.01 p=ns). In subgroups of CKD 1 and 2, HR was 0.78 (95% CI 0.53; 1.14) and 0.80 (95% CI 0.65; 0.98) i.e a treatment effect in the same range as the overall effect previously found in the FIDELIO-DKD study. Compared to the FIDELIO-DKD study, the FIGARO-DKD study enrolled a population with less advanced kidney disease. The renal event rate was therefore lower, and it is acknowledged that the statistical power to demonstrate a treatment effect in this population is affected. In line with the CHMP's opinion given in the SA, lack of statistical significance in the FIGARO results is not considered a main limiting factor to the pursued extension of indication, considering that a positive trend favouring finerenone over placebo has been demonstrated in the study population including Stage 1 and 2. Thus, it can be agreed that the eGFR category does not seem to produce heterogeneity in response, as also confirmed by the lack of statistical interaction between renal function and clinical outcomes in the presented pooled analysis.

The pooled analysis is in general in support for an effect across the different KDIGO categories, including CKD stage 1 and 2 for which extension of indication is sought.

For the 40% and 57% renal endpoints, the treatment effect was reduced in subjects with 'high' albuminuria compared to 'very high' albuminuria. The HRs for the 40% renal endpoint was 1.16 [95% CI 0.91; 1.47] compared to 0.74 [95% CI 0.62; 0.90]. The FIGARO-DKD study enrolled patients with high' albuminuria (30 mg/g - 300 mg/g) and eGFR 25-90 OR patients with'very high'albuminuria (≥300 mg/g) and eGFR ≥60. When interpreting data, there is thus both a biological relation between eGFR and albuminuria as well as a relationship due to the inclusion criteria. The effect of albuminuria however appears independent of GFR since the point estimates subjects with 'high' albuminuria were equal to or above 1 in all GFR categories whereas a beneficial effect was noted in GFR subgroups with 'very high' albuminuria. For the 57% endpoint, the same pattern was seen but the estimate is more uncertain given the generally lower incidence in the placebo group compared to the incidence for the 40% endpoint (5.02 vs. 2.3 n/100 p-yrs). In the previous FIDELIO-DKD study, few participants with 'high' albuminuria were enrolled since recruitment was capped at app. 10%, thus no reliable estimate of the effect in this group is available previously. A further post-hoc analysis using modelling indicates HRs >1 for the 40% renal endpoint for baseline UACR values below app. 400 mg/g. Also, a model-based exposure-response analysis for renal events indicated increased risk of renal events for finerenone treated subjects versus placebo for patients with baseline UACR below app. 400 mg/g. Furthermore, when eGFR curves are plotted for these subgroups, the treatment effect appears more pronounced in the 'very high' albuminuria group as shown by crossing of the curves at month 24 while no crossing of the curves is observed in the 'high' albuminuria group. Thus, it was discussed if the FIGARO trial provides evidence for a favourable

effect of finerenone on renal endpoints across all different eGFR ranges (from Stage 1 to Stage 4) but only in patients with “very high” albuminuria, since an opposite trend emerges in the group with “high” albuminuria.

Following the assessment of the responses the CHMP concluded that regarding renal endpoints, there was a marked heterogeneity regarding albuminuria for the 40% renal endpoint in the FIGARO-DKD study (HR = 1.16 [0.91; 1.47] for the “high” subgroup). No reliable estimate is available for the secondary 57% renal endpoint given low number of events. For the secondary endpoint UACR at month 4, a similar reduction was found in both the “high” and “very high” subgroups. Additional explorative data provided in the response shows a sustained reduction of albuminuria in both subgroups up to 36 months. For the exploratory analysis of the chronic eGFR slope, there was a positive effect on the slope in both subgroups compared to placebo, but the magnitude was reduced in patients in the “high” compared to the “very high” subgroup which may be expected given the lower progression rate of renal dysfunction in these patients. Thus, the bulk of data suggest no treatment effect on renal endpoints during the follow up time (up to 54 months; average treatment time 35 months) but the effect on GFR slope and UACR may indicate a future beneficial effect not yet seen in clinical endpoints.

Safety data may indicate a slight imbalance of serious drug-related AEs in the subgroup of patients with “high albuminuria”; however, this may be driven by the lower eGFR (<60) in the majority of subjects (66%) in the pooled analysis of data from FIDELIO and FIAGRO. In the subgroup of patients with “very high” albuminuria, 55% of the patients had an eGFR <60 and 45% had an eGFR >60.

For the primary CV endpoint, no heterogeneity regarding albuminuria was observed for the CV endpoints (0.87 vs. 0.90 for “high” vs. “very high”, respectively). The effect was driven by hospitalisations for heart failure but observed in a population without previous symptomatic heart failure (NYHA II-IV). In an exploratory post hoc “net clinical benefit” analysis, including both renal and CV events and also accounting for events of hyperkalaemia, HR < 1 were observed in both subgroups.

Taken together, the response on the renal clinical endpoints display heterogeneity concerning albuminuria however explorative data suggest possible future beneficial effects not yet seen during the follow up time. Finerenone had a beneficial effect on the primary CV endpoint in the FIGARO-DKD study, regardless of baseline albuminuria status. Thus, the totality of data, including findings from post hoc analyses, support that patients with both “high” and “very high” albuminuria benefit from the treatment.

The FIGARO study showed heterogeneity of response by potassium level in the overall population. For the 40% endpoint, the HR in patients with potassium >4.3 mM was 1.06 [95% CI 0.85; 1.32] compared to 0.75 [95% CI 0.62; 0.91] for patients ≤4.3 mM. The heterogeneity was still present when data was stratified by a higher cut-off of 4.5 mM (HR 0.77 vs. 1.24) however the estimate in the subgroup >4.5 mM is less reliable given fewer number of patients. When analyzing the GFR slopes in data stratified by a cut-off of 4.5 mM, the finerenone and the placebo curves cross at month 36 in the subgroup ≤4.5mM whereas no clear crossing of the curves was seen in the subgroup ≥4.5mM. However, the fewer number of patients in the ≥4.5mM group may have affected the appearance of the curve. A further post-hoc analysis using modelling indicates a better treatment effect (i.e. lower HRs) in patients with a lower baseline potassium whereas patients with serum potassium above 4.8 displayed a HR above 1. In the previous FIDELIO-DKD study, no heterogeneity in response related to serum potassium was however observed and there was no heterogeneity by baseline potassium for the CV endpoints in either study which is reassuring. Regarding the demographic characteristics of both trials, patients with the highest baseline potassium concentration (4.5 mmol/L) were equally distributed across the different subgroups by albuminuria and eGFR levels, contrarily to the expected inverse relationship between potassium and renal function. Therefore, the population of patients with potassium >4.5 mmol/L is quite heterogeneous and is not directly attributed to those with worse renal function. Given that the heterogeneity could not be reproduced in the two studies, that no biological rationale has been identified and that there was no

heterogeneity related to potassium for the CV endpoint in either of the studies, the issue is not further pursued.

The risk of serious events of hyperkalaemia for Kerendia is handled with routine risk minimisation. Instructions for monitoring serum potassium are included in the product information.

Explorative endpoints

A new diagnosis of heart failure, which was independently adjudicated by the cardiology CEC, occurred less frequently in the finerenone arm than in the placebo arm (Odds ratio 0.675, 95% CI 0.490;0.929, Wald test p=0.0160).

No treatment difference could be observed for a new diagnosis of atrial fibrillation or atrial flutter, which was also independently adjudicated by the cardiology CEC (FAS: 3.9% in each treatment arm, Odds ratio 1.000, 95% CI 0.779;1.284, Wald test p=0.9995.

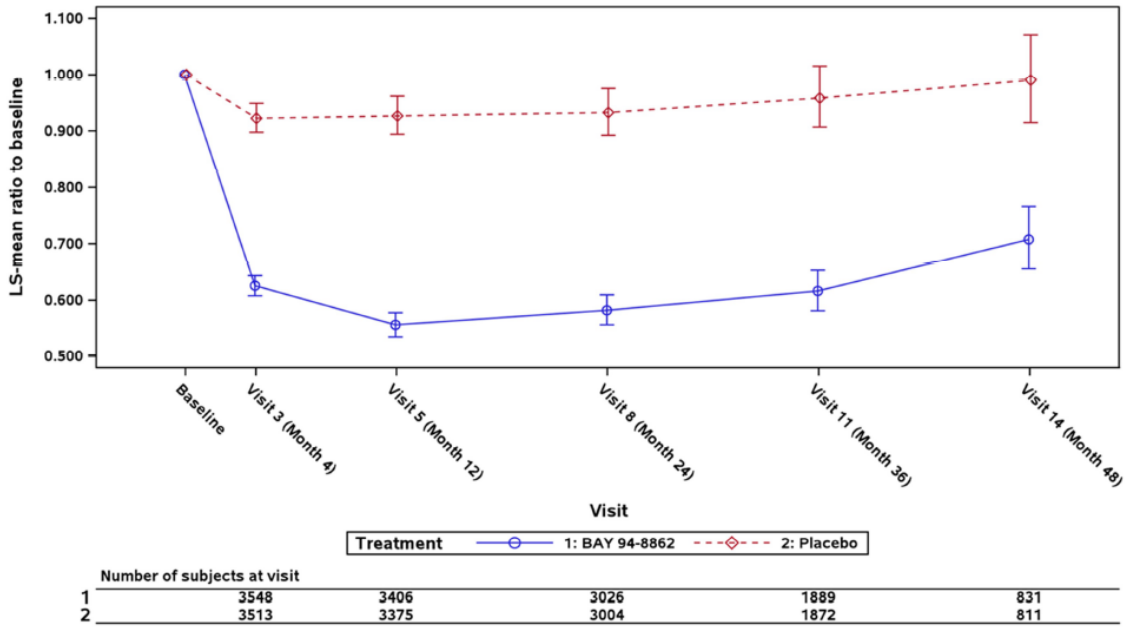
Regression of albuminuria from very high to high albuminuria and high albuminuria to normal albuminuria (accompanied by a UACR change of at least 30% from baseline) was seen in more subjects in the finerenone arm (47.8%) than in the placebo arm (31.0%) (Odds ratio 2.051, 95% CI 1.861;2.260, Wald test p<0.0001).

Table 26. Summary of results for new diagnoses of atrial fibrillation/atrial flutter, heart failure and regression of albuminuria (FAS).

	Finerenone	Placebo	Odds ratio Finerenone / Placebo	95% CI of Odds ratio	p-value for treatment group
	n/N (%)	n/N (%)			
New diagnosis of atrial fibrillation or atrial flutter	130/3358 (3.9%)	129/3349 (3.9%)	1.000	[0.779, 1.284]	0.9995
New diagnosis of heart failure	65/3396 (1.9%)	95/3385 (2.8%)	0.675	[0.490, 0.929]	0.0160
Regression of albuminuria	1710/3577 (47.8%)	1106/3566 (31.0%)	2.051	[1.861, 2.260]	<.0001

Values after onset of ESRD are not considered for this analysis.
CI = confidence interval, ESRD = end stage renal disease, FAS = full analysis set, n = number of subjects with event, N = Number of subjects without the condition at baseline, regression of albuminuria = regression from very high to high albuminuria and high albuminuria to albuminuria accompanied by a decrease in UACR of at least 30% from baseline, UACR = urinary albumin-to-creatinine ratio
Source: Table 14.2.3.2/1 to Table 14.2.3.2/3, Table 14.2.3.2/4 to Table 14.2.3.2/6

Least square means from a mixed model analysis for the ratio to baseline of UACR, which include measurements from all subjects whether on or off study drug, show that the finerenone treatment effect on UACR that was apparent at Month 4 (Section 2.1.4.3.4) was sustained over the duration of the study (Figure 36).



Least square means and 95% CIs result from a Mixed Model with factors treatment group, region, eGFR category at screening, type of albuminuria at screening, CV disease history, time, treatment*time, log-transformed baseline value nested within type of albuminuria at screening and log-transformed baseline value*time as covariate. Separate unstructured covariance patterns were estimated for each treatment group.
Values after the onset date of ESRD are excluded from this analysis.
CI = confidence interval, CV = cardiovascular, eGFR = estimated glomerular filtration rate, ESRD = end-stage renal disease, FAS = full analysis set, LS = least squares, UACR = urinary albumin-to-creatinine ratio
Source: Module 5.3.5.1, Report PH-39747, Figure 14.2.3.3/1

Figure 36. Line plots for least square means for ratio to baseline of UACR values by visit (FAS, FIGARO-DKD)

The explorative endpoint new diagnosis of heart failure occurred less frequently in the finerenone group (HR=0.675 [95% CI 0.490; 0.929]; nominal p=0.016). Similar frequencies were found in both treatment groups for the explorative endpoint new diagnosis of atrial fibrillation or atrial flutter while in the previous FIDELIO-DKD study, a numerical difference was found in favour of finerenone. Regression of albuminuria category (from very high to high albuminuria and high albuminuria to normal albuminuria) was more frequent in the finerenone arm than placebo. Also, for albuminuria, an explorative analysis showed that the UACR reduction by finerenone treatment, that was apparent at Month 4, was sustained over the duration of the study.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 27. Table 1. Summary of Efficacy for trial FIGARO-DKD.

Title: A randomized, double-blind, placebo-controlled, parallel-group, multicenter, event-driven Phase 3 study to investigate the efficacy and safety of finerenone on the reduction of cardiovascular morbidity and mortality in subjects with type 2 diabetes mellitus and the clinical diagnosis of diabetic kidney disease in addition to standard of care	
Study identifier	Protocol number 17530, EudraCT: 2015-000950-39, Report number PH-39747

Design	Randomized, double-blind, placebo-controlled, parallel-group, multicenter, event-driven Phase 3 study. This was a study to evaluate the efficacy and safety of finerenone compared to placebo (1:1 ratio) in addition to standard of care therapy, in patients with Type 2 diabetes and a clinical diagnosis of diabetic kidney disease. The starting dose of finerenone was based on the eGFR value at the screening visit: 10 mg once daily if eGFR between 25 to <60 mL/min/1.73m² (minimum dose); 20 mg once daily if eGFR ⩾60 mL/min/1.73m² (maximum dose). Investigators were encouraged to reach the maximum (target) dose of 20 mg without compromising safety. Restart after interruptions of >7 days was at the lower (10 mg) dose.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Event driven, expected approx. 3.5 to 4 years, First patient first visit 17 SEP 2015, Last patient last visit 02 FEB 2021 up to 16 weeks not applicable
Hypothesis	Superiority: Finerenone is superior to placebo in addition to a guideline-directed medical therapy with an ACEI or ARB in delaying the time to first occurrence of cardiovascular (CV) mortality and morbidity in subjects with type 2 diabetes mellitus (T2D) and the clinical diagnosis of diabetic kidney disease (DKD).		
Treatments groups	Finerenone, 10 or 20 mg tablets once daily		Mean treatment duration: 35.167 months, Mean study duration (defined as time from randomization to end-of-study visit or last contact date): 40.224 months, Number randomized: 3723 subjects, FAS: 3686 subjects
	Placebo		Mean treatment duration: 35.322 months, Mean study duration: 40.069 months, Number randomized: 3714 subjects, FAS: 3666 subjects
Endpoints and definitions	Primary endpoint	CV composite	Composite of CV death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for heart failure
	Secondary endpoints	40% renal composite	Composite of onset of kidney failure, a sustained decrease of eGFR ⩾40% from baseline over at least 4 weeks, or renal death
		All-cause hospitalization	Hospitalization by any cause
		All-cause mortality	Mortality by any cause
		Change in UACR	Change in UACR from baseline to Month 4
		57% renal composite	Composite of onset of kidney failure, a sustained decrease of eGFR ⩾57% from baseline over at least 4 weeks, or renal death
Database lock	19 APR 2021		
Results and Analysis			

Analysis description	Primary Analysis		
Analysis population and time point description	Of the 7437 randomized subjects, 85 subject identifiers were prospectively excluded from the analyses because of GCP violations, resulting in a FAS population of 7352 subjects (3686 subjects in the finerenone arm and 3666 subjects in the placebo arm). Vital status was ascertained after EOS notification for all but 18 subjects (0.2%, 5 in the finerenone arm, 13 in the placebo arm). Thus 3681 subjects (99.9%) in the finerenone arm and 3653 subjects (99.6%) in the placebo arm completed the study. The primary analysis was performed on the FAS based on the endpoint events (i.e. first occurrences) from randomization up until the end-of-study visit that were positively adjudicated by an independent Clinical Events Committee. A hierarchical testing procedure was used for the primary and secondary efficacy variables.		
Descriptive statistics and estimate variability	Treatment group	Finerenone	Placebo
	Number of subjects	3686 subjects	3666 subjects
	Primary CV composite endpoint		
	Number of subjects with first event (%)	458 (12.4%)	519 (14.2%)
	n/100 patient-years (95% CI)	3.87 (3.52;4.23)	4.45 (4.08;4.84)
	Secondary endpoints		
	40% renal composite		
	Number of subjects with first event (%)	350 (9.5%)	395 (10.8%)
	n/100 patient-years (95% CI)	3.15 (2.83;3.49)	3.58 (3.23;3.94)
	All-cause hospitalization		
	Number of subjects with first event (%)	1573 (42.7%)	1605 (43.8%)
	n/100 patient-years (95% CI)	16.91 (16.09;17.76)	17.52 (16.68;18.39)
	All-cause mortality		
	Number of subjects with first event (%)	333 (9.0%)	370 (10.1%)
	n/100 patient-years (95% CI)	2.68 (2.40;2.98)	3.01 (2.71;3.33)

	UACR change		
	Ratio to baseline at Month 4, Geom. mean (geom. SD)	0.6239 (2.4618)	0.9223 (2.3622)
	57% renal composite		
	Number of subjects with first event (%)	108 (2.9%)	139 (3.8%)
	n/100 patient-years (95% CI)	0.95 (0.78;1.13)	1.23 (1.03;1.44)
Effect estimate per comparison	Primary CV composite endpoint	Comparison groups	Finerenone vs Placebo
		Hazard ratio	0.87
		[95% CI]	[0.76; 0.98]
		P-value	0.0264
	Secondary endpoints		
	40% renal composite	Hazard ratio	0.87
		[95% CI]	[0.76; 1.01]
		P-value	0.0689
	All-cause hospitalization	Hazard ratio	0.97
		[95% CI]	[0.90; 1.04]
		P-value	0.3558
	All-cause mortality	Hazard ratio	0.89
		[95% CI]	[0.77; 1.04]
	UACR change	Ratio of LS means	0.676
		[95% CI]	[0.650; 0.704]
		p-value	<.0001
	57% renal composite	Hazard ratio	0.77
		[95% CI]	[0.60; 0.99]
		p-value	0.0406
Notes	For the comparison of finerenone versus placebo, the reduction in the primary CV efficacy endpoint was significantly superior. For the first secondary 40% renal composite endpoint a positive trend for the finerenone treatment effect was observed, that did not reach statistical significance. The remaining secondary endpoints all-cause hospitalization, all-cause mortality, change of UACR from baseline to Month 4 and the 57% renal composite endpoint were not tested formally, but in an exploratory manner.		

Analysis performed across trials (pooled analyses and meta-analysis)

Pooled analysis of the FIDELIO-DKD and the FIGARO-DKD trials

A tabulation of albuminuria and eGFR at baseline for the individual FIGARO-DKD and FIDELIO-DKD studies and the pooled dataset is provided in *Table 28*.

Table 28. Albuminuria and eGFR at baseline: by study and in the pool (FIGARO-DKD and FIDELIO-DKD; FAS).

Baseline values	FIGARO-DKD Finerenone N=3686 (100%)	FIGARO-DKD Placebo N=3666 (100%)	FIDELIO-DKD Finerenone N=2833 (100%)	FIDELIO-DKD Placebo N=2841 (100%)	FIGARO-DKD & FIDELIO-DKD Finerenone N=6519 (100%)	FIGARO-DKD & FIDELIO-DKD Placebo N=6507 (100%)
UACR (mg/g)						
Normal (<30)	109 (3.0%)	98 (2.7%)	11 (0.4%)	12 (0.4%)	120 (1.8%)	110 (1.7%)
High (≥30 to <300)	1726 (46.8%)	1688 (46.0%)	350 (12.4%)	335 (11.8%)	2076 (31.8%)	2023 (31.1%)
Very high (≥300)	1851 (50.2%)	1878 (51.2%)	2470 (87.2%)	2493 (87.8%)	4321 (66.3%)	4371 (67.2%)
Median categories	302.36	315.06	832.72	867.01	514.21	514.92
≤514.7	2397 (65.0%)	2409 (65.7%)	863 (30.5%)	842 (29.6%)	3260 (50.0%)	3251 (50.0%)
>514.7	1289 (35.0%)	1255 (34.2%)	1968 (69.5%)	1998 (70.3%)	3257 (50.0%)	3253 (50.0%)
eGFR (mL/min/1.73 m^2)[a]						
By KDIGO categories (stage)						
<30 (stage 4)	98 (2.7%)	96 (2.6%)	342 (12.1%)	354 (12.5%)	440 (6.7%)	450 (6.9%)
30 to <60 (stage 3)	1303 (35.3%)	1315 (35.9%)	2172 (76.7%)	2148 (75.6%)	3475 (53.2%)	3463 (53.2%)
60 to <90 (stage 2)	1631 (44.2%)	1600 (43.6%)	313 (11.0%)	332 (11.7%)	1944 (29.8%)	1932 (29.7%)
≥90 (stage 1)	654 (17.7%)	654 (17.8%)	5 (0.2%)	6 (0.2%)	659 (10.1%)	660 (10.1%)
Other eGFR categories						
<25	15 (0.4%)	12 (0.3%)	66 (2.3%)	69 (2.4%)	81 (1.2%)	81 (1.2%)
25 to <45	641 (17.4%)	610 (16.6%)	1476 (52.1%)	1505 (53.0%)	2117 (32.5%)	2115 (32.5%)
45 to <60	745 (20.2%)	789 (21.5%)	972 (34.3%)	928 (32.7%)	1717 (26.3%)	1717 (26.4%)
≥60	2285 (62.0%)	2254 (61.5%)	318 (11.2%)	338 (11.9%)	2603 (39.9%)	2592 (39.8%)
Mean	67.62	67.99	44.36	44.32	57.51	57.65
SD	21.65	21.74	12.54	12.57	21.59	21.75

[a] Missing (<0.1% in any arm) not shown
eGFR=estimated glomerular filtration rate, FAS= full analysis set, KDIGO= Kidney Disease: Improving Global Outcomes, N=number of subjects, SD=standard deviation, UACR=urinary albumin creatine ratio
Normalbuminuria: UACR <30 mg/g
High albuminuria: UACR ≥30 to <300 mg/g
Very high albuminuria: UACR ≥300 mg/g
Source: Module 5.3.5.3, Report PH-42134, Table 14.1.2/1

CV composite endpoint of CV death, non-fatal MI, non-fatal stroke, or hospitalization for heart failure

Summaries of the CV composite endpoint for the FIDELIO-DKD and the FIGARO-DKD trials are provided in *Table 29*.

For the CV composite endpoint, the benefit of finerenone compared with placebo was shown by statistically significant results for FIGARO-DKD (HR 0.87) and FIDELIO-DKD (HR 0.86) that were nominally significant in the pooled analysis (HR 0.86) across both Phase 3 studies (*Table 30*).

Kaplan-Meier curves for the pooled analysis are shown in *Figure 37*.

Table 29. CV composite endpoint: number of subjects with events and incidence rates (pooled analysis, FAS).

	Frequency of events				Incidence rates per 100 p-yrs			
	FIGARO-DKD		FIDELIO-DKD		FIGARO-DKD		FIDELIO-DKD	
	Finerenone	Placebo	Finerenone	Placebo	Finerenone	Placebo	Finerenone	Placebo
	N = 3686	N = 3666	N = 2833	N = 2841	N = 3686	N = 3666	N = 2833	N = 2841
CV composite endpoint	n (%)	n (%)	n (%)	n (%)	n/100 p-yrs	n/100 p-yrs	n/100 p-yrs	n/100 p-yrs
Number of subjects with CV composite endpoint	**458 (12.4%)**	**519 (14.2%)**	**367 (13.0%)**	**420 (14.8%)**	**3.87**	**4.45**	**5.11**	**5.92**
Components:								
CV death	194 (5.3%)	214 (5.8%)	128 (4.5%)	150 (5.3%)	1.56	1.74	1.69	1.99
Acute MI	15 (0.4%)	10 (0.3%)	11 (0.4%)	11 (0.4%)	0.12	0.08	0.15	0.15
Death due to CV procedures	6 (0.2%)	4 (0.1%)	1 (<0.1%)	1 (<0.1%)	0.05	0.03	0.01	0.01
Death due to heart failure	9 (0.2%)	14 (0.4%)	6 (0.2%)	13 (0.5%)	0.07	0.11	0.08	0.17
Death due to other CV causes	11 (0.3%)	9 (0.2%)	7 (0.2%)	1 (<0.1%)	0.09	0.07	0.09	0.01
Fatal stroke	12 (0.3%)	19 (0.5%)	13 (0.5%)	14 (0.5%)	0.10	0.15	0.17	0.19
Sudden cardiac death	53 (1.4%)	73 (2.0%)	35 (1.2%)	42 (1.5%)	0.43	0.59	0.46	0.56
Undetermined cause of death	88 (2.4%)	85 (2.3%)	55 (1.9%)	68 (2.4%)	0.71	0.69	0.73	0.90
Non-fatal MI	103 (2.8%)	102 (2.8%)	70 (2.5%)	87 (3.1%)	0.85	0.85	0.94	1.17
Non-fatal stroke	108 (2.9%)	111 (3.0%)	90 (3.2%)	87 (3.1%)	0.89	0.92	1.21	1.18
Hospitalization due to heart failure	117 (3.2%)	163 (4.4%)	139 (4.9%)	162 (5.7%)	0.96	1.36	1.89	2.21

Events were adjudicated by an independent adjudication committee and considered from randomization up until the End of Study visit. For composite outcomes and each component, the first event after randomization is considered. Subsequent events of the same type are not shown.
CV = cardiovascular, CV composite endpoint = CV death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for heart failure, FAS = full analysis set, MI = myocardial infarction, N = number of subjects, n = number of subjects with event, n/100 p-yrs = incidence rate estimated as the number of subjects with incidence events divided by the cumulative at-risk time in the reference population, where a subject was no longer at risk once an incident event occurred, p-yrs = patient years
Source: Module 5.3.5.3, Report PH-42134, Table 14.2.1/1, Table 14.2.1/2

Table 30. CV composite endpoint: Hazard ratio and p-value for the treatment comparisons finerenone vs placebo (pooled analysis, FAS).

	FIGARO-DKD		FIDELIO-DKD		FIGARO-DKD & FIDELIO-DKD		
	Finerenone vs. Placebo		Finerenone vs. Placebo		Finerenone vs. Placebo		
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	Interaction p-value
Time to first occurrence of CV composite endpoint	**0.87 (0.76,0.98)**	**0.0264**	**0.86 (0.75,0.99)**	**0.0339**	**0.86 (0.78,0.95)**	**0.0018**	0.8653
Components:							
CV death	0.90 (0.74,1.09)	0.2742	0.86 (0.68,1.08)	0.1927	0.88 (0.76,1.02)	0.0922	0.7190
Acute MI	1.48 (0.67,3.30)		1.00 (0.43,2.31)		1.20 (0.68,2.14)		0.4691
Death due to CV procedures	1.52 (0.43,5.38)		0.98 (0.06,15.71)		1.41 (0.45,4.44)		0.7738
Death due to heart failure	0.64 (0.27,1.47)		0.48 (0.18,1.25)		0.58 (0.31,1.08)		0.7071
Death due to other CV causes	1.18 (0.49,2.84)		7.02 (0.86,57.10)		1.78 (0.82,3.86)		0.1227
Fatal stroke	0.62 (0.30,1.27)		0.94 (0.44,2.00)		0.75 (0.44,1.26)		0.4402
Sudden cardiac death	0.71 (0.50,1.01)		0.83 (0.53,1.30)		0.75 (0.57,<1.00)		0.6182
Undetermined cause of death	1.04 (0.77,1.40)		0.81 (0.57,1.15)		0.93 (0.74,1.17)		0.2743
Non-fatal MI	0.99 (0.76,1.31)	0.9628	0.80 (0.58,1.09)	0.1540	0.91 (0.74,1.12)	0.3601	0.2975
Non-fatal stroke	0.97 (0.74,1.26)	0.7932	1.03 (0.76,1.38)	0.8579	0.99 (0.82,1.21)	0.9460	0.7765
Hospitalization due to heart failure	0.71 (0.56,0.90)	0.0043	0.86 (0.68,1.08)	0.1821	0.78 (0.66,0.92)	0.0030	0.2629

Stratified cox models with the stratification factors study (only pooled model), history of CV disease (pooled and FIGARO model), region, eGFR category at screening and type of albuminuria at screening were fitted. The p-value is based on a two-sided stratified log-rank test. The interaction p-value displays the study*treatment interaction based on a stratified model including study, treatment and study*treatment as covariates and removing study as stratification factor.
CI = confidence interval, CV = cardiovascular, CV composite endpoint = CV death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for heart failure, eGFR = estimated glomerular filtration rate, FAS = full analysis set, HR = hazard ratio for the comparison of finerenone versus placebo, MI = myocardial infarction
Source: Module 5.3.5.3, Report PH-42134, Table 14.2.1/3

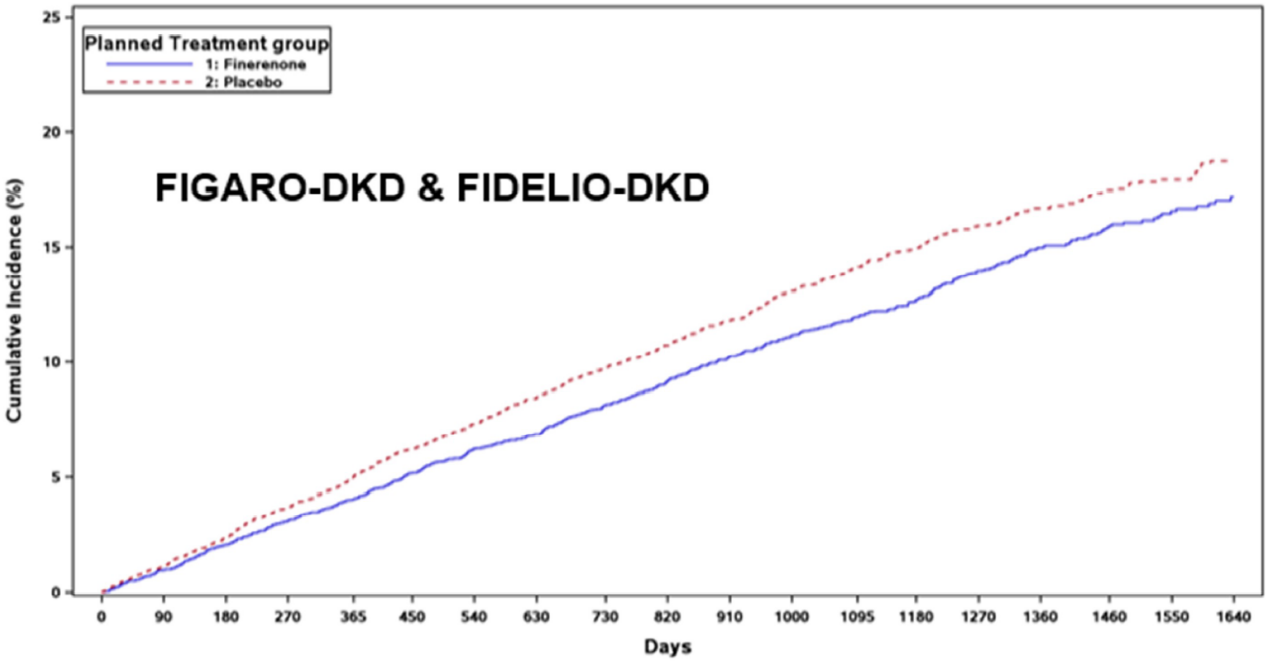


Figure 37. CV composite endpoint: cumulative incidence curves for time to first occurrence in the pooled analysis (FAS) of FIGARO-DKD, FIDELIO-DKD.

40% and 57% renal composite endpoints of onset of kidney failure, sustained decrease of eGFR ≥40% (or 57%) from baseline over at least 4 weeks, or renal death

Summaries of the 40% and 57% renal composite endpoints are provided in Table 31.

In FIGARO-DKD finerenone indicated a favourable treatment effect (HR 0.87), which however did not reach statistical significance. Statistical significance was reached in FIDELIO-DKD (HR 0.82) and nominal significance was reached in the pooled analysis (HR 0.85) across both Phase 3 studies (Table 32).

Table 31. 40% and 57% renal composite endpoints: number of subjects with events and incidence rate (FAS).

	Frequency of events				Incidence rates per 100 p-yrs			
	FIGARO-DKD		FIDELIO-DKD		FIGARO-DKD		FIDELIO-DKD	
	Finerenone N = 3686	Placebo N = 3666	Finerenone N = 2833	Placebo N = 2841	Finerenone N = 3686	Placebo N = 3666	Finerenone N = 2833	Placebo N = 2841
Renal composite endpoints	n (%)	n (%)	n (%)	n (%)	n/100 p-yrs	n/100 p-yrs	n/100 p-yrs	n/100 p-yrs
Number of subjects with 40% renal composite endpoint	**350 (9.5%)**	**395 (10.8%)**	**504 (17.8%)**	**600 (21.1%)**	**3.15**	**3.58**	**7.59**	**9.08**
Components:								
Kidney failure	46 (1.2%)	62 (1.7%)	208 (7.3%)	235 (8.3%)	0.40	0.54	2.99	3.39
ESRD	32 (0.9%)	49 (1.3%)	119 (4.2%)	139 (4.9%)	0.26	0.40	1.60	1.87
Sustained decrease in eGFR to <15 mL/min	28 (0.8%)	38 (1.0%)	167 (5.9%)	199 (7.0%)	0.24	0.33	2.40	2.87
Sustained decrease in eGFR ≥40% (relative to baseline)	338 (9.2%)	385 (10.5%)	479 (16.9%)	577 (20.3%)	3.04	3.49	7.21	8.73
Renal death	0	2 (<0.1%)	2 (<0.1%)	2 (<0.1%)	0	0.02	0.03	0.03
Number of subjects with 57% renal composite endpoint	**108 (2.9%)**	**139 (3.8%)**	**252 (8.9%)**	**326 (11.5%)**	**0.95**	**1.23**	**3.64**	**4.74**
Sustained decrease in eGFR ≥57% (relative to baseline)	90 (2.4%)	116 (3.2%)	167 (5.9%)	245 (8.6%)	0.79	1.02	2.41	3.54

Events were adjudicated by an independent adjudication committee and considered from randomization up until the End of Study visit. For composite outcomes and each component, the first event after randomization is considered. Subsequent events of the same type are not shown. Events based on a sustained decrease in eGFR are considered from randomization up until 5 months after the last eGFR is recorded at a clinic visit.
eGFR = estimated glomerular filtration rate, ESRD=end-stage renal disease, FAS = full analysis set, N=number of subjects, n=number of subjects with event, n/100 p-yrs = incidence rate estimated as number of subjects with incidence events divided by the cumulative at-risk time in the reference population, where a subject was no longer at risk once an incident event occurred, p-yrs =patient years, 40% (57%) renal composite endpoint=onset of kidney failure, sustained decrease of eGFR ≥40% (≥57%) from baseline over at least 4 weeks, or renal death
Source: Module 5.3.5.3, Report PH-42134, Table 14.2.2/1, Table 14.2.2/2

Table 32. 40% and 57% renal composite endpoints: Hazard ratio and p-value for the treatment comparisons finerenone vs placebo (FAS).

	FIGARO-DKD Finerenone vs. Placebo		FIDELIO-DKD Finerenone vs. Placebo		FIGARO-DKD & FIDELIO-DKD Finerenone vs. Placebo		
Renal composite endpoints	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	Interaction p-value
Time to first occurrence of 40% renal composite endpoint	**0.87 (0.76,1.01)**	**0.0689**	**0.82 (0.73,0.93)**	**0.0014**	**0.85 (0.77,0.93)**	**0.0004**	0.5787
Components:							
Kidney failure	0.72 (0.49,1.05)	0.0889	0.87 (0.72,1.05)	0.1409	0.84 (0.71,0.99)	0.0392	0.3924
ESRD	0.64 (0.41,<1.00)		0.86 (0.67,1.10)		0.80 (0.64,0.99)		0.2609
Sustained decrease in eGFR to <15 mL/min	0.71 (0.43,1.16)		0.82 (0.67,1.01)		0.81 (0.67,0.98)		0.5885
Sustained decrease in eGFR ≥40% (relative to baseline)	0.87 (0.75,>1.00)[b]	0.0526	0.81 (0.72,0.92)	0.0009	0.84 (0.76,0.92)	0.0002	0.5856
Renal death	0.20 (0.00,8.11)[a]	0.1539	1.02 (0.14,7.24)	0.9851	0.53 (0.10,2.91)	0.4599	0.9952
Time to first occurrence of 57% renal composite endpoint	**0.77 (0.60,0.99)**	**0.0406**	**0.76 (0.65,0.90)**	**0.0012**	**0.77 (0.67,0.88)**	**0.0002**	**0.9815**
Sustained decrease in eGFR ≥57% (relative to baseline)	0.76 (0.58,>1.00)[b]	0.0533	0.68 (0.55,0.82)	<.0001	0.70 (0.60,0.83)	<.0001	0.4811

Stratified cox models with the stratification factors study (only pooled model), history of CV disease (pooled and FIGARO model), region, eGFR category at screening and type of albuminuria at screening were fitted. The p-value is based on a two-sided stratified log-rank test. The interaction p-value displays the study*treatment interaction based on a stratified model including study, treatment and study*treatment as covariates and removing study as stratification factor.

a An unstratified model using Firth's penalized likelihood approach was applied due to zero cell counts and/or convergence issues

b All presented HRs and corresponding 95% CIs are rounded to 2 digits after the decimal. Upper limits preceded by the signs '<' or '>' indicate that the upper limit is rounded to 1.00 but the exact value is slightly below or above 1.00, respectively.

CI = confidence interval, CV = cardiovascular, eGFR = estimated glomerular filtration rate, ESRD=end-stage renal disease, FAS = full analysis set, HR = hazard ratio for the comparison of finerenone versus placebo, 40% (57%) renal composite endpoint=onset of kidney failure, sustained decrease of eGFR ≥40% (≥57%) from baseline over at least 4 weeks, or renal death, 57% renal composite endpoint=onset of kidney failure, sustained decrease of eGFR ≥57% from baseline over at least 4 weeks, or renal death

Source: Module 5.3.5.3, Report PH-42134, Table 14.2.2/3

Other secondary efficacy endpoints

For all-cause mortality, a treatment effect in favour of finerenone compared to placebo was observed that narrowly missed nominal statistical significance in the pooled analysis (HR 0.89, 95% CI 0.79;1.00). The result seen for all-cause mortality was due to lower incidence rates in the finerenone arm for CV death and fatal non-CV/non-renal events in both studies.

For all-cause hospitalization, there was a trend towards a treatment effect in favour of finerenone with a HR of 0.96 (95% CI 0.91;1.01) in the pooled analysis. The result seen for all-cause hospitalization was due to a treatment effect in favour of finerenone for CV hospitalization, that narrowly missed nominal statistical significance in the pooled analysis (HR 0.93, [95% CI 0.86;1.00]). The subcomponent hospitalization due to heart failure showed a strong result: Incidence rates in the finerenone arm were lower compared with placebo in both studies; the difference resulted in a nominally statistically significant result in FIGARO-DKD (HR 0.71, [95% CI 0.56; 0.90]) and the pooled analysis (HR 0.78, [95% CI 0.66; 0.92]).

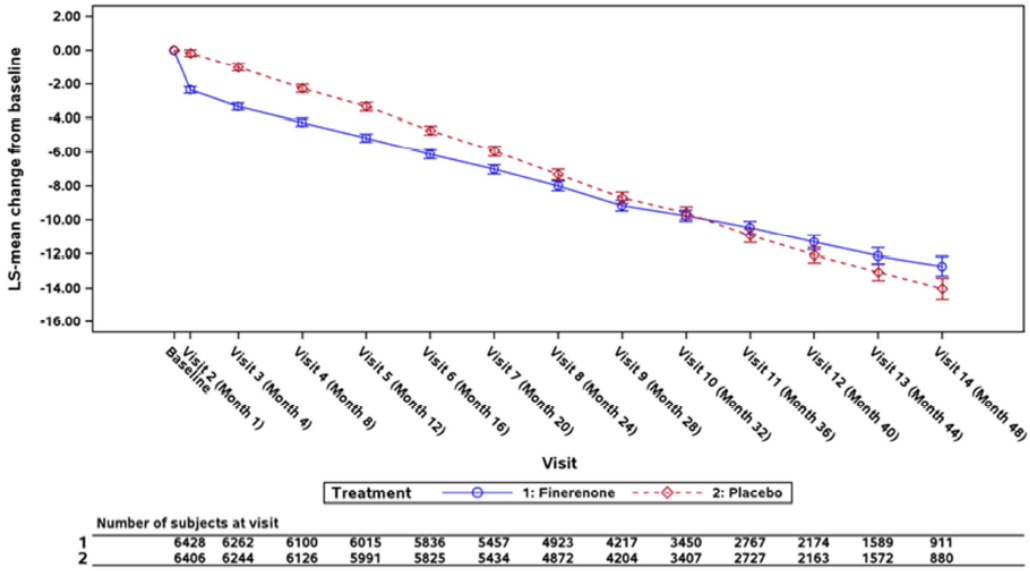
Decrease in eGFR

After baseline, the initial decline in eGFR was larger in the finerenone arm compared with placebo (Figure 38). At Month 4, the between-group difference of LS means (finerenone minus placebo) was -2.24 and -2.38 mL/min/1.73m^2 in FIGARO-DKD and FIDELIO-DKD, respectively.

Thereafter, the between-group difference decreased progressively and a chronic attenuation in the eGFR slope was seen in the finerenone treated subjects compared with placebo; crossing of the curves occurred at around Month 36 in FIGARO-DKD, Month 24 in FIDELIO-DKD and Month 32 in the pooled analysis.

In an additional ANCOVA, the annualized chronic eGFR slope from Month 4 to the PD or EOS Visit was analysed. The slower decline in eGFR for finerenone vs placebo in both studies supports the results obtained for the renal composite endpoints, indicating a delay in the progression of CKD with finerenone treatment as a long term effect. For the pooled analysis, the preservation of the chronic eGFR slope decline as judged by a positive value for chronic slope differences was:

• -2.495 vs -3.702 mL/min/1.73m^2 (finerenone vs placebo), resulting in a LS means difference for finerenone minus placebo of 1.207 mL/min/1.73m^2 (annualized) (p-value of F-test <0.0001)



Mixed Model with factors treatment group, study, region, type of albuminuria at screening, eGFR category at screening, CV disease history, time, baseline value nested within eGFR category at screening, treatment*time, baseline value* time and treatment*study interaction as covariate.
Separate unstructured covariance patterns are estimated for each treatment group. Values after the onset date of ESRD are excluded from this analysis.
CV = cardiovascular, eGFR = estimated glomerular filtration rate, ESRD = end stage renal disease, FAS = full analysis set
Source: Module 5.3.5.3, Report PH-42134, Figure 14.2.5/1

Figure 38. Line plot for least square means of eGFR absolute changes from baseline by visit for the pooled analysis (Pooled analysis, FAS).

Subgroup analyses

For the CV composite endpoint, the point estimates of the HRs in the various subgroups were generally consistent with the overall result of the pooled analysis for the CV composite endpoint, with the majority having HRs <1. No treatment interaction p-values <0.05 were observed. Forest plot of the cardiovascular endpoint for GFR categories for the pooled analysis is provided in Figure 43 whereas a forest plot for the subgroup 'region' for the pooled analysis is provided in Figure 44.

For the secondary 40% and 57% renal composite endpoints, some significant treatment interactions were indicated for either one or both renal composite endpoints. However, according to the applicant, there was no evidence in any subgroup for qualitative interaction with negative treatment effects, as indicated by the Gail-Simon test. Subgroup data for the 40% renal endpoint is summarized in Table 33. Forest plot on GFR subgroups of the ≥40% and ≥57% renal endpoints for the pooled FIDELIO-DKD and FIGARO-DKD studies are shown in Figure 43.

Table 33. Data for subgroups for the 40% renal endpoint with p-values for interaction <0.05 (FAS, pooled analysis)

Covariate	Category	Finerenone n/N (IR per 100pt-yrs))	Placebo n/N (IR per 100pt-yrs)	HR (95% CI)	p-value for interaction (Wald)	p-value for two-sided Gail-Simon Test*
	OVERALL	854/6519 (4.81)	995/6507 (5.64)	0.85 (0.77;0.93)		
Region (6 categories)	Western Europe	145/1344 (3.69)	169/1392 (4.18)	0.87 (0.70;1.09)	0.0493	0.9016
	Eastern Europe	174/1592 (4.01)	183/1534 (4.32)	0.93 (0.76;1.15)		
	North America	153/1026 (5.7)	175/1025 (6.45)	0.88 (0.71;1.10)		
	Asia	242/1600 (5.35)	335/1604 (7.62)	0.68 (0.58;0.81)		
	Latin America	106/719 (6.46)	102/715 (6.27)	1.05 (0.80;1.37)		
	Others	34/238 (5.41)	31/237 (4.87)	1.04 (0.63;1.70)		
Race (4 categories)	White	490/4449 (4.02)	545/4420 (4.49)	0.90 (0.79;1.02)	0.0110	0.4769
	Black	61/253 (10.13)	61/269 (9.68)	0.86 (0.58;1.26)		
	Asian	222/1432 (5.5)	318/1462 (7.9)	0.68 (0.57;0.81)		
	Other	81/385 (8.87)	71/356 (8.31)	1.17 (0.84;1.64)		
Baseline albuminuria (mg/g)	Normalbuminuria (UACR < 30 mg/g)	4/120 (1.02)	5/110 (1.52)	0.58 (0.09;3.57)	0.0322	0.3556
	High albuminuria (30 mg/g - < 300 mg/g)	164/2076 (2.52)	144/2023 (2.27)	1.11 (0.88;1.39)		
	Very high albuminuria (>= 300 mg/g)	686/4321 (6.32)	846/4371 (7.71)	0.81 (0.73;0.89)		
Basel. potass (mmol/L) median FAS	<= 4.30 mmol/L (median)	415/3318 (4.51)	534/3284 (5.92)	0.76 (0.66;0.86)	0.0157	0.5000
	> 4.30 mmol/L (median)	439/3200 (5.14)	461/3220 (5.34)	0.95 (0.83;1.08)		
Baseline BMI (kg/m2) category 3	< 20 kg/m2	6/48 (4.71)	10/54 (8.09)	0.57 (0.18;1.82)	0.0033	0.8336
	20 - < 25 kg/m2	128/748 (6.46)	146/754 (7.26)	0.81 (0.63;1.03)		
	25 - < 30 kg/m2	248/2152 (4.17)	353/2183 (5.99)	0.67 (0.57;0.79)		
	30 - < 35 kg/m2	259/2026 (4.69)	281/1976 (5.15)	0.94 (0.79;1.11)		
	>= 35 kg/m2	210/1522 (5.1)	204/1528 (4.92)	1.04 (0.85;1.27)		
Baseline BMI (kg/m2) category 2	< 30 kg/m2	382/2948 (4.74)	509/2991 (6.34)	0.71 (0.62;0.82)	0.0004	0.5000
	>= 30 kg/m2	469/3548 (4.87)	485/3504 (5.05)	0.99 (0.88;1.13)		

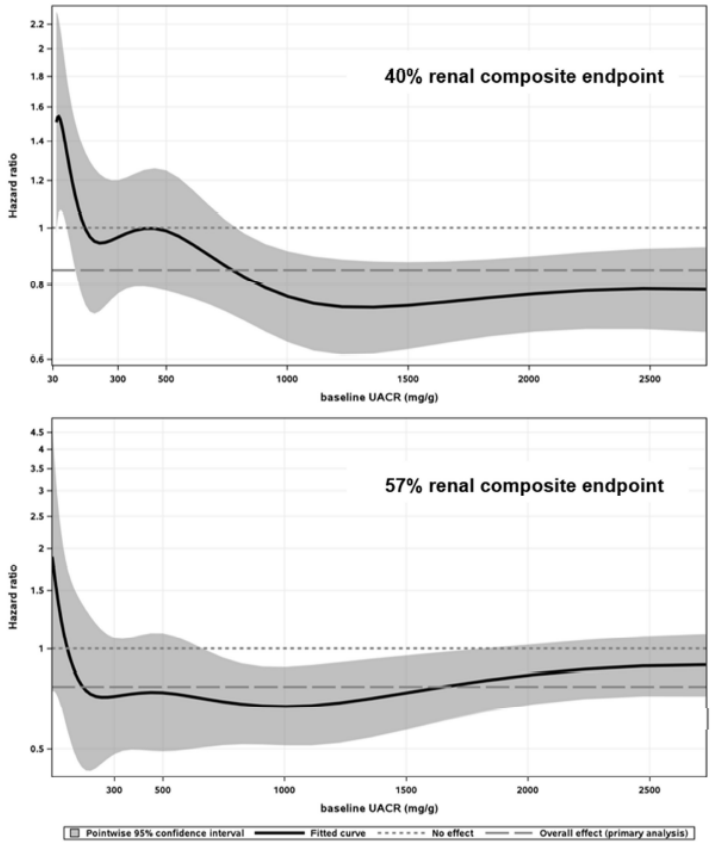
Events were adjudicated by an independent adjudication committee and considered from randomization up until the End of Study visit.
Events based on a sustained decrease in eGFR are considered from randomization up until 5 months after the last eGFR is recorded at a clinic visit.
A stratified cox proportional hazards model including treatment is calculated separately by subgroup category.
The interaction p-value is based on a stratified cox proportional hazards model including treatment, subgroup and treatment by subgroup interaction.
N.C. = Not calculated, because of no events in this subgroup.
*Only calculated in case interaction p-value <0.05.
**An unstratified model using Firth's penalized likelihood approach was applied due to zero cell counts and/or convergence issues.

Region and race: For the 40% renal composite endpoint, the lowest HRs were observed for subjects in Asia or Asian subjects, respectively (Table 33). HRs were 0.68 (Asia), 0.87 (Western Europe), 0.88 (North America), 0.93 (Eastern Europe), 1.04 (other regions) and 1.05 (Latin America). Subgroup analysis of the 57% renal composite endpoint also showed the lowest HRs for subjects in Asia or Asian subjects, respectively, but did not demonstrate significant treatment interaction by region or race.

Analyses by level of UACR: For the 40% renal composite endpoint, higher HRs were seen in subjects with 'high' albuminuria compared to those with 'very high' albuminuria (Table 33). Subgroup analysis of the 57% renal composite endpoint showed a similar trend, but did not demonstrate significant treatment interactions.

The stratified Cox proportional hazards model was fitted with covariates treatment, a cubic B-spline of baseline log(UACR) and its interaction with treatment. The fitted curves for HR by continuous baseline UACR indicate HRs <1.0 for UACR values above approximately 150 mg/g (Figure 39). Note that the confidence intervals widen for UACR <500 mg/g as the event numbers were low for the lower UACR values.

Analyses of eGFR over time showed the acute reduction in eGFR for subjects in all albuminuria subgroup categories. A stronger finerenone treatment effect on the total eGFR slope was observed earlier (crossover of the curves at Month 24) for subjects in the very high albuminuria subgroup compared to those with high albuminuria (no crossover up until Month 48) (Figure 40). A preservation of the chronic eGFR slope decline (from Month 4 onwards) was observed for both albuminuria subgroups as judged by positive values for chronic slope differences that reached nominal statistical significance in the very high albuminuria subgroup at screening or baseline.



A stratified Cox proportional hazards model is fitted with covariates treatment, a cubic B-spline of baseline log(UACR) with Q1, median and Q3 as knots and its interaction with treatment.
Stratification factors: study, region, albuminuria at screening, eGFR at screening and history of CV disease
CV = cardiovascular, eGFR = estimated glomerular filtration rate, FAS = full analysis set, Q = quartile, UACR = urinary albumin-to-creatinine ratio, 40% (57%) renal composite endpoint = onset of kidney failure, sustained decrease of eGFR ≥40% (≥57%) from baseline over at least 4 weeks, or renal death
Source: Module 5.3.5.3, Report PH-42134, Figure 14.2.6.6/1, Figure 14.2.6.6/5

Figure 39. Subgroup analysis for the 40% and 57% renal composite endpoints: continuous modelling using cubic splines in a Cox proportional hazards model (Pooled FIDELIO-DKD and FIGARO-DKD).

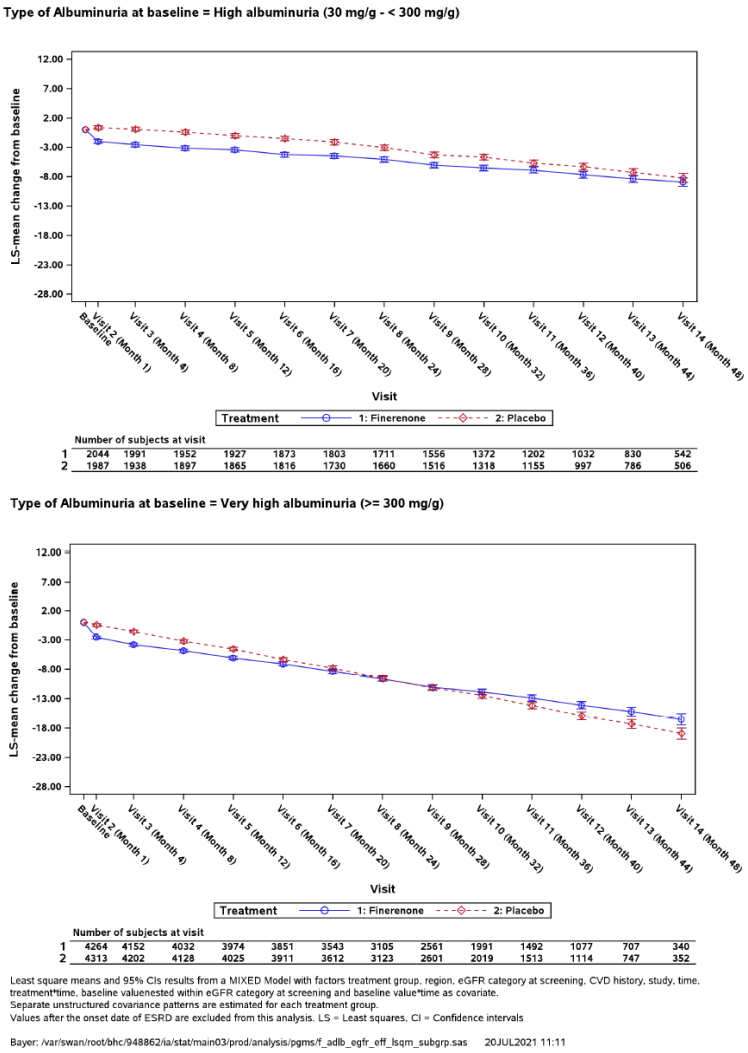
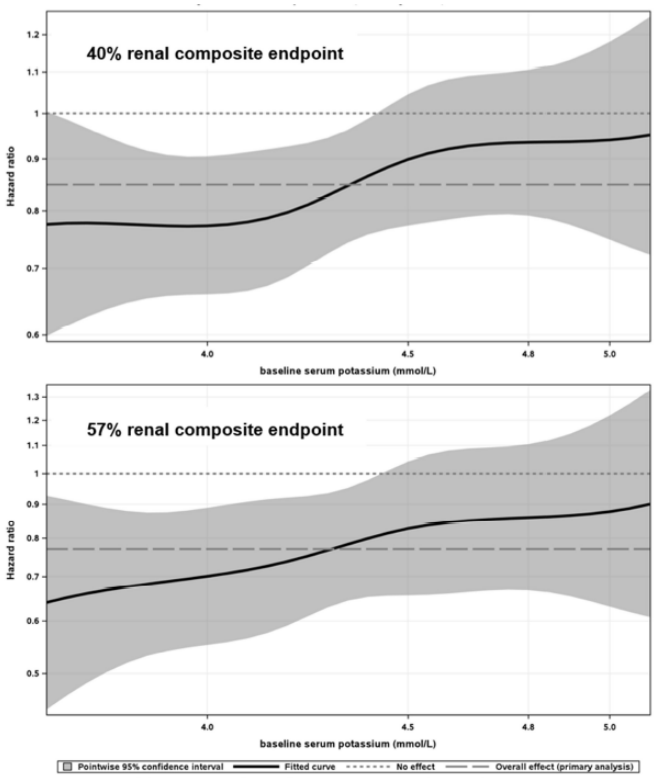


Figure 40. Line plot for least square means of eGFR absolute changes from baseline by visit and Type of Albuminuria at baseline (Pooled analysis, full analysis set).

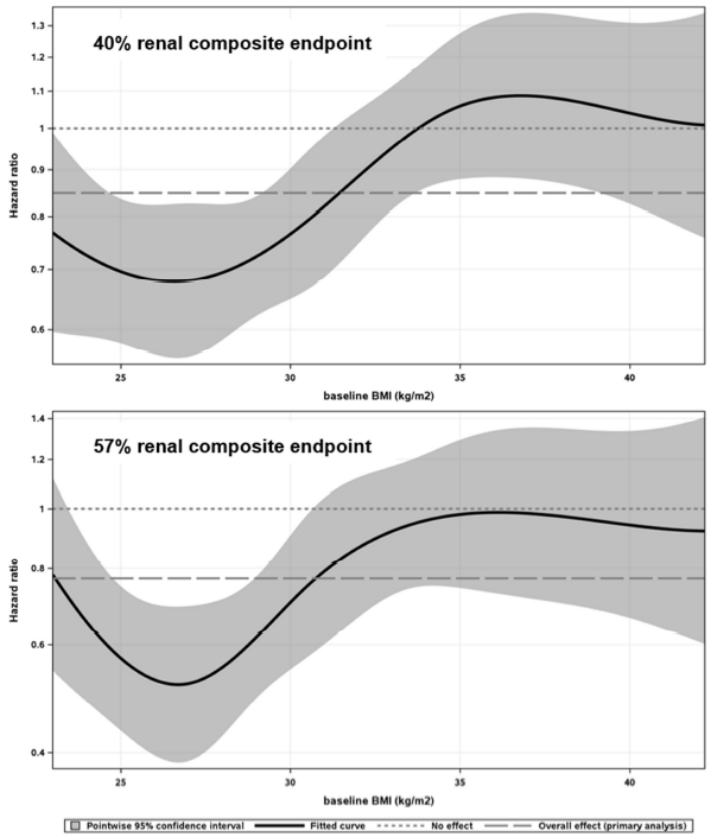
Baseline serum potassium: Baseline serum potassium categorization by median FAS value resulted in treatment interaction p-values <0.05 in both renal endpoints, with lower HRs for the lower serum potassium category (Table 33). The stratified Cox proportional hazards model was fitted with covariates treatment, a cubic B-spline of baseline serum potassium and its interaction with treatment. The fitted curves for HR by continuous baseline serum potassium show an increasing trend, but with a favourable treatment effect of finerenone with HRs <1.0 across all serum potassium levels. The confidence intervals included the respective overall treatment effect of the primary analysis of HR 0.87 and HR of 0.77 for the 40% and 57% renal composite endpoint, respectively (Figure 41).



A stratified Cox proportional hazards model is fitted with covariates treatment, a cubic B-spline of baseline serum potassium with the percentiles P33 and P66 as knots and its interaction with treatment.
Stratification factors: study, region, albuminuria at screening, eGFR at screening and history of CV disease
CV = cardiovascular, eGFR = estimated glomerular filtration rate, FAS = full analysis set, 40% (57%) renal composite endpoint = onset of kidney failure, sustained decrease of eGFR ≥40% (≥57%) from baseline over at least 4 weeks, or renal death
Source: Module 5.3.5.3, Report PH-42134, Figure 14.2.6.6/3, Figure 14.2.6.6/7

Figure 41. Hazard ratio for the 40% and 57% renal composite endpoints by baseline serum potassium, (pooled analysis across FIGARO-DKD and FIDELIO-DKD, FAS).

Baseline BMI: Subgroup analyses by BMI categories showed a significant treatment interaction for both renal endpoints (Table 33). The HRs for BMI <30kg/m^2 and ≥30kg/m^2 were 0.71 and 0.99, respectively, for the 40% renal composite endpoint and 0.63 and 0.93, respectively, for the 57% renal composite endpoint. HRs for BMI categories <20, 20 to <25, 25 to <30, 30 to <35, ≥35 kg/m^2) indicated a zig-zag pattern for the 40% renal composite endpoint and a U-shaped pattern for the 57% composite endpoint. The stratified Cox proportional hazards model was fitted with covariates treatment, a cubic B-spline of baseline BMI and its interaction with treatment. The results support the impression of a sigmoidal shape (Figure 42). Only for the 40% renal composite endpoint HRs >1.0 are seen with baseline BMIs >34 kg/m^2. For the 57% renal composite endpoint a consistently positive treatment effect of finerenone is seen by HRs <1.0 across all BMI values. The confidence intervals for higher BMI values included unity for both renal composite endpoints; for the 57% renal composite endpoint also the overall treatment effect of an HR of 0.77 of the primary analysis was included.



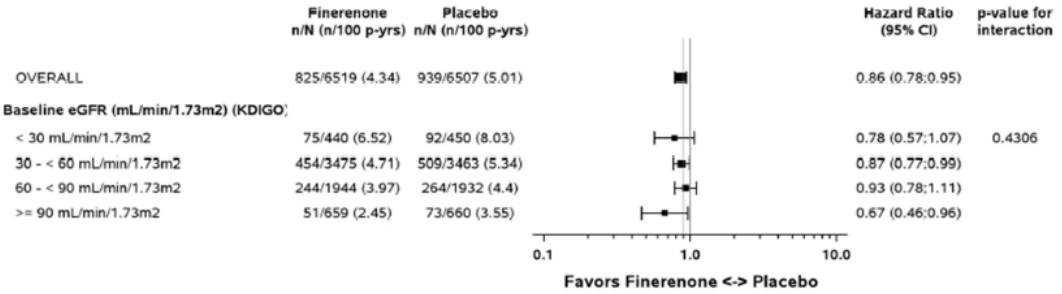
A stratified Cox proportional hazards model is fitted with covariates treatment, a cubic B-spline of baseline BMI with Q1, median and Q3 as knots and its interaction with treatment.
Stratification factors: study, region, albuminuria at screening, eGFR at screening and history of CV disease
CV = cardiovascular, BMI = body mass index, eGFR = estimated glomerular filtration rate, FAS = full analysis set, Q = quartile, 40% (57%) renal composite endpoint = onset of kidney failure, sustained decrease of eGFR ≥40% (≥57%) from baseline over at least 4 weeks, or renal death
Source: Module 5.3.5.3, Report PH-42134, Figure 14.2.6.6/4, Figure 14.2.6.6/8

Figure 42. Hazard ratio for the 40% and 57% renal composite endpoints by baseline BMI, (Pooled analysis across FIGARO-DKD and FIDELIO-DKD, FAS).

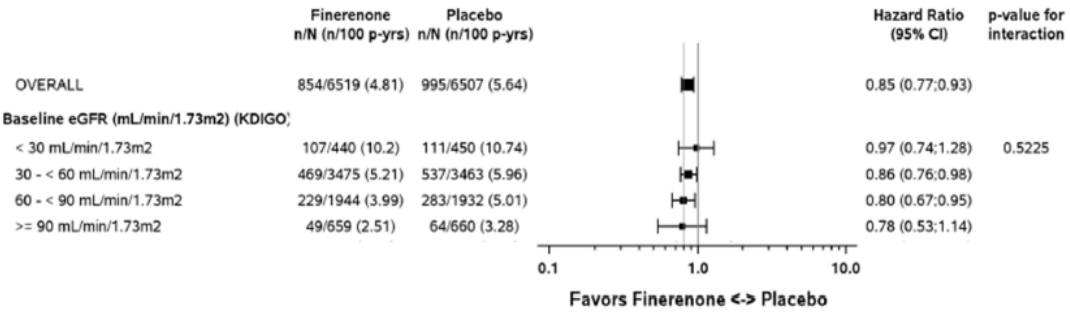
Baseline weight: Subgroup analysis by baseline weight resulted in a significant treatment interaction only for the 57% composite endpoint, most likely due to the small subject number in the weight group <50 kg. HRs were 1.96, 0.65 and 0.92 for <50, 50-<90 and ≥90 kg body weight; respective HRs for the 40% renal composite endpoint were 1.13, 0.77 and 0.97 and did not demonstrate significant treatment interaction.

eGFR values (in mL/min/1.73m^2) reflect the KDIGO-defined stage of CKD:
eGFR <30 = stage 4; eGFR 30 to <60 = stage 3; eGFR 60 to <90 = stage 2; eGFR ≥90 = stage 1

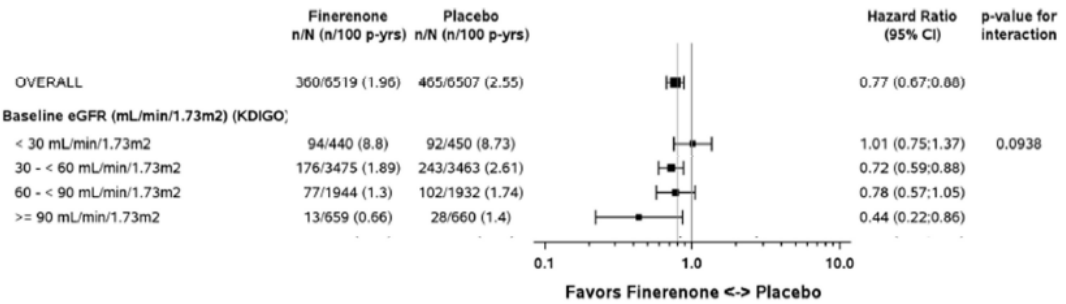
Forest plot showing hazard ratios for time to CV death, non-fatal myocardial infarction, non-fatal stroke or heart failure hospitalization by subgroups - panel 2 (full analysis set) - FIGARO-DKD & FIDELIO-DKD



Forest plot showing hazard ratios for time to onset of kidney failure, a sustained decrease of eGFR >= 40% from baseline over at least 4 weeks, or renal death by subgroups - panel 2 (full analysis set) - FIGARO-DKD & FIDELIO-DKD



Forest plot showing hazard ratios for time to onset of kidney failure, a sustained decrease of eGFR >= 57% from baseline over at least 4 weeks, or renal death by subgroups - panel 2 (full analysis set) - FIGARO-DKD & FIDELIO-DKD



A stratified cox proportional hazards model including treatment is calculated separately by subgroup category. The interaction p-value is based on a stratified cox proportional hazards model including treatment, subgroup and treatment by subgroup interaction. Events based on a sustained decrease in eGFR are considered from randomization up until 5 months after the last eGFR is recorded at a clinic visit. An unstratified model using Firth's penalized likelihood approach was applied due to zero cell counts and/or convergence issues.
Source: Module 5.3.5.3, Report PH-42134, Figures 14.2.6.1/2, /10 and /34

Figure 43. Forest plot of CV composite and renal composite endpoints by baseline eGFR category (reflecting KDIGO stages of CKD) in the pooled analysis of FIGARO-DKD and FIDELIO-DKD (FAS).

Forest plot showing hazard ratios for time to CV death, non-fatal myocardial infarction, non-fatal stroke or heart failure hospitalization by subgroups - panel 1 (full analysis set) - FIGARO-DKD & FIDELIO-DKD

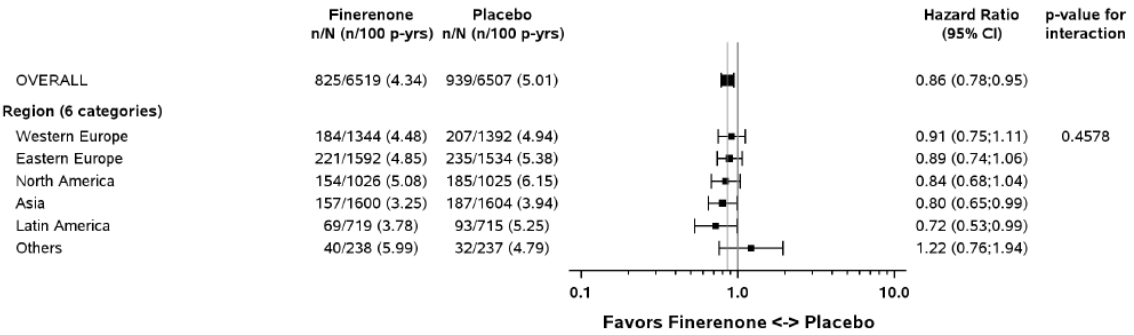


Figure 44. Forest plot showing hazard ratios for time to CV death, non-fatal myocardial infarction, non-fatal stroke or heart failure hospitalization by subgroups - panel 1 (full analysis set) – pooled FIGARO-DKD & FIDELIO-DKD. (Modified by Assessor)

The applicant has provided an explorative analysis on pooled data from the FIDELIO-DKD and the FIGARO-DKD studies. Baseline characteristics in the two studies are in general similar. However, the FIGARO-DKD study submitted with this application enrolled patients with a generally more mild CKD, i.e. higher eGFR and lower UACR than in the FIDELIO-DKD study. The pooled dataset contains app. 450 patients in CKD stage 4, 3500 patients in stage 3, 1950 patients in stage 2 and 650 patients in stage 1, per treatment arm, thus, all KDIGO categories are represented by reasonable numbers.

For the CV endpoint, treatment with finerenone resulted in a 14% relative hazard reduction compared with placebo (HR 0.86 [95% CI 0.78;0.95]; p=0.0018). In general, the treatment effect appears consistent across subgroups. Given that the CV endpoint to a large extent is driven by hospitalization for heart failure, possible regional differences are of interest given that treatment practices may vary. However, the response across the different region however appears similar which is reassuring. Also, given that patients with symptomatic HF were excluded, the study is less susceptible for this type of bias.

For the ≥40% renal composite endpoint, treatment with finerenone resulted in a 15% relative hazard reduction compared with placebo (HR 0.85 [95% CI 0.77;0.93]; p=0.0004) which is supported by a 23% reduction of the ≥57% renal composite (HR 0.77 [95% CI 0.67; 0.88]; p=0.0002). The pooled analysis of the FIDELIO-DKD and FIGARO-DKD studies encompass patients with a wider GFR range than the individual studies. For the KDIGO GFR categories with most participants, i.e. CKD stage 2 and 3, no heterogeneity in the response was noted for neither the ≥40% nor the ≥57% renal endpoint. The subgroup analysis may indicate a weaker effect of the treatment in CKD stage 4 (HR=0.97 and 1.01 for the ≥40% and the ≥57% endpoints, respectively) and a more pronounced effect in stage 1 (HR=0.78 and 0.44 for the ≥40% and the ≥57% endpoints, respectively). The response in different GFR subgroups may however be affected by different levels of albuminuria, due to the inclusion criteria.

In the FIGARO-DKD study, a more pronounced treatment effect on the ≥40% renal composite was observed in subjects with ‘very high’ albuminuria compared to ‘high’ albuminuria, which was also evident in the pooled analysis. The fitted curves for HR by continuous baseline UACR indicate HRs <1.0 for UACR values above approximately 150 mg/g.

For the chronic eGFR slope, the treatment effect of finerenone on the chronic eGFR slope was reduced in patients in the “high” compared to the “very high” subgroup (0.702 [95% CI 0.143;1.261] vs. 1.539 [95% CI 0.604; 2.475] mL/min/1.73m² per year compared to placebo). A similar pattern was seen in the pooled analysis (0.606 [95% CI 0.084 , 1.127] vs. 1.511 [95% CI 1.030 , 1.991] mL/min/1.73m² per year compared to placebo).

The observed reduced treatment effect on the ≥40% renal composite endpoint in patients with higher baseline serum potassium observed in the FIGARO-DKD study was also observed in the pooled analysis. The influence was however less pronounced and HRs below 1 were observed for all potassium levels.

In the pooled analysis, patients with elevated BMI displayed a reduced treatment effect on the ≥40% renal composite, suggesting HRs >1.0 with baseline BMIs >34. The issue has been previously discussed based on data from the FIDELIO-DKD study during the initial approval procedure without reaching any conclusions.

In addition, the Applicant provided a pooled analysis of CV and renal endpoints by subgroups as stratified based on the combined evaluation of eGFR and UACR levels. Analyses by the overlapping populations between the studies, i.e. the comparable risk populations, are displayed pooled in *Figure 45* and *Figure 47* for the CV and renal endpoints, respectively. Post-hoc analyses for the subgroup eGFR*UACR at baseline are shown in *Figure 46* and *Figure 48* for the CV and renal endpoints, respectively.

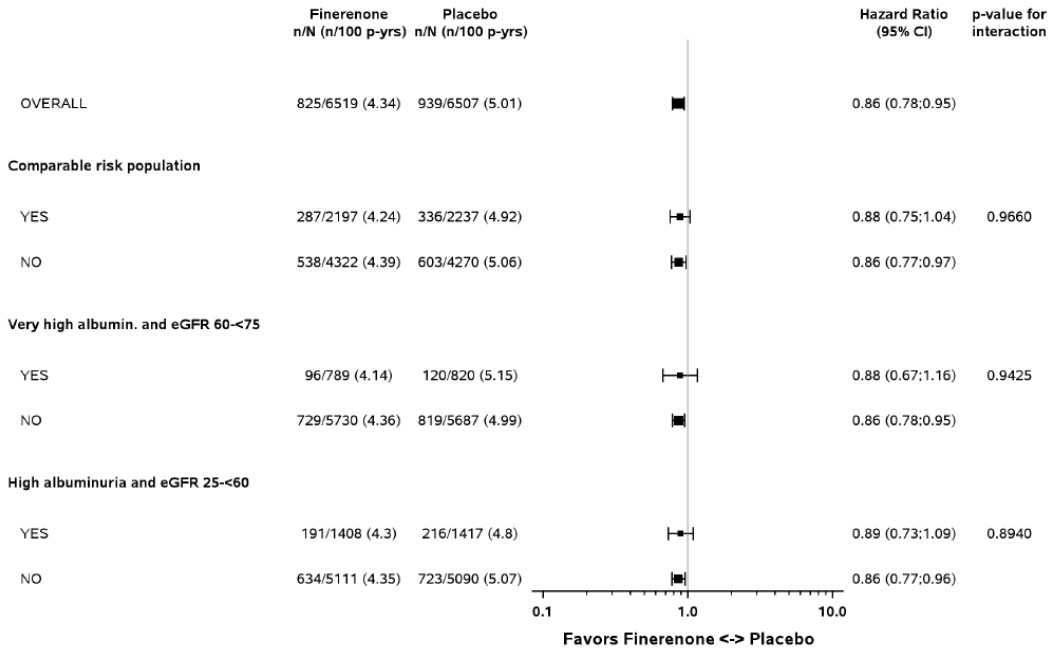
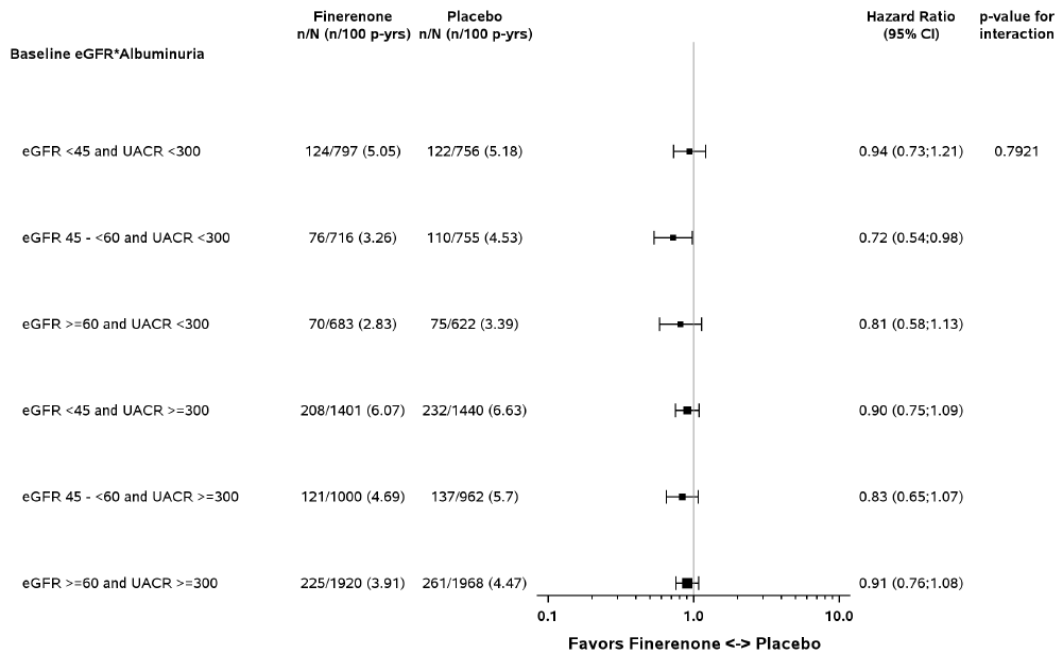
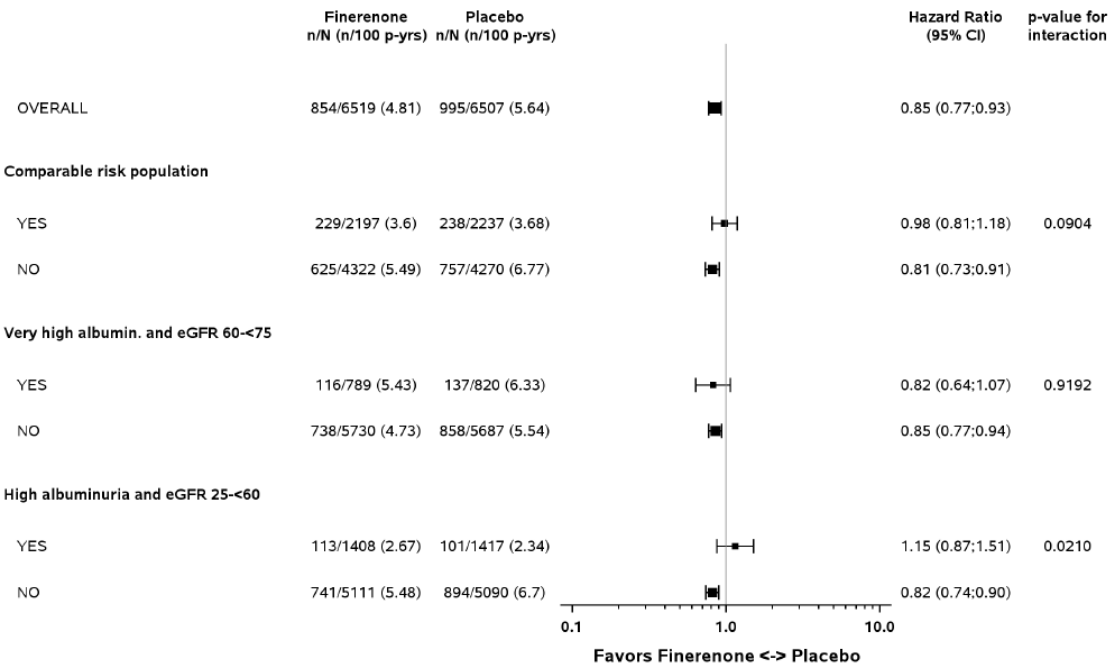


Figure 45. Forest plot showing hazard ratios for time to CV death, non-fatal myocardial infarction, non-fatal stroke or heart failure hospitalization by comparable risk populations (full analysis set) FIGARO-DKD & FIDELIO-DKD - Panel 1.



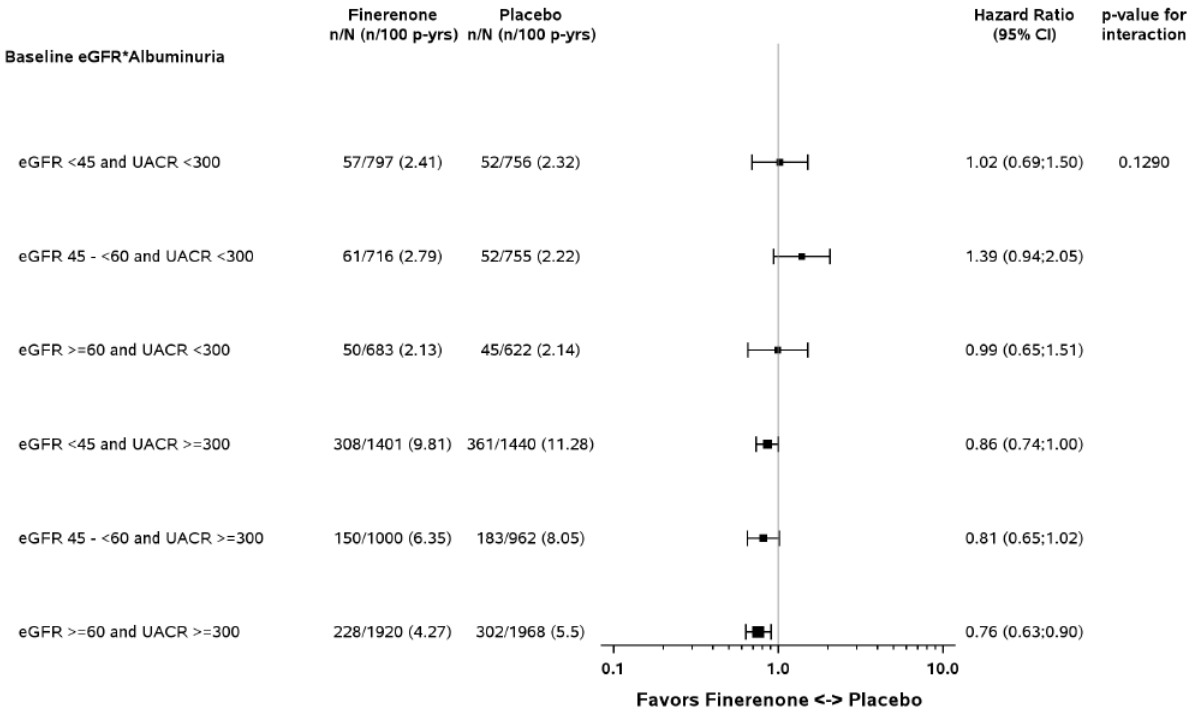
Events were adjudicated by an independent adjudication committee and considered from randomization up until the End of Study visit.
A stratified cox proportional hazards model including treatment is calculated separately by subgroup category.
The interaction p-value is based on a stratified cox proportional hazards model including treatment, subgroup and treatment by subgroup interaction.
Bayer: /var/swan/root/bhc/948862/ia/stat/main03/prod/analysis/pgms/tf_adtte_risk_posthoc.sas 20JUL2021 11:11

Figure 46. Forest plot showing hazard ratios for time to CV death, non-fatal myocardial infarction, non-fatal stroke or heart failure hospitalization by comparable risk populations (full analysis set) FIGARO-DKD & FIDELIO-DKD - Panel 2.



Events were adjudicated by an independent adjudication committee and considered from randomization up until the End of Study visit.
A stratified cox proportional hazards model including treatment is calculated separately by subgroup category.
The interaction p-value is based on a stratified cox proportional hazards model including treatment, subgroup and treatment by subgroup interaction.
Bayer: /var/swan/root/bhc/948862/ia/stat/main03/prod/analysis/pgms/tf_adtte_risk_posthoc.sas 20JUL2021 11:11

Figure 47. Forest plot showing hazard ratios for time to onset of kidney failure, a sustained decrease of eGFR >= 40% from baseline over at least 4 weeks, or renal death by comparable risk populations (full analysis set) FIGARO-DKD & FIDELIO-DKD - Panel 1.



Events were adjudicated by an independent adjudication committee and considered from randomization up until the End of Study visit.
A stratified cox proportional hazards model including treatment is calculated separately by subgroup category.
The interaction p-value is based on a stratified cox proportional hazards model including treatment, subgroup and treatment by subgroup interaction.
Bayer: /var/swan/root/bhc/948862/ia/stat/main03/prod/analysis/pgms/tf_adtte_risk_posthoc.sas 20JUL2021 11:11

Figure 48. Forest plot showing hazard ratios for time to onset of kidney failure, a sustained decrease of eGFR >= 40% from baseline over at least 4 weeks, or renal death by comparable risk populations (full analysis set) FIGARO-DKD & FIDELIO-DKD - Panel 2.

While no heterogeneity was observed across categories by eGFR/UCAR levels in terms of CV outcomes, the pooled analysis of the renal endpoints revealed a significant difference in response to treatment across subgroups depending on level of albuminuria. Within the Stage 3 and 4 KDIGO categories (eGFR<60 ml/min/m^2), treatment favoured finerenone in patients with “very high” albuminuria but not in those with “high” albuminuria. In the assessment of the initial MAA, the effect of different degrees of albuminuria could not be fully characterised due to the limited numerosity of the “high” albuminuria group of the FIDELIO trial. The implementation of this subcategory with the subpopulation of patients recruited in the FIGARO trial offers the possibility for a data revision. The pooled analysis demonstrates that the effect of treatment remains beneficial (HR<1) for all eGFR categories in the presence of “very high” levels of albuminuria, whilst HR≥0.99 was observed for “high” albuminuria patients, including those with Stage 3 and 4 CKD (eGFR<60 ml/min/m^2). The heterogeneity in the effect was reflected in section 5.1 of the SmPC of Kerendia.

Ancillary analyses

Baseline albuminuria

To address the heterogeneity observed for the secondary 40% renal endpoint in relation to baseline albuminuria, the applicant has conducted additional analyses.

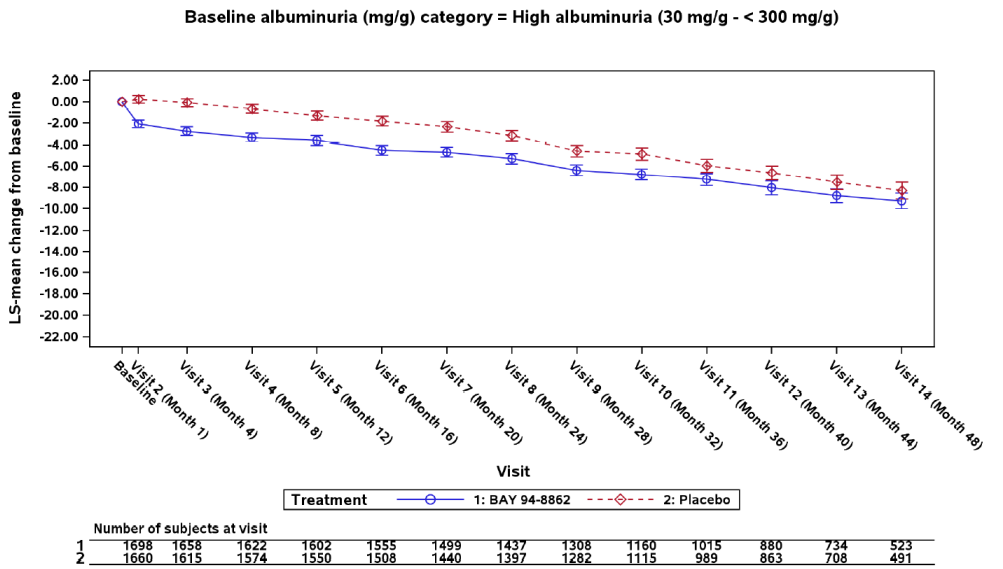
Line plots of the eGFR absolute changes from baseline for the “high” and “very high” subgroups are provided in *Figure 30*.

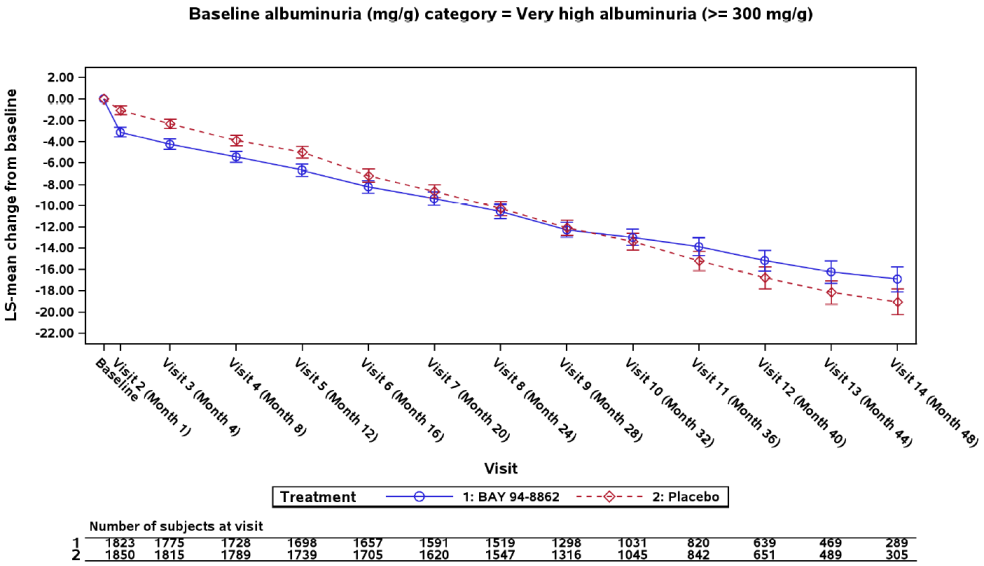
For the chronic eGFR slope, the treatment effect of finerenone on the chronic eGFR slope was reduced in patients in the “high” compared to the “very high” subgroup (0.702 [95% CI 0.143;1.261] vs. 1.539 [95% CI 0.604; 2.475] mL/min/1.73m^2 per year compared to placebo). This may be expected given that also the decline in the placebo group in the “high” albuminuria subgroup was less pronounced than in the

“very high” albuminuria subgroup (-1.8 mL/min/1.73 m2 vs. -5.0 mL/min/1.73 m2 per year), reflecting the lower progression rate of renal dysfunction in these patients. The eGFR curves in the “very high” group cross at month 24 while no crossing is observed during the study in the “high” albuminuria subgroup.

For the pooled data, a similar picture was observed (chronic slope differences of 0.606 and 1.511 mL/min/1.73m² per year for high albuminuria and very high albuminuria at baseline, respectively. For the secondary endpoint UACR at month 4, a similar reduction was found in both the “high” and “very high” subgroups (*Figure 50*). Additional explorative data shows a sustained reduction in both subgroups up to 36 months (*Figure 51*).

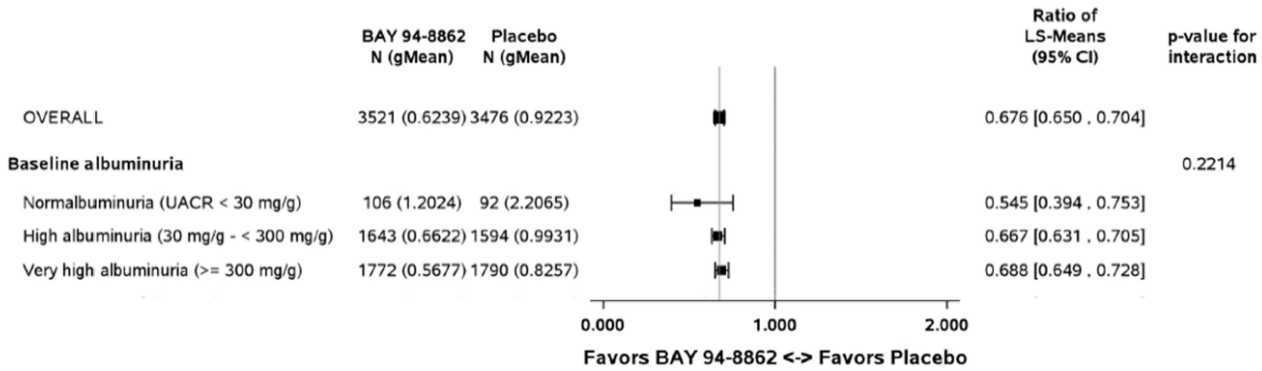
An additional net clinical benefit (NCB) outcome was defined. This NCB outcome is restricted to fatal events and events with irreversible harm (i.e. efficacy outcomes including all-cause mortality, stroke, MI, hospitalization for HF, and kidney failure; safety outcomes including fatal, life-threatening and AEs leading to persistent or significant disability / incapacity for hyperkalaemia [defined in the EU RMP version 2.2 as an important identified risk] and acute renal failure) in the pooled Phase 3 studies FIDELIO-DKD and FIGARO-DKD. The NCB outcome can be considered as a composite efficacy and safety endpoint and was analysed using a stratified Cox proportional hazards model (*Table 34*).





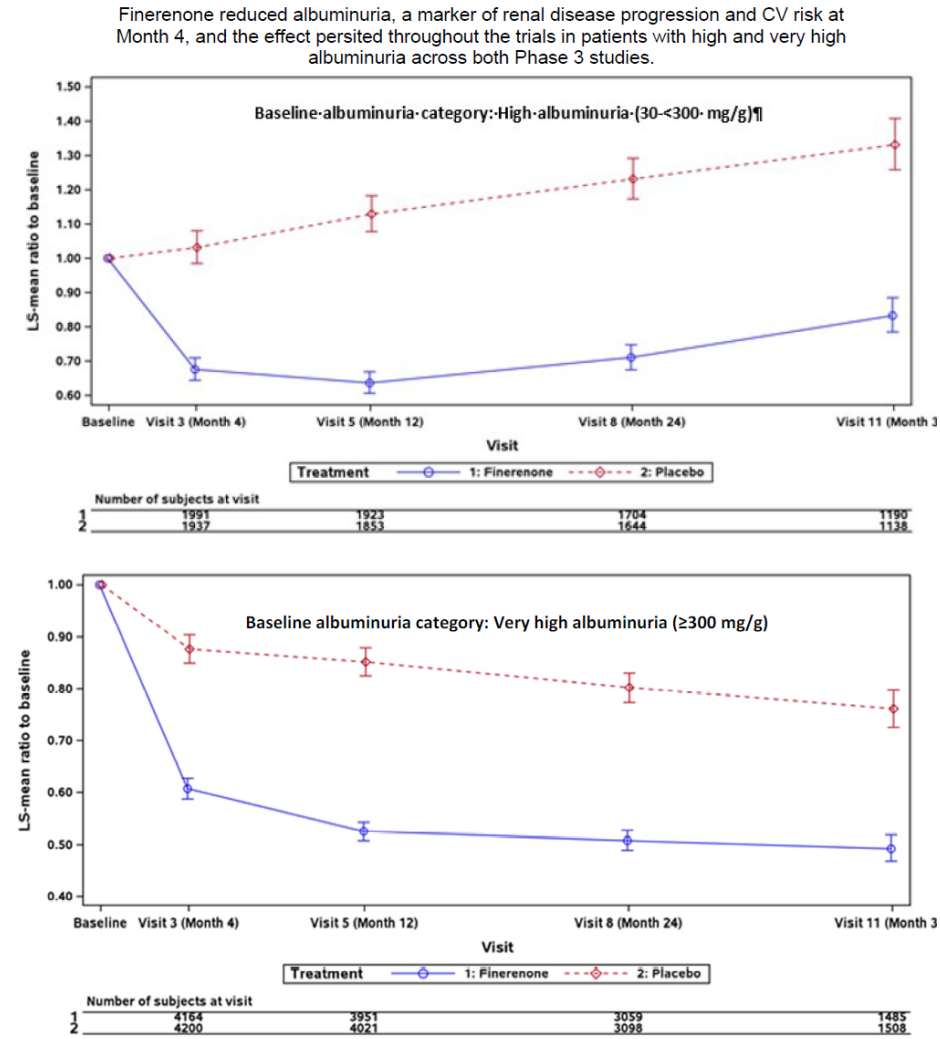
Least square means and 95% CIs result from a MIXED Model with factors treatment group, region, eGFR category at screening, type of albuminuria at screening, CVD history, time, treatment*time, baseline value nestedwithin eGFR category at screening and baseline value*time as covariate.
Separate unstructured covariance patterns are estimated for each treatment group.
Values after the onset date of ESRD are excluded from this analysis. LS = Least squares, CI = Confidence intervals

Figure 49. Line plot for least square means of eGFR absolute changes from baseline by visit and Baseline albuminuria (mg/g) category (FIGARO-DKD, full analysis set)



For Month 4, the closest observation to Day 120 within a time window of 120 +/- days after randomization is used. If no measurements are available in this time window, the subject is excluded from this analysis. ANCOVA with factors treatment group, region, eGFR category at screening, type of albuminuria at screening, CVD history, .log-transformed baseline value as covariate nested within type of albuminuria, subgroup and treatment group by subgroup interaction.
BAY 94-8862 = finerenone, gMean = geometric mean of the ratio of UACR at Month 4 at baseline. CI = confidence interval, CV(D) = cardiovascular (disease), eGFR = estimated glomerular filtration rate, FAS = full analysis set, LS = least squares, N = number of subjects, UACR = urinary albumin-to-creatinine ratio
Source: Module 5.3.5.1, PH-39747, Figure 14.2.4/53

Figure 50. Forest plot of analysis of covariance for ratio to baseline at Month 4 of UACR by stratification factors (FAS, FIGARO-DKD).



LS means and 95% CI results from a MIXED Model with factors treatment group, region, eGFR category at screening, type of albuminuria at screening, CVD history, time, treatment*time, study, study*treatment, log-transformed baseline value nested within type of albuminuria at screening and log-transformed baseline value*time as covariate.
Separate Toeplitz covariance patterns are estimated in each treatment group
Values after onset of ESRD are excluded from this analysis
CV(D) = cardiovascular (disease), eGFR = estimated glomerular filtration rate, FAS = full analysis set, LS = least squares, UCAR = urinary albumin-to-creatinine ratio
Source: bay948862_ia_ema_2nd_list_of_questions_final_fidelio_figaro, Figure 1.1/2

Figure 51. Line plots for LS means for ratio to baseline of UACR values by visit by albuminuria subgroup (FAS; Pooled FIGARO-DKD and FIDELIO-DKD).

Table 34. Net clinical benefit: Cox proportional hazards model for time to first CV death, renal death, non-CV non-renal death, non-fatal MI, non-fatal stroke, kidney failure, HF hospitalization, fatal or irreversible

hyperkalemia1 or fatal or irreversible adverse events in the SMQ Acute renal failure (broad) by baseline albuminuria (FAS) - FIGARO-DKD & FIDELIO-DKD.

Albuminuria at baseline	Finerenone n/N (IR per 100pt-yrs)	Placebo n/N (IR per 100pt-yrs)	HR (95% CI)	p-value for interaction (Wald)	p-value for 2-sided Gail-Simon Test*
OVERALL	1191/6519 (6.66)	1361/6507 (7.71)	**0.86** (0.79; 0.93)		
Normalbuminuria (UACR <30 mg/g)	10/120 (2.57)	22/110 (6.83)	**0.40** (0.17; 0.95)	0.0383	0.7500
High albuminuria (30 mg/g - <300 mg/g)	363/2076 (5.58)	387/2023 (6.18)	**0.90** (0.78; 1.04)		
Very high albuminuria (≥300 mg/g)	817/4321 (7.43)	951/4371 (8.60)	**0.86** (0.78; 0.95)		

[1] MLG hyperkalemia including PTs hyperkalemia and blood potassium increase.
Efficacy events were adjudicated by an independent adjudication committee and considered from randomization up until the End of Study visit.
A stratified cox proportional hazards model including treatment is calculated separately by subgroup category.
The interaction p-value is based on a stratified cox proportional hazards model including treatment, subgroup and treatment by subgroup interaction.
*Only calculated in case interaction p-value <0.05.
Only the first event of the composite outcome of renal, CV and safety (MLG hyperkalemia or Narrow SMQ Acute renal failure) events occurring after randomization is considered. Subsequent events are not considered.
Fatal or irreversible AE are defined by events with reason for seriousness in Results in death, Is life threatening or Persistent or significant disability / incapacity.
AE = adverse event, CV = cardio-vascular, FAS = full analysis set, HF = heart failure, HR = hazard ratio, MedDRA = Medical Dictionary for Regulatory Activities, MI = myocardial infarction, MLG = Bayer MedDRA Labeling Grouping, N = number of subjects, n = number of subjects per category, PT = preferred term, pt-yrs = patient-years, SMQ = Standard MedDRA Query, UACR = urinary albumin-to-creatinine ratio
Source: bay948862_ia_ema_2nd_list_of_questions_final_fidelio_figaro, Table 1.5/1

2.4.2. Discussion on clinical efficacy

The application for variation is based on efficacy data from the FIGARO-DKD study.

Design and conduct of clinical studies

The FIGARO-DKD Study 17530 was a randomized, double-blind, placebo controlled, parallel-group, multicenter, event-driven Phase 3 study in patients with T2D and CKD.

Like the FIDELIO-DKD study, the pivotal study for the initial market authorisation for finerenone, subjects with CKD and T2D were enrolled and had to be treated with the individual maximum tolerated labelled dose of either an ACEI or an ARB. Eligible patients had persistent high albuminuria (UACR ≥30 to <300 mg/g) and eGFR 25-90 mL/min or very high albuminuria (UACR ≥300 mg/g) and eGFR ≥60mL/min. Thus, patients had in general higher GFR and lower degree of albuminuria than the previous study in order to enrich the study for CV rather than renal events, in line with the CHMP advice.

The study was amended twice globally, and the amendments are in general considered appropriate.

The starting dose of study drug (10 or 20 mg) depended on the eGFR level at the screening visit and is in line with the currently approved SmPC. Up-titration to the target dose of 20 mg was permitted if serum potassium was ≤4.8 mmol/L and if eGFR had not decreased below a certain degree. The study drug dose could be titrated up or down according to the potassium response and investigators were encouraged to reach the maximum dose of 20 mg without compromising safety.

The primary endpoint was the time to the first occurrence of the composite endpoint of CV death or non-fatal MI, non-fatal stroke, or hospitalization for heart failure (abbreviated as the CV composite endpoint).

The key secondary endpoint was the time to the first occurrence of the renal composite endpoint of onset of kidney failure, a sustained decrease of eGFR ≥40% from baseline over at least 4 weeks, or renal death. Other secondary endpoints focused on all-cause hospitalization, all-cause mortality and UACR as

well as a secondary renal composite that defined a more pronounced eGFR decrease compared to the primary endpoint (≥57% vs. ≥40%).

The endpoints were similar to the FIDELIO-DKD study, but the primary and the key secondary endpoint have shifted places.

The statistical analysis as planned could overall be agreed. The FIGARO-DKD study shared a number of design and analysis features with the FIDELIO-DKD study. In that respect it is acknowledged that besides the different endpoint order, the two studies had slightly differently defined multiple testing procedures (MTPs). Both are considered appropriate as are based on a hierarchical testing procedure. The MTP in the FIDELIO-DKD study also included a weighted Bonferroni-Holm procedure for the primary and the key secondary endpoint. In both studies the remaining secondary endpoints were to be tested only if both the primary and most important secondary endpoint achieved formal statistical significance. The first secondary endpoint in the FIGARO-DKD study was the primary endpoint in FIDELIO-DKD study and vice versa, time to all-cause hospitalization and all-cause mortality had shifted place in the hierarchical order.

The latest version of the submitted SAP was version 6.0, dated 15 Feb 2021. The FIGARO-DKD study was completed on 02 Feb 2021 and database release occurred 19 April 2021. The changes made to the SAP has thoroughly been accounted for. Some were major, however none that raise any serious concern, and none that appears to have been inspired by the analysis of the FIDELIO-DKD study that was completed in April 2020.

Supportive analyses to account for the COVID-19 pandemic for primary and secondary time-to-event efficacy endpoints were planned (amendment to the SAP) and have been presented considering four different versions for the COVID-19 onset date (country-specific, global, individual pandemic related disruption date, individual COVID-19 AE date). Based on the analyses performed on the primary endpoint, the impact of the COVID-19 pandemic appears to have been limited.

In addition, a number of post-hoc analyses have been performed for further assessments after that subgroup analyses revealed treatment interactions ($p<0.05$) concerning baseline factors correlating with stage of kidney disease. In that respect, they are appreciated. The post-hoc analyses were briefly described in a separate SAP (version 1.0, 28 May 2021). Although the value of pre-definition is inherently less when it comes to analyses that by nature are data-driven, the SAP lacked details. Regarding continuous modelling of baseline UACR and potassium for renal composite endpoints there were no details, and the applicant was requested to clarify how and why a cubic B-spline was decided to best fit the data. Recognising the exploratory objective, the brief description presented by the applicant is accepted although does not add the details that were thought to be missing in the provided SAP. It is supported that candidates for knots were not only data-driven but also based on medical judgement while the selection of a cubic B-spline function was considered as a compromise between smoothness of the curves and overfitting the data. Furthermore, during the procedure, additional exploratory analyses were submitted further characterizing the response in relation to baseline albuminuria.

With respect to the presented pooled analysis of data from both the FIGARO- and the FIDELIO-DKD study, the applicant confirmed that the SAP for the pooled analysis was part of report PH-42134. This SAP was dated 24 FEB 2021 (version 3.0).

Efficacy data and additional analyses

The FIGARO-DKD study encompassed 3723 patients randomized to finerenone and 3714 patients randomized to placebo. The percentage of randomized subjects that completed the study was high (98.9% finerenone; 98.4% placebo). Over 80% of the participants took the medication for over 24 months.

Baseline characteristics were similar in the two treatment arms and were comparable to the previous FIDELIO-DKD study, except that eGFR was higher and UACR lower in the present study due to different inclusion criteria. Also, the occurrence of diabetic retinopathy was less frequent in the present study compared to the FIDELIO-DKD (app. 30% compared to 45%). Almost all patients had hypertension. Approximately 40% of patients had hyperlipidaemia, 30% coronary artery disease and 30% diabetic neuropathy. Mean values of HbA1c were app. 7.7% in both groups.

The primary endpoint intended to support the proposed amendment to the indication *"prevention of cardiovascular (CV) events in adults with CKD"*. Treatment with finerenone resulted in a 13% relative risk reduction compared with placebo for the CV composite endpoint of CV death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for heart failure (HR 0.87 [95% CI 0.76; 0.98]; p=0.0264). The primary endpoint of the study was thus met. The relative risk reduction was of a similar magnitude as observed in the previous FIDELIO-DKD study where this CV composite was defined as the key secondary endpoint (HR 0.86 [95% CI 0.747; 0.989]).

The Kaplan-Meier curves did separate starting 6 months after treatment initiation, which indicates a sustained effect. The absolute risk reduction based on Kaplan-Meier cumulative incidences for the primary CV endpoint was 2.0% at Month 36 and 2.1% at Month 42, corresponding to NNTs to prevent one primary endpoint event of 51 and 47 subjects, respectively.

The effect is driven by hospitalizations due to heart failure (HR 0.71 [95% CI 0.56; 0.90]; p=0.0043). The components non-fatal stroke and non-fatal MI were unchanged by the treatment whereas CV death was numerically slightly lower in the finerenone compared to the placebo arm (194/3686 vs. 214/3666 cases; HR 0.90 [95% CI 0.74; 1.09]; p=ns).

Of note, the rate of CV events was similar between the two study populations (12.4% vs 14.2% and 13% vs 14.8% in the FIGARO and FIDELIO, respectively), with a prevailing incidence of hospitalization for heart failure among the individual components of the composite endpoint. The two populations can be therefore regarded as homogenous and complementary in terms of CV risk. This is supported by the categorization of risk of disease progression as estimated on the basis of the combined eGFR/UACR analysis (KDIGO 2012 guidelines), which indicates that recruitment in both the FIDELIO and FIGARO mainly included the "high" and "very high" risk categories however with some representation of patients with "moderate" risk.

The treatment effect on the primary endpoint was generally consistent in subgroups with no statistically significant interactions for the stratification factors or other key subgroups. The treatment effect in Europe appears less pronounced (HR=0.95) than in the other regions. However, in the previous FIDELIO-DKD study and in the pooled analysis of the FIGARO-DKD and the FIDELIO-DKD studies, the effect was comparable to the effect in other regions. Uniform results across regions are important given that the CV endpoint was driven by CV hospitalization that may be sensitive to regional practice.

Finerenone had no effect on all-cause hospitalisation (HR = 0.97 [95% CI 0.90;1.04]; log rank test nominal p=0.3558) but had an effect on the component hospitalization due to heart failure, as previously discussed.

For all-cause mortality, finerenone treatment resulted in a 11% relative risk reduction compared to placebo (HR = 0.89 [95% CI 0.77;1.04]; log rank test nominal p=0.1337). The difference was not significant but indicates no general detrimental effect of the treatment, in line with previous findings from the FIDELIO-DKD study.

The study excluded symptomatic patients with heart failure (NYHA II-IV) with reduced ejection fraction, thus an HF hospitalisation can be regarded as the first manifestation of a more significant HF. In line with this, the exploratory endpoint new diagnosis of heart failure occurred less frequently in the finerenone group (HR=0.675 [95% CI 0.490; 0.929]; nominal p=0.016).

The key secondary endpoint intends to support a broadening of the indication to encompass all stages of CKD (with albuminuria) associated with type 2 diabetes (i.e. deletion of “stage 3 and 4” from the currently approved indication). Treatment with finerenone resulted in a 13% relative hazard reduction compared with placebo of the first secondary endpoint time to the first occurrence of onset of kidney failure, a sustained decrease of eGFR ≥40% from baseline over at least 4 weeks, or renal death (HR 0.87 [95% CI 0.76; 1.01] p=0.0689]) but the result did not reach statistical significance. In the previous FIDELIO-DKD study, this composite was defined as the primary endpoint and turned out significant with a slightly lower point estimate (HR = 0.825 [95% CI 0.732; 0.928]).

The Kaplan-Meier curves did separate after 24 months and indicate a sustained effect after this timepoint. In the previous FIGARO-DKD study, a sustained effect was also noted, but with an earlier curve separation at 12 months. When analysing the components of the composite, directionally consistent changes in kidney failure and sustained decrease in eGFR ≥40% (relative to baseline) were observed. For renal death, too few cases occurred (2 in the placebo group) to draw any conclusions.

Given that the secondary 40% renal composite endpoint did not meet the pre-planned criterion for significance, the remaining secondary endpoints were not tested formally, but in an exploratory manner.

The secondary 57% renal composite defined a more pronounced eGFR decrease that corresponds to a doubling of serum creatinine, compared to the primary endpoint that involved a ≥40% reduction. Treatment with finerenone resulted in a 23% relative hazard reduction compared with placebo (HR 0.77 [95% CI 0.60;0.99]; log rank test nominal p=0.0406) i.e. a similar risk reduction as seen in the previous FIDELIO-DKD study, providing support for renoprotection.

In line with the treatment effect observed in the previous FIDELIO-DKD study, UACR from baseline to month 4 was reduced in the finerenone group compared to placebo (HR=0.676 [95% CI 0.650; 0.704]; nominal p-value of F-test <0.0001) which supports the renoprotective mode of action. In addition, the explorative endpoint “regression of albuminuria from very high to high albuminuria and high albuminuria to normal albuminuria (accompanied by a UACR change of at least 30% from baseline)” was seen in more subjects in the finerenone arm (47.8%) than in the placebo arm (31.0%) (Odds ratio 2.051, [95% CI 1.861;2.260], Wald test nominal p<0.0001).

The responses in the 40% and 57% renal endpoints were heterogenous in subgroups of albuminuria, GFR and serum potassium.

Due to the inclusion criteria, there was a distinct relationship between albuminuria and eGFR at screening: the subgroup of ‘high’ albuminuria corresponded to subjects with lower range of eGFR of ≥25 to ≤90 mL/min/1.73 m^2 whereas the subgroup of ‘very high’ albuminuria corresponded to subjects with higher eGFR of ≥60 mL/min/1.73 m^2.

For the 40% renal endpoint, the treatment effect was reduced in subjects with ‘high’ albuminuria compared to ‘very high’ albuminuria; the HRs were 1.16 [95% CI 0.91; 1.47] compared to 0.74 [95% CI 0.62; 0.90]. For the 57% endpoint, the same pattern was seen but the estimate in the “high” subgroup is uncertain given the generally lower incidence in the placebo group compared to the incidence for the 40% endpoint (5.02 vs. 2.3 n/100 p-yrs). In the previous FIDELIO-DKD study, few participants with ’high’ albuminuria were enrolled, thus no reliable estimate of the effect in this population is available previously. A further post-hoc analysis using modelling indicates HRs >1 for the 40% renal endpoint for subjects with baseline UACR values below app. 400 mg/g. For the chronic eGFR slope, the treatment effect of finerenone on the chronic eGFR slope was reduced in patients in the “high” compared to the “very high” subgroup (0.702 [95% CI 0.143;1.261] vs. 1.539 [95% CI 0.604; 2.475] mL/min/1.73m^2 per year compared to placebo). This may be expected given that also the decline in the placebo group in the “high” albuminuria subgroup was less pronounced than in the “very high” albuminuria subgroup (-1.8 mL/min/1.73 m^2 vs. -5.0 mL/min/1.73 m^2 per year), reflecting the lower progression rate of renal

dysfunction in these patients. Nevertheless, both subgroups demonstrate a positive difference compared to the corresponding placebo groups. The eGFR curves in the “very high” group cross at month 24 while no crossing is observed during the study in the “high” albuminuria subgroup. For the secondary endpoint UACR at month 4, a similar reduction was found in both the “high” and “very high” subgroups. Additional explorative data provided in the response shows a sustained reduction in both subgroups up to 36 months.

Heterogeneity was also found for subgroups of GFR for the 40% and 57% renal endpoints. Given the inclusion criteria, most patients were in the ≥60 mL/min/1.73m^2 group of screening eGFR i.e. the population for the proposed indication broadening. A positive treatment effect was shown in this group as well as the 25-40 mL/min/1.73m^2 group. However, finerenone treated patients in the 45-60 mL/min/1.73m^2 group displayed an increased HR (1.62 [95% CI 1.12; 2.34]) for both the 40% and the 57% endpoints compared to the other GFR categories. Given that most patients in this GFR subgroup had ‘high’ albuminuria, the increased HR may be related to the degree of albuminuria rather than GFR. This is supported by data from the FIDELIO-DKD trial (where few participants were in category ‘high’) that showed no heterogeneity with regards to GFR. In summary, a positive treatment effect was found in eGFR subgroups in the range relevant for the proposed broadening of the indication whereas some subgroups, already covered by the present indication, displayed HR:s >1 which may be related to an interaction with the degree of albuminuria.

For serum potassium, patients with higher levels appears to have a reduced treatment effect. For the 40% endpoint, the HR in patients with potassium >4.3 mM was 1.06 [95% CI 0.85; 1.32] compared to 0.75 [95% CI 0.62; 0.91] for patients ≤4.3 mM. The heterogeneity was still present when data was stratified by a higher cut-off of 4.5 mM (HR 0.77 vs. 1.24). A further post-hoc analysis using modelling indicates a better treatment effect (i.e. lower HRs) in patients with a lower baseline potassium. Patients with serum potassium above 4.8 mM displayed a HR above 1. In the previous FIDELIO-DKD study, no heterogeneity in response related to serum potassium was however found. Patients with the highest potassium concentration at baseline (4.5 mmol/L) were equally distributed across the different subgroups by albuminuria and eGFR levels, contrarily to the expected inverse relationship between potassium and renal function. Therefore, the population of patients with potassium >4.5 mmol/L is quite heterogeneous and is not directly attributed to those with worse renal function. Given that the heterogeneity could not be reproduced in the two studies, that no biological rationale has been identified and that there was no heterogeneity related to potassium for the CV endpoint in either of the studies, the issue is not further pursued.

Efficacy data from the pooled analysis

The applicant has provided an explorative analysis on pooled data from the FIDELIO-DKD and the FIGARO-DKD studies. For the CV endpoint, treatment with finerenone resulted in a 14% relative hazard reduction compared with placebo (HR 0.86 [95% CI 0.78;0.95]; p=0.0018), driven by a reduction in hospitalizations for heart failure. The Kaplan-Meier curves start to diverge at month 6, supporting a sustained effect, in line with data from the individual FIDELIO-DKD and FIGARO-DKD studies. In general, the response appears consistent across subgroups, including regions.

In the pooled analysis, treatment with finerenone resulted in a 15% relative hazard reduction of the ≥40% renal composite endpoint compared with placebo (HR 0.85 [95% CI 0.77;0.93]; p=0.0004) which is supported by a 23% reduction of the ≥57% renal composite (HR 0.77 [95% CI 0.67; 0.88]; p=0.0002). The pooled analysis encompasses app. 450 patients in CKD stage 4, 3500 patients in stage 3, 1950 patients in stage 2 and 650 patients in stage 1 per treatment arm, thus, all KDIGO categories are represented by reasonable numbers. For the KDIGO GFR categories with most participants, i.e. CKD stage 2 and 3, the point estimates were in line with the overall HR for the ≥40% and the ≥57% renal endpoints. The subgroup analysis indicates a weaker effect of the treatment in CKD stage 4 (HR=0.97

and 1.01 for the ≥40% and the ≥57% endpoints, respectively) and a more pronounced effect in stage 1 (HR=0.78 and 0.44 for the ≥40% and the ≥57% endpoints, respectively). In conclusion, the pooled analysis is in general in support for an effect across the different KDIGO categories, including CKD stage 1 and 2 for which extension of indication is sought, however, heterogeneity in relation to baseline albuminuria was observed in line with the main analysis of the FIGARO-DKD study.

2.4.3. Conclusions on the clinical efficacy

The application for variation is based on efficacy data from the FIGARO-DKD study encompassing 7334 patients with CKD and T2D treated with the individual maximum tolerated labelled dose of either an ACEI or an ARB. Treatment with finerenone resulted in a 13% relative risk reduction compared with placebo for the composite endpoint of CV death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for heart failure. Thus, a statistically significant effect has been shown in line with data from the previous FIDELIO-DKD study. The effect as documented by the primary endpoint was driven by hospitalizations for heart failure while there was no effect on nonfatal myocardial infarction and stroke. The applicant proposed a reference to section 5.1 with respect to “cardiovascular protection” but has agreed to change the reference to “renal and CV events” in order to align the SmPC with other recently approved products.

The key secondary renal endpoint in the FIGARO-DKD study intends to support a broadening of the indication to encompass all stages of CKD (with albuminuria) associated with type 2 diabetes (i.e. deletion of “stage 3 and 4” from the currently approved indication). Treatment with finerenone resulted in a 13% relative hazard reduction compared with placebo of the first secondary endpoint time to the first occurrence of onset of kidney failure, a sustained decrease of eGFR ⩾40% from baseline over at least 4 weeks, or renal death. The endpoint was not significant, however, in line with the CHMP’s opinion given in the SA, lack of statistical significance in the FIGARO results is not considered a main limiting factor to the pursued extension of indication, considering that a positive trend favouring finerenone over placebo has been demonstrated in the study population including Stage 1 and 2. Data is thus in general in support for an effect across the different KDIGO categories, including CKD stage 1 and 2 for which extension of indication is sought. For the key secondary renal endpoint, the treatment effect was reduced in subjects with ‘high’ albuminuria (HR=1.16 [95% CI 0.91; 1.47]) compared to ‘very high’ albuminuria (HR=0.74 [95% CI 0.62; 0.90]). Data on UACR however suggest a similar and sustained response in both subgroups. Also, for the exploratory analysis of the chronic eGFR slope there was a positive effect on the slope in both subgroups compared to placebo, but the magnitude was reduced in patients in the “high” compared to the “very high” subgroup which may be expected given the lower progression rate of renal dysfunction in these patients. Thus, data suggest no treatment effect on renal clinical endpoints during the follow up time but the effect on GFR slope and UACR indicate a future beneficial effect not yet seen in clinical endpoints. Finerenone had a beneficial effect on the primary CV endpoint in the FIGARO-DKD study, regardless of baseline albuminuria status. Thus, the totality of data, including findings from post hoc analyses, support that patients with both “high” and “very high” albuminuria benefit from the treatment.

2.5. Clinical safety

Introduction

Kerendia is indicated for the treatment of CKD (stage 3 and 4 with albuminuria) associated with type 2 diabetes in adults. The main evidence of efficacy submitted to support the indication was the FIDELIO-DKD study in T2DM patients with CKD (mean eGFR 44 mL/min/1.73 m^2) and albuminuria (mean UACR 806 mg/g). The major safety concern in the FIDELIO-DKD study was hyperkalaemia that increased with

decreasing renal function. SAEs of hyperkalaemia were reported more frequently for finerenone than for placebo and a higher incidence of hyperkalaemia leading to discontinuation and to hospitalisation was reported for finerenone compared with placebo. The risk for serious events of hyperkalaemia for Kerendia is handled with routine risk minimisation.

The FIGARO-DKD study included T2DM patients with CKD (mean eGFR 68 mL/min/1.73 m^2) and albuminuria (mean UACR 287 mg/g). The safety results of FIGARO-DKD are presented individually followed by a summary of the pooled analysis of FIGARO-DKD and FIDELIO-DKD.

When comparing extent of exposure between FIDELIO-DKD and FIGARO-DKD, the differences in patient population enrolled as well as the approximately 1 year longer observation time of FIGARO-DKD compared with FIDELIO-DKD should be considered. These differences led to the observed higher total exposure in FIGARO-DKD, and the generally better-preserved kidney function led to a lower frequency of study drug dose interruptions and a higher proportion of subjects on the higher dose compared with FIDELIO-DKD.

Patient exposure

Extent of exposure in FIGARO-DKD

In the FIGARO-DKD study, 3,683 subjects were treated with finerenone for a total exposure of 10,802 patient-years, with 3,321 subjects (90%) for at least 52 weeks, 2,990 subjects (81%) for at least 2 years, 1,832 (50%) for at least 3 years and 824 subjects (22%) for at least 4 years. The mean duration of exposure was 35.2 and 35.4 months in the finerenone and placebo arms, respectively.

In FIDELIO-DKD study, 2,827 subjects were treated with finerenone for a total exposure of 6,346 patient-years, with 2,446 subjects (87%) for at least 52 weeks, 1,631 subjects (58%) for at least 2 years, 724 (25%) for at least 3 years and 51 subjects (1.8%) for at least 4 years. The mean duration of exposure was 26.9 and 27.6 months in the finerenone and placebo arms, respectively.

Table 35 Duration of treatment with study (SAF)

	FIGARO-DKD		FIDELIO-DKD		FIGARO & FIDELIO	
	Finerenone N=3683 (100%)	Placebo N=3658 (100%)	Finerenone N=2827 (100%)	Placebo N=2831 (100%)	Finerenone N=6510 (100%)	Placebo N=6489 (100%)
Treatment duration (months)						
Mean (SD)	35.20 (14.86)	35.40 (14.62)	26.94 (12.36)	27.26 (12.15)	31.61 (14.42)	31.85 (14.18)
Median	35.88	35.93	27.07	27.20	31.70	31.70
Min, Max	0.0,61.0	0.0, 61.4	0.0, 51.5	0.1, 51.5	0.0, 61.0	0.0, 61.4
Cumulative treatment duration (months)						
At least 1 month	3638 (98.8%)	3621 (99.0%)	2791 (98.7%)	2788 (98.5%)	6429 (98.8%)	6409 (98.8%)
At least 4 months	3542 (96.2%)	3530 (96.5%)	2681 (94.8%)	2706 (95.6%)	6223 (95.6%)	6236 (96.1%)
At least 12 months	3321 (90.2%)	3340 (91.3%)	2446 (86.5%)	2472 (87.3%)	5767 (88.6%)	5812 (89.6%)
At least 24 months	2990 (81.2%)	2959 (80.9%)	1631 (57.7%)	1661 (58.7%)	4621 (71.0%)	4620 (71.2%)
At least 36 months	1832 (49.7%)	1828 (50.0%)	724 (25.6%)	718 (25.4%)	2556 (39.3%)	2546 (39.2%)
At least 48 months	824 (22.4%)	836 (22.9%)	51 (1.8%)	52 (1.8%)	875 (13.4%)	888 (13.7%)
Cumulative treatment duration over all subjects (100 patient-years)	108.02	107.91	63.46	64.31	171.49	172.21

The overall exposure for FIGARO-DKD and FIGARO-DKD was 17,149 PY for finerenone and 17,221 PY for placebo. The cumulative exposure was lower in FIDELIO-DKD compared with FIGARO-DKD, due to the overall shorter observation time in FIDELIO-DKD. The patient population enrolled in FIGARO-DKD had a less advanced CKD and a lower risk of progression to renal outcomes compared with the FIDELIO-DKD study population. About 30% more patients were treated in the FIGARO-DKD (n=7,341) than in FIDELIO-DKD (n=5,658). The follow-up time in FIGARO-DKD was approximately 1 year longer compared with FIDELIO-DKD.

Demographic and other characteristics of study population FIGARO-DKD

In the FIGARO-DKD study, most subjects in the SAF had a baseline eGFR of ≥60 mL/min/1.73m^2 (62.0% finerenone, 61.5% placebo). The mean eGFR value at baseline was 67.83 mL/min/1.73m^2.

The median UACR at baseline in the SAF was 308.74 mg/g. Similar numbers of subjects were categorized as having high albuminuria (30 mg/g to <300 mg/g: 46.4%) and very high albuminuria at baseline (≥300 mg/g: 50.8%).

The mean serum potassium value at baseline in the SAF was 4.33 mmol/L and 28.5% of subjects had serum potassium values of >4.5 mmol/L, 5.8% had >4.8 to ≤5.0 mmol/L, and 4.6% had >5.0 mmol/L at baseline.

Table 36 Demographics and other baseline characteristics (SAF)

	FIGARO-DKD		FIDELIO-DKD		FIGARO & FIDELIO	
	Finerenone N=3683 (100%)	Placebo N=3658 (100%)	Finerenone N=2827 (100%)	Placebo N=2831 (100%)	Finerenone N=6510 (100%)	Placebo N=6489 (100%)
Race						
White	2668 (72.4%)	2601 (71.1%)	1773 (62.7%)	1809 (63.9%)	4441 (68.2%)	4410 (68.0%)
Black or African American	113 (3.1%)	145 (4.0%)	139 (4.9%)	124 (4.4%)	252 (3.9%)	269 (4.1%)
Asian	716 (19.4%)	736 (20.1%)	717 (25.4%)	721 (25.5%)	1433 (22.0%)	1457 (22.5%)
American Indian or Alaska native	73 (2.0%)	70 (1.9%)	77 (2.7%)	75 (2.6%)	150 (2.3%)	145 (2.2%)
Native Hawaiian or other pacific islander	17 (0.5%)	13 (0.4%)	11 (0.4%)	7 (0.2%)	28 (0.4%)	20 (0.3%)
Not reported	9 (0.2%)	7 (0.2%)	9 (0.3%)	9 (0.3%)	18 (0.3%)	16 (0.2%)
Multiple	87 (2.4%)	86 (2.4%)	101 (3.6%)	86 (3.0%)	188 (2.9%)	172 (2.7%)
Sex						
Male	2527 (68.6%)	2571 (70.3%)	1949 (68.9%)	2024 (71.5%)	4476 (68.8%)	4595 (70.8%)
Female	1156 (31.4%)	1087 (29.7%)	878 (31.1%)	807 (28.5%)	2034 (31.2%)	1894 (29.2%)
Age (years)						
n	3683	3658	2827	2831	6510	6489
Mean (SD)	64.13 (9.68)	64.12 (10.00)	65.45 (8.94)	65.66 (9.16)	64.70 (9.39)	64.79 (9.68)
Min, max	27.0, 89.0	23.0, 93.0	32.0, 90.0	28.0, 97.0	27.0, 90.0	23.0, 97.0
Baseline BMI (kg/m²)						
n	3672	3651	2817	2828	6489	6479
Mean (SD)	31.46 (6.04)	31.40 (5.93)	31.13 (6.03)	31.10 (6.00)	31.31 (6.04)	31.27 (5.96)
Min, max	15.8, 83.9	15.9, 57.2	15.5, 63.7	14.5, 63.2	15.5, 83.9	14.5, 63.2
Region						
Western Europe	724 (19.7%)	758 (20.7%)	616 (21.8%)	631 (22.3%)	1340 (20.6%)	1389 (21.4%)
Eastern Europe	1028 (27.9%)	989 (27.0%)	562 (19.9%)	543 (19.2%)	1590 (24.4%)	1532 (23.6%)
North America	559 (15.2%)	548 (15.0%)	466 (16.5%)	476 (16.8%)	1025 (15.7%)	1024 (15.8%)
Asia	811 (22.0%)	813 (22.2%)	790 (27.9%)	786 (27.8%)	1601 (24.6%)	1599 (24.6%)
Latin America	424 (11.5%)	417 (11.4%)	294 (10.4%)	294 (10.4%)	718 (11.0%)	711 (11.0%)
Others	137 (3.7%)	133 (3.6%)	99 (3.5%)	101 (3.6%)	236 (3.6%)	234 (3.6%)
History of CVD						
CVD present	1673 (45.4%)	1651 (45.1%)	1301 (46.0%)	1299 (45.9%)	2974 (45.7%)	2950 (45.5%)
CVD absent	2010 (54.6%)	2007 (54.9%)	1526 (54.0%)	1532 (54.1%)	3536 (54.3%)	3539 (54.5%)
Baseline UACR (mg/g)						
n	3683	3656	2826	2831	6509	6487
Geom. Mean (Geom. SD)	284.22 (3.58)	289.46 (3.53)	799.54 (2.65)	813.33 (2.67)	445.32 (3.54)	454.35 (3.51)
Median	302.65	315.65	833.39	865.44	514.21	514.46
Q1, Q3	105.32, 749.05	111.36, 732.60	441.52, 1628.14	450.47, 1641.56	197.51, 1129.36	198.24, 1161.21
Baseline albuminuria category						
missing	0	2 (<0.1%)	1 (<0.1%)	0	1 (<0.1%)	2 (<0.1%)
Normalbuminuria (UACR < 30 mg/g)	109 (3.0%)	97 (2.7%)	11 (0.4%)	12 (0.4%)	120 (1.8%)	109 (1.7%)
High albuminuria (30 mg/g - < 300 mg/g)	1724 (46.8%)	1682 (46.0%)	349 (12.3%)	335 (11.8%)	2073 (31.8%)	2017 (31.1%)
Very high albuminuria (>= 300 mg/g)	1850 (50.2%)	1877 (51.3%)	2466 (87.2%)	2484 (87.7%)	4316 (66.3%)	4361 (67.2%)
Baseline eGFR (CKD-EPI) (mL/min/1.73m2)						
n	3683	3657	2827	2831	6510	6488
Mean (SD)	67.64 (21.64)	68.01 (21.72)	44.36 (12.54)	44.33 (12.58)	57.53 (21.59)	57.68 (21.75)
Median	67.40	67.80	43.00	43.00	53.70	53.60
Q1, Q3	50.40, 84.60	51.10, 84.60	34.50, 52.50	34.70, 52.50	40.10, 72.30	40.50, 72.60
Baseline eGFR category						
missing	0	1 (<0.1%)	0	0	0	1 (<0.1%)
<25 mL/min/1.73m²	15 (0.4%)	12 (0.3%)	66 (2.3%)	69 (2.4%)	81 (1.2%)	81 (1.2%)
25 - <45 mL/min/1.73m²	639 (17.3%)	607 (16.6%)	1473 (52.1%)	1499 (52.9%)	2112 (32.4%)	2106 (32.5%)
45 - 60 mL/min/1.73m²	744 (20.2%)	787 (21.5%)	971 (34.3%)	926 (32.7%)	1715 (26.3%)	1713 (26.4%)
≥60 mL/min/1.73m²	2285 (62.0%)	2251 (61.5%)	317 (11.2%)	337 (11.9%)	2602 (40.0%)	2588 (39.9%)
Baseline eGFR (KDIGO) category						
missing	0	1 (<0.1%)	0	0	0	1 (<0.1%)
<30 mL/min/1.73m²	97 (2.6%)	96 (2.6%)	341 (12.1%)	352 (12.4%)	438 (6.7%)	448 (6.9%)
30 - <60 mL/min/1.73m²	1301 (35.3%)	1310 (35.8%)	2169 (76.7%)	2142 (75.7%)	3470 (53.3%)	3452 (53.2%)
60 - <90 mL/min/1.73m²	1631 (44.3%)	1598 (43.7%)	312 (11.0%)	331 (11.7%)	1943 (29.8%)	1929 (29.7%)
≥90 mL/min/1.73m²	654 (17.8%)	653 (17.9%)	5 (0.2%)	6 (0.2%)	659 (10.1%)	659 (10.2%)
Baseline serum potassium (mmol/L)						
n	3683	3656	2827	2831	6510	6487
Mean (SD)	4.33 (0.43)	4.33 (0.43)	4.37 (0.45)	4.37 (0.46)	4.35 (0.44)	4.35 (0.44)
Median	4.30	4.30	4.40	4.40	4.30	4.30
Q1, Q3	4.10, 4.60	4.10, 4.60	4.10, 4.70	4.10, 4.70	4.10, 4.60	4.10, 4.60

Table 26 Demographics and other baseline characteristics (SAF) (contin)

	FIGARO-DKD		FIDELIO-DKD		FIGARO & FIDELIO	
	Finerenone N=3683 (100%)	Placebo N=3658 (100%)	Finerenone N=2827 (100%)	Placebo N=2831 (100%)	Finerenone N=6510 (100%)	Placebo N=6489 (100%)
Baseline serum potassium category						
missing	0	2 (<0.1%)	0	0	0	2 (<0.1%)
≤4.5 mmol/L	2643 (71.8%)	2608 (71.3%)	1879 (66.5%)	1858 (65.6%)	4522 (69.5%)	4466 (68.8%)
>4.5 mmol/L	1040 (28.2%)	1048 (28.6%)	948 (33.5%)	973 (34.4%)	1988 (30.5%)	2021 (31.1%)
Baseline serum potassium category						
missing	0	2 (<0.1%)	0	0	0	2 (<0.1%)
≤4.8 mmol/L	3294 (89.4%)	3283 (89.7%)	2440 (86.3%)	2449 (86.5%)	5734 (88.1%)	5732 (88.3%)
>4.8 to ≤5.0 mmol/L	223 (6.1%)	203 (5.5%)	191 (6.8%)	188 (6.6%)	414 (6.4%)	391 (6.0%)
>5.0 mmol/L	166 (4.5%)	170 (4.6%)	196 (6.9%)	194 (6.9%)	362 (5.6%)	364 (5.6%)
Baseline SBP (mmHg)						
n	3683	3658	2826	2831	6509	6489
Mean (SD)	135.81 (13.97)	135.70 (14.06)	138.02 (14.31)	137.98 (14.42)	136.77 (14.16)	136.69 (14.26)
Min, max	82.7, 208.0	85.7, 200.0	77.0, 197.0	82.3, 195.3	77.0, 208.0	82.3, 200.0
Baseline HbA1c (%)						
n	3678	3652	2821	2828	6499	6480
Mean (SD)	7.75 (1.39)	7.69 (1.35)	7.66 (1.33)	7.69 (1.36)	7.71 (1.36)	7.69 (1.35)
Min, max	4.4, 14.5	4.5, 12.6	4.3, 12.5	3.8, 12.9	4.3, 14.5	3.8, 12.9
Duration of T2D (years)						
n	3680	3655	2821	2826	6501	6481
Mean (SD)	14.53 (8.60)	14.44 (8.45)	16.59 (8.77)	16.55 (8.77)	15.43 (8.73)	15.36 (8.65)
Min, max	0.0, 61.3	0.1, 54.1	0.2, 53.2	0.2, 62.1	0.0, 61.3	0.1, 62.1

In the FIGARO-DKD study, most subjects had a baseline eGFR of ≥60 mL/min/1.73m^2 with albuminuria (mean eGFR 68 mL/min/1.73m^2, mean UACR 287 mg/g in the SAF). In the FIDELIO-DKD study, subjects had a lower eGFR and more than two times higher mean baseline UACR (mean eGFR 44 mL/min/1.73m^2, mean UACR 806 mg/g in the SAF).

The safety population in FIGARO-DKD and FIDELIO-DKD had a mean age of 65 years, about 15% were ≥75 years of age and 0.8% were ≥85 years of age. Serum potassium values of >4.5 mmol/L at baseline was noted in 28% and 34% of the subjects in FIGARO-DKD and FIDELIO-DKD, respectively.

Overall, the safety database is considered to be representative of a broad general population of adults with T2DM and includes a sufficient number of subjects with long duration of disease, in both the FIGARO-DKD and the FIDELIO-DKD studies.

Disposition of patients

A total of 3,646 subjects were discontinued from study drug: 1,831 subjects (28.1%) in the finerenone arm and 1,815 subjects (27.9%) in the placebo arm. The most frequently reported primary reasons for not completing the treatment were: adverse event (9.0% in the finerenone arm, 8.7% in the placebo arm), withdrawal by subject (6.2% in the finerenone arm, 5.9% in the placebo arm), death (5.3% in the finerenone arm, 6.3% in the placebo arm) and physician decision (4.6% in the finerenone arm, 3.7% in the placebo arm). More subjects in FIDELIO-DKD (approximately 10% in both treatment arms) did not complete treatment due to adverse or outcome event compared with FIGARO-DKD (approximately 7% in both treatment arms (Table 37).

Table 37 Disposition: End of treatment (full analysis set) - FIGARO-DKD & FIDELIO-DKD

	FIGARO-DKD		FIDELIO-DKD		FIGARO-DKD & FIDELIO-DKD	
	Finerenone N=3686 (100%)	Placebo N=3666 (100%)	Finerenone N=2833 (100%)	Placebo N=2841 (100%)	Finerenone N=6519 (100%)	Placebo N=6507 (100%)
Completed epoch	2677 (72.6%)	2652 (72.3%)	2011 (71.0%)	2040 (71.8%)	4688 (71.9%)	4692 (72.1%)
Not completed	1009 (27.4%)	1014 (27.7%)	822 (29.0%)	801 (28.2%)	1831 (28.1%)	1815 (27.9%)
Primary reason						
ADVERSE EVENT	275 (7.5%)	272 (7.4%)	309 (10.9%)	296 (10.4%)	584 (9.0%)	568 (8.7%)
DEATH	214 (5.8%)	251 (6.8%)	130 (4.6%)	157 (5.5%)	344 (5.3%)	408 (6.3%)
WITHDRAWAL BY SUBJECT	244 (6.6%)	218 (5.9%)	158 (5.6%)	169 (5.9%)	402 (6.2%)	387 (5.9%)
LOST TO FOLLOW-UP	1 (<0.1%)	2 (<0.1%)	5 (0.2%)	4 (0.1%)	6 (<0.1%)	6 (<0.1%)
PREGNANCY	0	0	0	1 (<0.1%)	0	1 (<0.1%)
PROGRESSIVE DISEASE	0	0	0	1 (<0.1%)	0	1 (<0.1%)
NON-COMPLIANCE WITH STUDY DRUG	12 (0.3%)	12 (0.3%)	18 (0.6%)	7 (0.2%)	30 (0.5%)	19 (0.3%)
PHYSICIAN DECISION	150 (4.1%)	130 (3.5%)	151 (5.3%)	112 (3.9%)	301 (4.6%)	242 (3.7%)
TECHNICAL PROBLEMS	42 (1.1%)	59 (1.6%)	32 (1.1%)	32 (1.1%)	74 (1.1%)	91 (1.4%)
DETERIORATION OF GENERAL CONDITIONS	0	2 (<0.1%)	1 (<0.1%)	3 (0.1%)	1 (<0.1%)	5 (<0.1%)
PROTOCOL DEVIATION	14 (0.4%)	16 (0.4%)	7 (0.2%)	14 (0.5%)	21 (0.3%)	30 (0.5%)
SITE TERMINATED BY SPONSOR	3 (<0.1%)	3 (<0.1%)	6 (0.2%)	2 (<0.1%)	9 (0.1%)	5 (<0.1%)
LOGISTICAL REASON	1 (<0.1%)	0	0	0	1 (<0.1%)	0
SUBJECT DECISION	6 (0.2%)	4 (0.1%)	0	0	6 (<0.1%)	4 (<0.1%)
SUBJECT DECISION: COVID-19 PANDEMIC RELATED	26 (0.7%)	21 (0.6%)	0	0	26 (0.4%)	21 (0.3%)
PHYSICIAN DECISION: COVID-19 PANDEMIC RELATED	7 (0.2%)	3 (<0.1%)	0	0	7 (0.1%)	3 (<0.1%)
LOGISTICAL REASON: COVID-19 PANDEMIC RELATED	4 (0.1%)	11 (0.3%)	0	0	4 (<0.1%)	11 (0.2%)
OTHER	10 (0.3%)	10 (0.3%)	5 (0.2%)	3 (0.1%)	15 (0.2%)	13 (0.2%)

In the FIGARO-DKD, about 28% of the subjects discontinued from study drug (balanced between finerenone and placebo). The most common reason for discontinuation from study drug was discontinuation due to adverse events (7.5% and 7.4% for finerenone and placebo), withdrawal by subject (6.6% and 5.9% for finerenone and placebo) and death (5.8% and 6.8% for finerenone and placebo). More subjects in FIDELIO-DKD (approximately 11% in both treatment arms) did not complete treatment due to adverse or outcome event compared with FIGARO-DKD (approximately 7% in both treatment arms).

Adverse events

Study FIGARO-DKD

The proportion of subjects with TEAEs was similar across treatment arms, with 85.1% reporting a TEAE in the finerenone arm compared with 85.5% in the placebo arm. In most subjects, TEAEs were reported as mild or moderate in maximum intensity.

In most subjects in FIGARO-DKD, TEAEs were assessed as being either mild (29.1% and 29.2% for finerenone and placebo) or moderate in maximum intensity (38.6% and 37.1% for finerenone and placebo). A total of 639 subjects (17.3%) in the finerenone arm and 705 subjects (19.3%) in the placebo arm had at least 1 TEAE assessed as severe in maximum intensity.

The overall percentage of subjects with TEAEs leading to permanent discontinuation of study drug was 5.6% in the finerenone arm and 5.0% in the placebo arm (Table 38).

Integrated data from study FIGARO-DKD and FIDELIO-DKD

In terms of proportions of subjects with TEAEs, the treatment arms were balanced in both studies, with approximately 86% of subjects in each treatment arm in the pooled analysis (85% in FIGARO-DKD, 87% in FIDELIO-DKD).

In most of subjects in the pooled analysis (FIGARO-DKD and FIDELIO-DKD), TEAEs were assessed as being either mild (29.1% and 28.2% for finerenone and placebo) or moderate in maximum intensity (39.4%) and (38.8% for finerenone and placebo). A total of 1140 subjects (17.5%) in the finerenone arm and 1261 subjects (19.4%) in the placebo arm had at least 1 TEAE assessed as severe in maximum intensity.

The overall number of subjects with TEAEs leading to permanent discontinuation of study drug was 6.4% in the finerenone arm and 5.4% in the placebo arm, with slightly higher numbers seen in FIDELIO-DKD compared with FIGARO-DKD. This difference is mostly driven by the higher incidence of hyperkalaemia TEAEs leading to treatment discontinuation in the finerenone arm in both studies.

Table 38 Overall summary of number of subjects with TEAEs (safety analysis set) - FIGARO-DKD & FIDELIO-DKD

	FIGARO-DKD		FIDELIO-DKD		FIGARO-DKD & FIDELIO-DKD	
	Finerenone N=3683 (100%)	Placebo N=3658 (100%)	Finerenone N=2827 (100%)	Placebo N=2831 (100%)	Finerenone N=6510 (100%)	Placebo N=6489 (100%)
Number (%) of subjects with adverse events						
Any AE	3134 (85.1%)	3129 (85.5%)	2468 (87.3%)	2478 (87.5%)	5602 (86.1%)	5607 (86.4%)
Maximum intensity for any AE						
MILD	1072 (29.1%)	1067 (29.2%)	822 (29.1%)	764 (27.0%)	1894 (29.1%)	1831 (28.2%)
MODERATE	1423 (38.6%)	1357 (37.1%)	1145 (40.5%)	1158 (40.9%)	2568 (39.4%)	2515 (38.8%)
SEVERE	639 (17.3%)	705 (19.3%)	501 (17.7%)	556 (19.6%)	1140 (17.5%)	1261 (19.4%)
Any study drug-related AE	560 (15.2%)	413 (11.3%)	646 (22.9%)	449 (15.9%)	1206 (18.5%)	862 (13.3%)
Maximum intensity for study drug-related AE						
MILD	314 (8.5%)	262 (7.2%)	368 (13.0%)	257 (9.1%)	682 (10.5%)	519 (8.0%)
MODERATE	213 (5.8%)	129 (3.5%)	226 (8.0%)	164 (5.8%)	439 (6.7%)	293 (4.5%)
SEVERE	33 (0.9%)	22 (0.6%)	52 (1.8%)	28 (1.0%)	85 (1.3%)	50 (0.8%)
Any AE related to procedures required by the protocol	69 (1.9%)	35 (1.0%)	52 (1.8%)	53 (1.9%)	121 (1.9%)	88 (1.4%)
Any AE leading to discontinuation of study drug	207 (5.6%)	183 (5.0%)	207 (7.3%)	168 (5.9%)	414 (6.4%)	351 (5.4%)
Any SAE	1158 (31.4%)	1215 (33.2%)	902 (31.9%)	971 (34.3%)	2060 (31.6%)	2186 (33.7%)
Any study drug-related SAE	35 (1.0%)	27 (0.7%)	48 (1.7%)	34 (1.2%)	83 (1.3%)	61 (0.9%)
Any SAE related to procedures required by the protocol	3 (<0.1%)	0	2 (<0.1%)	4 (0.1%)	5 (<0.1%)	4 (<0.1%)
Any SAE leading to discontinuation of study drug	70 (1.9%)	76 (2.1%)	75 (2.7%)	78 (2.8%)	145 (2.2%)	154 (2.4%)
AE with outcome death	79 (2.1%)	100 (2.7%)	31 (1.1%)	51 (1.8%)	110 (1.7%)	151 (2.3%)

The incidence of TEAEs was similar for finerenone and placebo, respectively, in the FIGARO-DKD study (85.1% vs 85.5%) and in the pooled analysis with data from the FIGARO-DKD and FIDELIO-DKD studies (86.1% vs 86.4%). The incidence of drug-related TEAEs was higher for finerenone compared with placebo, respectively, in the FIAGARO-DKD study (15.2% vs 11.3%) and in the pooled analysis (18.5% vs 13.3%) and was mostly driven by study drug-related hyperkalaemia.

TEAEs leading to permanent discontinuation of study drug was slightly higher in the finerenone group compared with the placebo group in the FIGARO-DKD study (5.6% vs 5.0%) and in the pooled analysis of the FIGARO and FIDELIO studies (6.4% vs 5.4%). See also below in Discontinuation due to adverse events.

In the FIGARO-DKD study, most of the TEAEs (about 67%) were mild or moderate in intensity and 18% were severe in intensity; balanced between the finerenone and placebo groups. The intensity of AEs was described in almost all of the cases. The distribution of mild, moderate and severe AEs, respectively, were the same in the pooled analysis.

Common adverse events

Study FIGARO-DKD

The more frequently reported common TEAEs in the finerenone arm in FIGARO-DKD were the MedDRA PTs *hyperkalemia* (9.1% finerenone vs 4.4% placebo), *arthralgia* (8.1% vs 7.2%), *upper respiratory tract infection* (6.1% vs 5.6%) and *dizziness* (5.3% finerenone vs 4.6% placebo), Table 39. Among TEAEs reported with a frequency of ≥1% difference between the treatment arms, those with a higher frequency in the finerenone arm were *hyperkalemia* (9.1% vs 4.4%), *hyperuricaemia* (4.5% vs 2.8%) and *hypotension* (4.2% vs 2.5%) (Table 40).

Pooled analysis of data from studies FIGARO-DKD and FIDELIO-DKD

The most frequently reported TEAEs in the pooled analysis from studies FIGARO-DKD and FIDELIO-DKD in Table 39. Hyperkalemia (12.0% of subjects in the finerenone arm vs 5.9% of subjects in the placebo arm) and decreased GFR (5.3% in the finerenone arm vs 4.2% in the placebo arm) were the only 2 commonly reported TEAEs (≥5% of subjects on finerenone) that were reported more frequently in the

finerenone arm than in the placebo arm (difference ≥1.0%). TEAEs reported with a frequency of ≥1% difference between the treatment arms in Table 41.

Table 39 Number of subjects with common **(≥5%** in any treatment arm) TEAEs and incidence rates by PT (SAF)

PT MedDRA version 23.1	FIGARO-DKD Finerenone N=3683 (100%) IR per 100 p-yrs	FIGARO-DKD Placebo N=3658 (100%) IR per 100 p-yrs	FIDELIO-DKD Finerenone N=2827 (100%) IR per 100 p-yrs	FIDELIO-DKD Placebo N=2831 (100%) IR per 100 p-yrs	FIGARO & FIDELIO Finerenone N= 6510 (100%) IR per 100 p-yrs	FIGARO & FIDELIO Placebo N= 6489 (100%) IR per 100 p-yrs
Number (%) of subjects with at least 1 such AE	**3134 (85.1%)** **92.10**	**3129 (85.5%)** **89.33**	**2468 (87.3%)** **123.52**	**2478 (87.5%)** **127.70**	**5602 (86.1%)** **103.72**	**5607 (86.4%)** **103.01**
Hyperkalaemia	335 (9.1%) **3.33**	161 (4.4%) **1.55**	446 (15.8%) **7.81**	221 (7.8%) **3.62**	781 (12.0%) **4.95**	382 (5.9%) **2.31**
Nasopharyngitis	318 (8.6%) **3.24**	327 (8.9%) **3.31**	241 (8.5%) **4.16**	250 (8.8%) **4.23**	559 (8.6%) **3.58**	577 (8.9%) **3.66**
Arthralgia	300 (8.1%) **3.00**	262 (7.2%) **2.59**	196 (6.9%) **3.31**	197 (7.0%) **3.25**	496 (7.6%) **3.11**	459 (7.1%) **2.84**
Back pain	261 (7.1%) **2.58**	253 (6.9%) **2.50**	175 (6.2%) **2.95**	175 (6.2%) **2.88**	436 (6.7%) **2.71**	428 (6.6%) **2.64**
Urinary tract infection	252 (6.8%) **2.48**	240 (6.6%) **2.34**	179 (6.3%) **3.01**	192 (6.8%) **3.15**	431 (6.6%) **2.68**	432(6.7%) **2.65**
Anaemia	216 (5.9%) **2.10**	206 (5.6%) **1.99**	209 (7.4%) **3.50**	191 (6.7%) **3.11**	425 (6.5%) **2.61**	397 (6.1%) **2.41**
Diarrhoea	239 (6.5%) **2.37**	222 (6.1%) **2.17**	184 (6.5%) **3.11**	189 (6.7%) **3.13**	423 (6.5%) **2.64**	411 (6.3%) **2.53**
Hypertension	207 (5.6%) **2.02**	308 (8.4%) **3.06**	212 (7.5%) **3.57**	273 (9.6%) **4.55**	419 (6.4%) **2.59**	581 (9.0%) **3.62**
Upper respiratory tract infection	226 (6.1%) **2.24**	205 (5.6%) **2.01**	181 (6.4%) **3.06**	189 (6.7%) **3.12**	407 (6.3%) **2.54**	394 (6.1%) **2.42**
Oedema peripheral	198 (5.4%) **1.93**	280 (7.7%) **2.77**	186 (6.6%) **3.12**	304 (10.7%) **5.12**	384 (5.9%) **2.37**	584 (9.0%) **3.64**
Glomerular filtration rate decreased	169 (4.6%) **1.63**	141 (3.9%) **1.35**	179 (6.3%) **2.98**	133 (4.7%) **2.14**	348 (5.3%) **2.13**	274 (4.2%) **1.64**
Dizziness	195 (5.3%) **1.92**	169 (4.6%) **1.64**	146 (5.2%) **2.44**	153 (5.4%) **2.50**	341 (5.2%) **2.11**	322 (5.0%) **1.96**
Hypoglycaemia	189 (5.1%) **1.85**	181 (4.9%) **1.75**	151 (5.3%) **2.52**	194 (6.9%) **3.20**	340 (5.2%) **2.10**	375 (5.8%) **2.29**
Bronchitis	194 (5.3%) **1.90**	181 (4.9%) 1.77	134 (4.7%) **2.23**	151 (5.3%) **2.48**	328 (5.0%) **2.03**	332 (5.1%) **2.03**
Constipation	186 (5.1%) **1.82**	171 (4.7%) **1.66**	131 (4.6%) **2.18**	163 (5.8%) **2.68**	317 (4.9%) **1.96**	334 (5.1%) **2.04**
Pneumonia	143 (3.9%) **1.38**	206 (5.6%) **2.00**	128 (4.5%) **2.11**	181 (6.4%) **2.95**	271 (4.2%) **1.65**	387 (6.0%) **2.35**

Table 40 TEAEs with a difference in reporting of **≥1%** of subjects between the treatment arms by PT (SAF) – FIGARO-DKD

PT MedDRA version 23.1	Finerenone N= 3683 (100%)	Placebo N= 3658 (100%)
Difference of ≥1% of subjects: higher frequency in finerenone		
Hyperkalaemia	335 (9.1%)	161 (4.4%)
Hyperuricaemia	167 (4.5%)	104 (2.8%)
Hypotension	156 (4.2%)	90 (2.5%)
Difference of ≥1% of subjects: higher frequency in placebo		
Hypertension	207 (5.6%)	308 (8.4%)
Oedema peripheral	198 (5.4%)	280 (7.7%)
Pneumonia	143 (3.9%)	206 (5.6%)
Hypokalaemia	42 (1.1%)	88 (2.4%)

Table 41 TEAEs with a difference in reporting of **≥1%** of subjects between the treatment arms by PT (SAF) – FIGARO-DKD + FIDELIO-DKD

Preferred term MedDRA version 23.1	Number of subjects with event (%) Finerenone N=6510 (100%)	Number of subjects with event (%) Placebo N=6489 (100%)
Hyperkalaemia	781 (12.0%)	382 (5.9%)
Hypotension	282 (4.3%)	177 (2.7%)
Blood potassium increased	151 (2.3%)	75 (1.2%)
Glomerular filtration rate decreased	348 (5.3%)	274 (4.2%)
Hyperuricaemia	292 (4.5%)	220 (3.4%)
Hypokalaemia	70 (1.1%)	149 (2.3%)
Pneumonia	271 (4.2%)	387 (6.0%)
Hypertension	419 (6.4%)	581 (9.0%)
Oedema peripheral	384 (5.9%)	584 (9.0%)

Treatment-emergent adverse events related to study drug

In FIGARO-DKD, 560 subjects (15.2%) in the finerenone arm had study drug related TEAEs compared with 413 subjects (11.3%) in the placebo arm. The most frequently reported study drug related TEAEs in the finerenone arm were hyperkalemia (5.7% vs 2.7% for finerenone vs placebo).

In the pooled analysis, the number of subjects with study drug related TEAEs was higher in the finerenone arm (18.5%) than in the placebo arm (13.3%). The difference is mostly driven by the higher number of subjects observed with study drug-related hyperkalemia TEAEs in the finerenone arm in both studies.

COVID-19: adverse event analysis (FIGARO-DKD)

The percentage of subjects with COVID-19 AEs during the study was generally low and lower in the finerenone arm (84 subjects, 2.3%) than in the placebo arm (116 subjects, 3.2%).

The current section 4.8 of the SmPC for Kerendia includes “hyperkalaemia” (very common), “hyponatremia” (common), “hypotension” (common), “pruritus” (common), “GFR decreased” (common) and “haemoglobin decreased” (uncommon). Moreover, “hyperuricaemia” has been proposed to be included in section 4.8 with the frequency “common”, based on data from the FIGARO study (4.5% vs 2.8%) for finerenone vs placebo and from the pooled analysis with data from the FIGARO-DKD and FIDELIO-DKD studies (4.5% vs 3.4%). This is endorsed.

Serious adverse event/deaths/other significant events

Deaths

In FIGARO-DKD, 339 subjects in the finerenone arm and 383 subjects in the placebo arm died in the FAS. In addition to the subjects in the SAF, 2 subjects, who never took study drug, died of CV death of an undetermined cause. Overall, the number of fatal outcome or adverse events in the SAF was lower in the finerenone arm (338 subjects, 9.2%) than in the placebo arm (382 subjects, 10.4%) Table 42.

In the pooled analysis, the number of fatal outcome or adverse events in the SAF was lower in the finerenone arm (557 subjects, 8.6%) than in the placebo arm (631 subjects, 9.7%) (Table 42).

Table 42 Overview of death (SAF)

	FIGARO-DKD		FIDELIO-DKD		FIDELIO & FIGARO	
Overview of death	**Finerenone N=3683 (100%)**	**Placebo N=3658 (100%)**	**Finerenone N=2827 (100%)**	**Placebo N=2831 (100%)**	**Finerenone N=6510 (100%)**	**Placebo N=6489 (100%)**
Fatal AEs and OEs	338 (9.2%)	382 (10.4%)	219 (7.7%)	249 (8.8%)	557 (8.6%) [a]	631 (9.7%) [a]
Fatal treatment-emergent AEs and OEs	179 (4.9%)	218 (6.0%)	89 (3.1%)	135 (4.8%)	268 (4.1%)	353 (5.4%)
Fatal treatment-emergent AEs	79 (2.1%)	100 (2.7%)	31 (1.1%)	51 (1.8%)	110 (1.7%)	151 (2.3%)
Post-treatment fatal AEs and OEs	159 (4.3%)	164 (4.5%)	132 (4.7%)	114 (4.0%)	291 (4.5%)	278 (4.3%)
Post-treatment fatal AEs	78 (2.1%)	86 (2.4%)	58 (2.1%)	54 (1.9%)	136 (2.1%)	140 (2.2%)

AE = adverse event, OE = outcome event

In the FIGARO study, adjudicated reasons for deaths for subjects in the SAF were well comparable to the results presented for the FAS (Table 43). Fewer sudden cardiac deaths (53 subjects in the finerenone arm vs 73 subjects in the placebo arm), deaths due to heart failure (9 subjects in the finerenone arm vs 14 subjects in the placebo arm), and fatal stroke (12 subjects in the finerenone arm vs 19 subjects in the

placebo arm) mainly contributed to the lower number of CV deaths in the finerenone arm. No renal deaths were reported in the finerenone arm and the percentage of subjects with non-CV or non-renal causes of death was lower in the finerenone arm (139 subjects, 3.8%) than in the placebo arm (154 subjects, 4.2%).

In the FIGARO study, 179 subjects (4.9%) in the finerenone arm and 218 subjects (6.0%) in the placebo arm died due to treatment-emergent adverse or outcome event. The most frequently reported treatment-emergent fatal adverse or outcome event was the PT death (not otherwise specified) in both treatment arms (finerenone: 31 subjects, 0.8%; placebo: 22 subjects, 0.6%). Cardiac disorders as well as general disorders and administration site conditions were the SOCs with the highest number of subjects with fatal events in both arms. The most common treatment-emergent adverse or outcome event with outcome death in the SAF are provided in Table 44. All other events occurred in 1 to 5 subjects per treatment arm.

Table 43 Adjudicated reasons for death: number (%) of subjects (SAF)

	FIGARO-DKD		FIDELIO-DKD		FIDELIO & FIGARO	
Adjudicated events	**Finerenone N=3683 (100%)**	**Placebo N=3658 (100%)**	**Finerenone N=2827 (100%)**	**Placebo N=2831 (100%)**	**Finerenone N=6510 (100%)**	**Placebo N=6489 (100%)**
All-cause mortality	332 (9.0%)	369 (10.1%)	217 (7.7%)	243 (8.6%)	549 (8.4%)	612 (9.4%)
CV death	193 (5.2%)	213 (5.8%)	126 (4.5%)	149 (5.3%)	319 (4.9%)	362 (5.6%)
CV death - acute myocardial infarction	15 (0.4%)	10 (0.3%)	11 (0.4%)	11 (0.4%)	26 (0.4%)	21 (0.3%)
CV death - sudden cardiac death	53 (1.4%)	73 (2.0%)	35 (1.2%)	42 (1.5%)	88 (1.4%)	115 (1.8%)
CV death - death due to heart failure	9 (0.2%)	14 (0.4%)	5 (0.2%)	13 (0.5%)	14 (0.2%)	27 (0.4%)
CV death - death due to CV procedures	6 (0.2%)	4 (0.1%)	1 (<0.1%)	1 (<0.1%)	7 (0.1%)	5 (<0.1%)
CV death - death due to other CV causes	11 (0.3%)	9 (0.2%)	7 (0.2%)	1 (<0.1%)	18 (0.3%)	10 (0.2%)
CV death - undetermined cause of death	87 (2.4%)	84 (2.3%)	54 (1.9%)	67 (2.4%)	141 (2.2%)	151 (2.3%)
CV death - fatal stroke	12 (0.3%)	19 (0.5%)	13 (0.5%)	14 (0.5%)	25 (0.4%)	33 (0.5%)
Renal death	0	2 (<0.1%)	2 (<0.1%)	2 (<0.1%)	2 (<0.1%)	4 (<0.1%)
Fatal non-CV/non-renal death	139 (3.8%)	154 (4.2%)	89 (3.1%)	92 (3.2%)	228 (3.5%)	246 (3.8%)
Fatal non-CV/non-renal: infection	62 (1.7%)	58 (1.6%)	37 (1.3%)	35 (1.2%)	99 (1.5%)	93 (1.4%)
Fatal non-CV/non-renal: malignancy	50 (1.4%)	72 (2.0%)	31 (1.1%)	31 (1.1%)	81 (1.2%)	103 (1.6%)
Fatal non-CV/non-renal: other	27 (0.7%)	24 (0.7%)	21 (0.7%)	26 (0.9%)	48 (0.7%)	50 (0.8%)

Table 44 Most common treatment-emergent adverse or outcome events with outcome death by PT **(≥0.2%):** number (%) of subjects (SAF)

	FIGARO-DKD		FIDELIO-DKD		FIDELIO & FIGARO	
PT MedDRA version 23.1	**Finerenone N=3683 (100%)**	**Placebo N=3658 (100%)**	**Finerenone N=2827 (100%)**	**Placebo N=2831 (100%)**	**Finerenone N=6510 (100%)**	**Placebo N=6489 (100%)**
Number (%) of subjects with event	179 (4.9%)	218 (6.0%)	89 (3.1%)	135 (4.8%)	268 (4.1%)	353 (5.4%)
Death	31 (0.8%)	22 (0.6%)	12 (0.4%)	17 (0.6%)	43 (0.7%)	39 (0.6%)
Acute myocardial infarction	12 (0.3%)	11 (0.3%)	6 (0.2%)	5 (0.2%)	18 (0.3%)	16 (0.2%)
Cardiac arrest	8 (0.2%)	12 (0.3%)	5 (0.2%)	7 (0.2%)	13 (0.2%)	19 (0.3%)
Myocardial infarction	7 (0.2%)	8 (0.2%)	3 (0.1%)	6 (0.2%)	10 (0.2%)	14 (0.2%)
Cardiovascular disorder	6 (0.2%)	10 (0.3%)	3 (0.1%)	5 (0.2%)	9 (0.1%)	15 (0.2%)
Sudden cardiac death	6 (0.2%)	7 (0.2%)	2 (<0.1%)	3 (0.1%)	8 (0.1%)	10 (0.2%)
Cerebrovascular accident	2 (<0.1%)	6 (0.2%)	5 (0.2%)	7 (0.2%)	7 (0.1%)	13 (0.2%)
Cardiac failure	4 (0.1%)	11 (0.3%)	2 (<0.1%)	6 (0.2%)	6 (<0.1%)	17 (0.3%)
COVID-19	5 (0.1%)	9 (0.2%)	0	0	5 (<0.1%)	9 (0.1%)
Pneumonia	4 (0.1%)	7 (0.2%)	1 (<0.1%)	5 (0.2%)	5 (<0.1%)	12 (0.2%)
Sudden death	4 (0.1%)	4 (0.1%)	2 (<0.1%)	5 (0.2%)	6 (<0.1%)	9 (0.1%)

In the FIGARO-DKD study, the number of fatal outcome or AEs was overall slightly lower in the finerenone group (9.2%) than in the placebo group (10.4%). Adjudicated reasons for deaths (all-cause mortality) were also slightly lower for finerenone (9.0%) compared with placebo (10.1%). Adjudicated CV deaths (5.2% vs 5.8%), renal deaths (0% vs <0.1%) and fatal non-CV/non-renal death (3.8% vs 4.2%) were overall slightly lower for finerenone vs placebo, respectively. Moreover, 4.9% in the finerenone group and 6.0% in the placebo group died due to TEAEs or outcome events with outcome death. The results of the pooled analysis were similar.

Other serious adverse events

Study FIGARO-DKD

In the FIGARO-DKD study, serious TEAEs in the SAF were reported less frequently in the finerenone arm: 1,158 subjects (31.4%) in the finerenone arm versus 1,215 subjects (33.2%) in the placebo arm.

The 3 most frequently reported serious TEAEs in in the finerenone arm were pneumonia (2.0%), cellulitis (1.1%) and acute kidney injury (1.0). In the placebo arm, the 3 most frequently reported serious TEAEs were pneumonia (3.1%), acute kidney injury (1.3%) and urinary tract infection (1.1%, Table 45).

Serious TEAEs were assessed as severe in intensity in 503 subjects (13.7%) in the finerenone arm and in 554 subjects (15.1%) in the placebo arm.

Table 45 Most common **(≥1%)** serious TEAEs by PT: number (%) of subjects and incidence rates (SAF)

	FIGARO-DKD		FIDELIO-DKD		FIGARO & FIDELIO	
PT MedDRA version 23.1	Finerenone N=3683 (100%) IR per 100 p-yrs	Placebo N=3658 (100%) IR per 100 p-yrs	Finerenone N=2827 (100%) IR per 100 p-yrs	Placebo N=2831 (100%) IR per 100 p-yrs	Finerenone N=6510 (100%) IR per 100 p-yrs	Placebo N=6489 (100%) IR per 100 p-yrs
Pneumonia	73 (2.0%) **0.70**	113 (3.1%) **1.08**	70 (2.5%) **1.14**	103 (3.6%) **1.65**	143 (2.2%) **0.86**	216 (3.3%) **1.29**
Acute kidney injury	38 (1.0%) **0.36**	46 (1.3%) **0.44**	56 (2.0%) **0.91**	51 (1.8%) **0.81**	94 (1.4%) **0.56**	97 (1.5%) **0.58**
Cellulitis	40 (1.1%) **0.38**	28 (0.8%) **0.27**	26 (0.9%) **0.42**	22 (0.8%) **0.35**	66 (1.0%) **0.40**	50 (0.8%) **0.30**
Hyperkalaemia	23 (0.6%) **0.22**	4 (0.1%) **0.04**	42 (1.5%) **0.68**	12 (0.4%) **0.19**	65 (1.0%) **0.39**	16 (0.2%) **0.09**
Urinary tract infection	28 (0.8%) **0.27**	39 (1.1%) **0.37**	21 (0.7%) **0.34**	23 (0.8%) **0.36**	49 (0.8%) **0.29**	62 (1.0%) **0.37**
Hypoglycaemia	17 (0.5%) **0.16**	28 (0.8%) **0.26**	21 (0.7%) **0.34**	31 (1.1%) **0.49**	38 (0.6%) **0.23**	59 (0.9%) **0.35**

Pooled analysis of data from studies FIGARO-DKD and FIDELIO-DKD

Overall, serious TEAEs in the SAF were reported less frequently in the finerenone arm: 2060 subjects (31.6%, 14.72 per 100 p-yrs) in the finerenone arm versus 2186 subjects (33.7%, 15.51 per 100 p-yrs) in the placebo arm. There were no relevant differences between FIGARO-DKD and FIDELIO-DKD.

In the FIGARO-DKD study, the incidence of serious TEAEs was slightly lower for finerenone (31%) compared with placebo (33%). The most frequently reported serious TEAE was “pneumonia”, which occurred less frequently in finerenone-treated subjects (2.0%) than in placebo (3.1% placebo). The results of the pooled analysis were similar.

Adverse events of special interest

Hyperkalaemia

In the following subsections, the term hyperkalaemia refers to the combined MedDRA PTs *blood potassium increased* and *hyperkalaemia*.

Study FIGARO-DKD

In FIGARO-DKD, there was approximately a 2-fold increase in the proportion of subjects with any treatment-emergent hyperkalaemia in the finerenone arm compared with placebo (10.8% vs 5.3%). Study-drug related treatment-emergent hyperkalaemia events were reported in 6.5% of the subjects in the finerenone arm compared with 3.1% in the placebo arm. The number of subjects with TEAEs reported as serious (0.7% in the finerenone arm and 0.1% in the placebo arm). TEAEs leading to permanent discontinuation of study drug (1.2% in the finerenone arm and 0.4% in the placebo arm), or hospitalization (0.6% in the finerenone arm and <0.1% in the placebo arm) was comparatively small. Life-threatening hyperkalaemia events occurred in 1 subject in the finerenone arm and 2 subjects in the placebo arm. The events recovered in all 3 cases. No treatment-emergent hyperkalaemia event resulted in the subject’s death. 1 subject in the placebo arm died of post-treatment hyperkalaemia (Table 46).

In the majority of the subjects, treatment-emergent hyperkalaemia was assessed as mild or moderate as maximum intensity and resolved at the end of the study.

In the finerenone arm, the 396 subjects with treatment-emergent hyperkalaemia had a total of 580 such events reported. In the placebo arm, the 193 subjects with treatment-emergent hyperkalaemia had a

total of 262 such events. In both treatment arms, the highest percentage of subjects had 1 treatment-emergent hyperkalaemia event (281 subjects, 7.6% finerenone in the SAF; 143 subjects, 3.9% placebo). More recurrent events occurred in the finerenone arm than in the placebo arm (Table 47).

Table 46 Number of subjects (%) with treatment-emergent hyperkalaemia (based on MLG hyperkalaemia) including serum laboratory potassium values by category (SAF)

	FIGARO-DKD		FIDELIO-DKD		FIGARO & FIDELIO	
	Finerenone N = 3683 (100%)	**Placebo N = 3658 (100%)**	**Finerenone N = 2827 (100%)**	**Placebo N = 2831 (100%)**	**Finerenone N = 6510 (100%)**	**Placebo N = 6489 (100%)**
Any hyperkalemia TEAE	396 (10.8%)	193 (5.3%)	516 (18.3%)	255 (9.0%)	912 (14.0%)	448 (6.9%)
Drug-related	240 (6.5%)	114 (3.1%)	333 (11.8%)	135 (4.8%)	573 (8.8%)	249 (3.8%)
Leading to permanent discontinuation of study drug	46 (1.2%)	13 (0.4%)	64 (2.3%)	25 (0.9%)	110 (1.7%)	38 (0.6%)
Serious	25 (0.7%)	4 (0.1%)	44 (1.6%)	12 (0.4%)	69 (1.1%)	16 (0.2%)
Drug-related	17 (0.5%)	3 (<0.1%)	26 (0.9%)	5 (0.2%)	43 (0.7%)	8 (0.1%)
Leading to permanent discontinuation	5 (0.1%)	1 (<0.1%)	5 (0.2%)	1 (<0.1%)	10 (0.2%)	2 (<0.1%)
Leading to hospitalization	21 (0.6%)	2 (<0.1%)	40 (1.4%)	8 (0.3%)	61 (0.9%)	10 (0.2%)
Life-threatening	1 (<0.1%)	2 (<0.1%)	3 (0.1%)	3 (0.1%)	4 (<0.1%)	5 (<0.1%)
Fatal	0	0	0	0	0	0
PT Hyperkalaemia	335 (9.1%)	161 (4.4%)	446 (15.8%)	221 (7.8%)	781 (12.0%)	382 (5.9%)
Drug-related	210 (5.7%)	100 (2.7%)	286 (10.1%)	114 (4.0%)	496 (7.6%)	214 (3.3%)
Severe	20 (0.5%)	4 (0.1%)	33 (1.2%)	9 (0.3%)	53 (0.8%)	13 (0.2%)
Serious	23 (0.6%)	4 (0.1%)	42 (1.5%)	12 (0.4%)	65 (1.0%)	16 (0.2%)
Drug-related serious	15 (0.4%)	3 (<0.1%)	24 (0.8%)	5 (0.2%)	39 (0.6%)	8 (0.1%)
Life-threatening	0	2 (<0.1%)	3 (0.1%)	3 (0.1%)	3 (<0.1%)	5 (<0.1%)
PT Blood potassium increased	70 (1.9%)	35 (1.0%)	81 (2.9%)	40 (1.4%)	151 (2.3%)	75 (1.2%)
Drug-related	32 (0.9%)	17 (0.5%)	53 (1.9%)	22 (0.8%)	85 (1.3%)	39 (0.6%)
Severe	2 (<0.1%)	1 (<0.1%)	2 (<0.1%)	0	4 (<0.1%)	1 (<0.1%)
Serious	2 (<0.1%)	0	2 (<0.1%)	0	4 (<0.1%)	0
Drug-related serious	2 (<0.1%)	0	2 (<0.1%)	0	4 (<0.1%)	0
Life-threatening	1 (<0.1%)	0	0	0	1 (<0.1%)	0
Serum potassium [a]	**Num/Den (%)**	**Num/Den (%)**	**Num/Den (%)**	**Num/Den (%)**	**Num/Den (%)**	**Num/Den (%)**
>5.5 mmol/L	478/3617 (13.2%)	214/3595 (6.0%)	597/2785 (21.4%)	256/2775 (9.2%)	1075/ 6402 (16.8%)	470/6370 (7.4%)
>6 mmol/L	85/3637 (2.3%)	42/ 3617 (1.2%)	126/2802 (4.5%)	38/2796 (1.4%)	211/6439 (3.3%)	80/6413 (1.2%)

Table 47 Treatment-emergent adverse events: number of events in MLG Hyperkalaemia by treatment group (SAF)

	FIGARO-DKD		FIDELIO-DKD		FIGARO & FIDELIO	
	Finerenone N = 3683 (100%)	Placebo N = 3658 (100%)	Finerenone N = 2827 (100%)	Placebo N = 2831 (100%)	Finerenone N = 6510 (100%)	Placebo N = 6489 (100%)
Number (%) of subjects with at least 1 AE	396 (10.8%)	193 (5.3%)	516 (18.3%)	255 (9.0%)	912 (14.0%)	448 (6.9%)
Total number of events	580	262	793	342	1373	604
Number of events/subject						
1	281 (7.6%)	143 (3.9%)	335 (11.9%)	188 (6.6%)	616 (9.5%)	331 (5.1%)
2	67 (1.8%)	36 (1.0%)	121 (4.3%)	51 (1.8%)	188 (2.9%)	87 (1.3%)
3	33 (0.9%)	12 (0.3%)	42 (1.5%)	13 (0.5%)	75 (1.2%)	25 (0.4%)
4	11 (0.3%)	0	9 (0.3%)	2 (<0.1%)	20 (0.3%)	2 (<0.1%)
5	2 (<0.1%)	1 (<0.1%)	3 (0.1%)	1 (<0.1%)	5 (<0.1%)	2 (<0.1%)
6	2 (<0.1%)	1 (<0.1%)	4 (0.1%)	0	6 (<0.1%)	1 (<0.1%)
7	0	0	1 (<0.1%)	0	1 (<0.1%)	0
8	0	0	1 (<0.1%)	0	1 (<0.1%)	0

In the FIGARO-DKD study, the incidence of hyperkalaemia was 2 times increased for finerenone versus placebo (10.8% vs 5.3%). Drug-related hyperkalaemia were reported in 6.5% of the subjects in the finerenone group compared with 3.1% in the placebo group. Serious events of hyperkalaemia were reported more frequently for finerenone (0.7%) than for placebo (0.1%). Moreover, a higher incidence of hyperkalaemia leading to permanent discontinuation (1.2% vs 0.4%) was reported for finerenone compared with placebo.

More subjects treated with finerenone, compared with placebo, reported one AE (7.6% vs 3.9%), two AEs (1.8% vs 1.0%) and three AEs (0.9% vs 0.3%) of hypokalaemia, respectively. In total, 580 events of hyperkalaemia were reported among 396 finerenone-treated subjects, of which 71%, 17% and 8%, respectively, experienced 1,2 and 3 events, respectively, of hyperkalaemia.

A higher incidence for finerenone, than for placebo, had changes in serum potassium to >5.5 mmol/L (13.2% vs 6.0%) and to >6.0 mmol/L (2.3% vs 1.2%), respectively, at any time during treatment.

The results of the pooled analysis were in general similar. The overall percentage of subjects with hyperkalaemia was generally lower in FIGARO-DKD compared with FIDELIO-DKD, including drug-related events of hyperkalaemia, serious events and events leading to permanent discontinuation of study drug.

The risk of hyperkalaemia is handled with monitoring of serum potassium and dose adjustments, including warning and precautions in the product information.

Subgroup analyses - hyperkalaemia

<u>eGFR at baseline</u>

The lower the eGFR at baseline, the higher the percentage of subjects with treatment emergent hyperkalemia: More subjects in the eGFR categories <60 mL/min/1.73m^2 had treatment-emergent hyperkalemia compared with subjects in the higher eGFR categories and overall. This was observed in both treatment arms (Table 48).

<u>Serum potassium at baseline and hyperkalemia in medical history</u>

The higher the serum potassium at baseline, the higher the percentage of subjects with treatment-emergent hyperkalemia. This was observed in both treatment arms. Similarly, subjects in both treatment arms with a medical history of hyperkalemia (based on the MLG hyperkalemia) had more treatment-emergent hyperkalemia events during the study than subjects without hyperkalemia in their medical history (Table 48).

Age at run-in visit

In the finerenone arm, the percentage of subjects with treatment-emergent hyperkalemia increased with age starting with ≥65 years, while subjects between 18 and 65 years had lower percentages of subjects with hyperkalemia compared with the overall results. This was not seen in the placebo arm, where percentages of subjects were relatively stable across all age groups. The number of subjects between 18 and 44 years of age at baseline was low (approximately 3% in both treatment arms) and results should be interpreted with caution (Table 48).

Comparable risk populations

In addition to the subgroup analyses presented above, the analysis of subjects with comparable risk focusses on those subjects from FIGARO-DKD and FIDELIO-DKD with the same baseline characteristics: subjects with very high albuminuria and eGFR 60 to <75 mL/min/1.73m^2, those with high albuminuria and eGFR 25 to <60 mL/min/1.73m^2, and those with either of these combinations of eGFR and albuminuria categories is presented in Table 49.

Table 48 Number of subjects with treatment-emergent hyperkalaemia for selected subgroups (safety analysis set)

	FIGARO-DKD		FIDELIO-DKD		FIGARO & FIDELIO	
Subgroup	Finerenone n/N (%)	Placebo n/N (%)	Finerenone n/N (%)	Placebo n/N (%)	Finerenone n/N (%)	Placebo n/N (%)
Overall	**396 /3683 (10.8%)**	**193 /3658 (5.3%)**	**516 /2827 (18.3%)**	**255 /2831 (9.0%)**	**912 /6510 (14.0%)**	**448 /6489 (6.9%)**
Baseline eGFR category						
<25 mL/min/1.73m^2	4 /15 (26.7%)	2 /12 (16.7%)	14 /66 (21.2%)	9 /69 (13.0%)	18 /81 (22.2%)	11 /81 (13.6%)
25 - <45 mL/min/1.73m^2	132 /639 (20.7%)	56 /607 (9.2%)	325 /1473 (22.1%)	159 /1499 (10.6%)	457 /2112 (21.6%)	215 /2106 (10.2%)
45 - <60 mL/min/1.73m^2	96 /744 (12.9%)	49 /787 (6.2%)	143 /971 (14.7%)	58 /926 (6.3%)	239 /1715 (13.9%)	107 /1713 (6.2%)
≥60 mL/min/1.73m^2	164 /2285 (7.2%)	86 /2251 (3.8%)	34 /317 (10.7%)	29 /337 (8.6%)	198 /2602 (7.6%)	115 /2588 (4.4%)
Baseline eGFR (KDIGO) category						
<30 mL/min/1.73m^2	30 /97 (30.9%)	14 /96 (14.6%)	85 /341 (24.9%)	42 /352 (11.9%)	115 /438 (26.3%)	56 /448 (12.5%)
30 - <60 mL/min/1.73m^2	202 /1301 (15.5%)	93 /1310 (7.1%)	397 /2169 (18.3%)	184 /2142 (8.6%)	599 /3470 (17.3%)	277 /3452 (8.0%)
60 - <90 mL/min/1.73m^2	143 /1631 (8.8%)	70 /1598 (4.4%)	34 /312 (10.9%)	29 /331 (8.8%)	177 /1943 (9.1%)	99 /1929 (5.1%)
≥90 mL/min/1.73m^2	21 /654 (3.2%)	16 /653 (2.5%)	0 /5 (0.0%)	0 /6 (0.0%)	21 /659 (3.2%)	16 /659 (2.4%)
Baseline serum potassium category						
≤4.5 mmol/L	208 /2643 (7.9%)	93 /2608 (3.6%)	283 /1879 (15.1%)	125 /1858 (6.7%)	491 /4522 (10.9%)	218 /4466 (4.9%)
> 4.5 mmol/L	188 /1040 (18.1%)	100 /1048 (9.5%)	233 /948 (24.6%)	130 /973 (13.4%)	421 /1988 (21.2%)	230 /2021 (11.4%)
Baseline serum potassium 10th category						
≤4.8 mmol/L	311 /3294 (9.4%)	151 /3283 (4.6%)	404 /2440 (16.6%)	200 /2449 (8.2%)	715 /5734 (12.5%)	351 /5732 (6.1%)
>4.8 to ≤5.0 mmol/L	47 /223 (21.1%)	25 /203 (12.3%)	50 /191 (26.2%)	26 /188 (13.8%)	97 /414 (23.4%)	51 /391 (13.0%)
>5.0 mmol/L	38 /166 (22.9%)	17 /170 (10.0%)	62 /196 (31.6%)	29 /194 (14.9%)	100 /362 (27.6%)	46 /364 (12.6%)
Age group category						
18 - 44 years	6 /127 (4.7%)	9 /123 (7.3%)	9 /49 (18.4%)	10 /65 (15.4%)	15 /176 (8.5%)	19 /188 (10.1%)
45 - 64 years	130 /1625 (8.0%)	97 /1632 (5.9%)	215 /1152 (18.7%)	122 /1106 (11.0%)	345 /2777 (12.4%)	219 /2738 (8.0%)
65 - <75 years	192 /1436 (13.4%)	59 /1379 (4.3%)	228 /1195 (19.1%)	99 /1199 (8.3%)	420 /2631 (16.0%)	158 /2578 (6.1%)
75 - <85 years	64 /466 (13.7%)	26 /494 (5.3%)	63 /413 (15.3%)	24 /436 (5.5%)	127 /879 (14.4%)	50 /930 (5.4%)
≥85 years	4 /29 (13.8%)	2 /30 (6.7%)	1 /18 (5.6%)	0 /25 (0.0%)	5 /47 (10.6%)	2 /55 (3.6%)

Table 49 Study-stratified relative risk and assessment of heterogeneity for treatment-emergent hyperkalemia by comparable risk populations (safety analysis set) - FIGARO-DKD & FIDELIO-DKD

Subgroup		Finerenone n/N (%)	Placebo n/N (%)	Finerenone vs. Placebo	
				Relative Risk (95% CI)	p-value of heterogeneity
Overall		912 /6510 (14.0%)	448 /6489 (6.9%)	2.0 (1.8, 2.3)	0.959
Comparable risk population	NO	575 /4319 (13.3%)	283 /4257 (6.6%)	2.0 (1.8, 2.3)	0.956
	YES	337 /2191 (15.4%)	165 /2232 (7.4%)	2.1 (1.7, 2.5)	0.938
Very high albumin. and eGFR 60-<75	NO	816 /5723 (14.3%)	393 /5670 (6.9%)	2.1 (1.8, 2.3)	0.994
	YES	96 /787 (12.2%)	55 /819 (6.7%)	1.8 (1.3, 2.5)	0.587
High albuminuria and eGFR 25-<60	NO	671 /5106 (13.1%)	338 /5076 (6.7%)	2.0 (1.8, 2.2)	0.954
	YES	241 /1404 (17.2%)	110 /1413 (7.8%)	2.2 (1.8, 2.7)	0.492

In the FIGARO-DKD, the incidence of hyperkalaemia increased with decreasing renal function across eGFR strata: eGFR ≥60 mL/min/1.73m^2 (7.2% vs 3.8%), eGFR 45 ≤60 mL/min/1.73m^2 (12.9% vs 6.2%) and eGFR 25-45 mL/min/1.73m^2 (20.7% vs 9.2%). This was seen for the studies individually as well as in the pooled analysis of FIGARO-DKD and FIDELIO-DKD.

Moreover, there were higher frequencies of treatment-emergent hyperkalemia in higher baseline serum potassium categories in both treatment arms.

In the finerenone group, incidences of hyperkalaemia were slightly higher for subjects 65 years or older (13-15%) and lower incidences were observed in subjects 45-64 years (8%) compared to the overall population (11%). The number of subjects in the age group 18-44 years is too limited (n<10) to draw any conclusions.

Worsening of renal function

An overview of the number of subjects with treatment-emergent events related to worsening of renal function including laboratory eGFR values by category is provided in Table 50.

The overall number of subjects with treatment-emergent worsening renal function requiring hospitalization is presented in Table 51.

The overall number of subjects with permanent discontinuation of study drug due to treatment-emergent worsening renal function is presented in Table 52.

<u>eGFR relative decrease of ≥30%, ≥40%, ≥50% or ≥57%: change in subgroup values</u>

Most subjects in both groups had a relative eGFR decrease of ≥30% or ≥40% with a higher percentage of subjects in the finerenone arm (42.5% and 21.7%, respectively) compared to placebo (36.9% and 20.3%, respectively). The proportion of subjects with a decline in eGFR of ≥57% was lower in the finerenone arm (5.0%) than in the placebo arm (6.3%). The results of FIGARO-DKD and FIDELIO-DKD are largely comparable with a higher percentage of subjects with changes in eGFR in all categories in FIDELIO-DKD (Table 50).

<u>eGFR over time</u>

A decline in eGFR over time was observed in both treatment arms, as expected based on the known progressive course of the underlying disease. In line with its mode of action, a larger decrease in eGFR was observed for subjects in the finerenone arm with a mean difference between finerenone and placebo of approximately 2.0 mL/min/1.73m^2 up to Month 4. Thereafter, an attenuated decline in eGFR was observed in the finerenone arm compared to placebo Figure 52.

Table 50 Number of subjects with treatment-emergent worsening of renal function including serum laboratory eGFR values by category (SAF)

	FIGARO-DKD		FIDELIO-DKD		FIGARO & FIDELIO	
	Finerenone N = 3683 (100%)	**Placebo N = 3658 (100%)**	**Finerenone N = 2827 (100%)**	**Placebo N = 2831 (100%)**	**Finerenone N = 6510 (100%)**	**Placebo N = 6489 (100%)**
Any worsening of renal function TEAE						
Leading to hospitalization	42 (1.1%)	46 (1.3%)	68 (2.4%)	66 (2.3%)	110 (1.7%)	112 (1.7%)
Leading to permanent discontinuation of study drug	24 (0.7%)	10 (0.3%)	28 (1.0%)	32 (1.1%)	52 (0.8%)	42 (0.6%)
Relevant PTs						
PT Glomerular filtration rate decreased	169 (4.6%)	141 (3.9%)	179 (6.3%)	133 (4.7%)	348 (5.3%)	274 (4.2%)
Drug-related	28 (0.8%)	18 (0.5%)	39 (1.4%)	15 (0.5%)	67 (1.0%)	33 (0.5%)
Severe	8 (0.2%)	9 (0.2%)	12 (0.4%)	9 (0.3%)	20 (0.3%)	18 (0.3%)
Serious	4 (0.1%)	1 (<0.1%)	5 (0.2%)	4 (0.1%)	9 (0.1%)	5 (<0.1%)
Drug-related serious	0	0	0	1 (<0.1%)	0	1 (<0.1%)
Life-threatening	0	0	0	0	0	0
Leading to death	0	0	0	0	0	0
PT Acute kidney injury	91 (2.5%)	98 (2.7%)	129 (4.6%)	136 (4.8%)	220 (3.4%)	234 (3.6%)
Drug-related	19 (0.5%)	8 (0.2%)	34 (1.2%)	18 (0.6%)	53 (0.8%)	26 (0.4%)
Severe	23 (0.6%)	32 (0.9%)	29 (1.0%)	36 (1.3%)	52 (0.8%)	68 (1.0%)
Serious	38 (1.0%)	46 (1.3%)	56 (2.0%)	51 (1.8%)	94 (1.4%)	97 (1.5%)
Drug-related serious	9 (0.2%)	3 (<0.1%)	9 (0.3%)	6 (0.2%)	18 (0.3%)	9 (0.1%)
Life-threatening	0	3 (<0.1%)	0	1 (<0.1%)	0	4 (<0.1%)
Leading to death	0	0	0	1 (<0.1%)	0	1 (<0.1%)
Treatment-emergent relative eGFR decrease [a]	**Num/Den (%)**	**Num/Den (%)**	**Num/Den (%)**	**Num/Den (%)**	**Num/Den (%)**	**Num/Den (%)**
≥30%	1462/ 3640 (40.2%)	1157/ 3620 (32.0%)	1277/ 2802 (45.6%)	1209/ 2797 (43.2%)	2739/ 6442 (42.5%)	2366/ 6417 (36.9%)
≥40%	705/ 3640 (19.4%)	607/ 3620 (16.8%)	695/ 2802 (24.8%)	695/ 2797 (24.8%)	1400/ 6442 (21.7%)	1302/ 6417 (20.3%)
≥50%	297/ 3640 (8.2%)	291/ 3620 (8.0%)	340/ 2802 (12.1%)	392/ 2797 (14.0%)	637/ 6442 (9.9%)	683/ 6417 (10.6%)
≥57%	148/ 3640 (4.1%)	162/ 3620 (4.5%)	171/ 2802 (6.1%)	242/ 2797 (8.7%)	319/ 6442 (5.0%)	404/ 6417 (6.3%)

Figure 52 Line plot for least square means of eGFR absolute changes from baseline by visit (FAS, FIGARO-DKD)

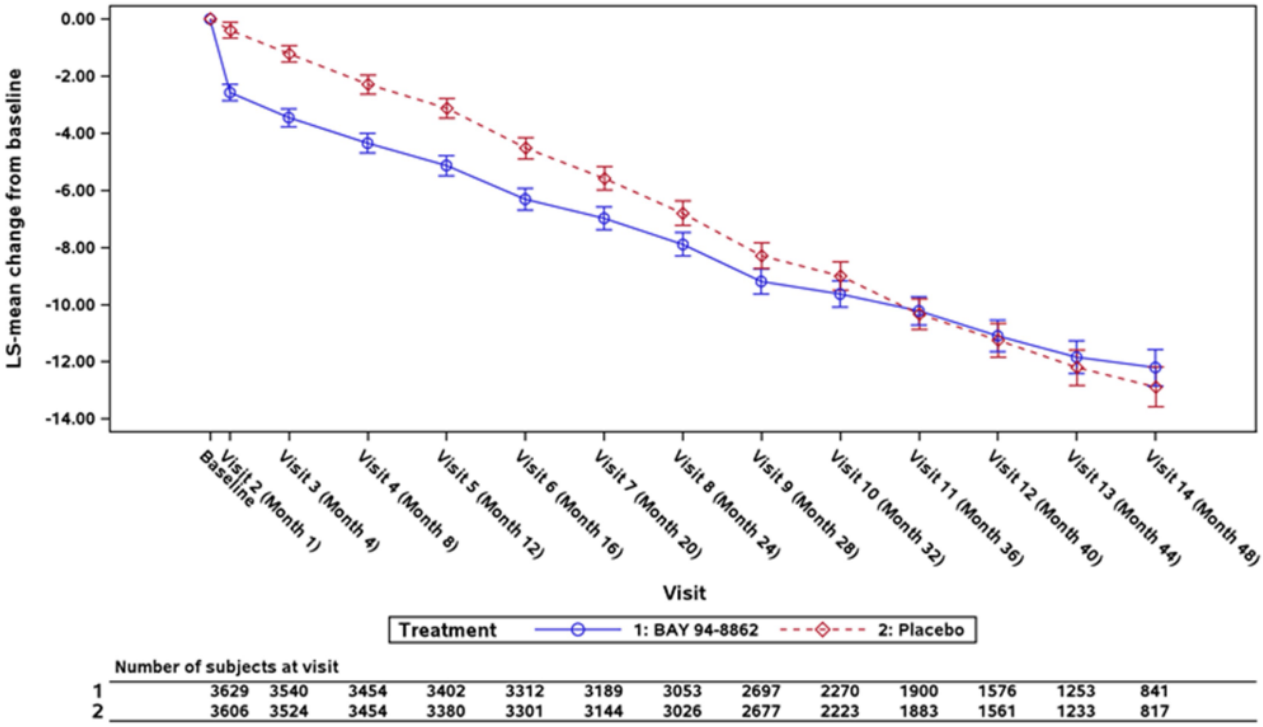


Table 51 Treatment-emergent worsening of renal function requiring hospitalization: number (%) of subjects (SAF)

	FIGARO-DKD		FIDELIO-DKD		FIDELIO+FIGARO	
Primary SOC **PT** MedDRA version 23.1	**Finerenone N=3683 (100%)**	**Placebo N=3658 (100%)**	**Finerenone N=2827 (100%)**	**Placebo N=2831 (100%)**	**Finerenone N=6510 (100%)**	**Placebo N=6489 (100%)**
Number (%) of subjects with at least 1 such AE	42 (1.1%)	46 (1.3%)	68 (2.4%)	66 (2.3%)	110 (1.7%)	112 (1.7%)
Investigations	5 (0.1%)	3 (<0.1%)	3 (0.1%)	6 (0.2%)	8 (0.1%)	9 (0.1%)
Blood creatinine increased	2 (<0.1%)	2 (<0.1%)	0	3 (0.1%)	2 (<0.1%)	5 (<0.1%)
Glomerular filtration rate decreased	3 (<0.1%)	1 (<0.1%)	3 (0.1%)	3 (0.1%)	6 (<0.1%)	4 (<0.1%)
Renal and urinary disorders	37 (1.0%)	43 (1.2%)	65 (2.3%)	62 (2.2%)	102 (1.6%)	105 (1.6%)
Acute kidney injury	32 (0.9%)	39 (1.1%)	53 (1.9%)	47 (1.7%)	85 (1.3%)	86 (1.3%)
Renal failure	3 (<0.1%)	2 (<0.1%)	7 (0.2%)	7 (0.2%)	10 (0.2%)	9 (0.1%)
Renal impairment	2 (<0.1%)	2 (<0.1%)	7 (0.2%)	8 (0.3%)	9 (0.1%)	10 (0.2%)

Table 52 Permanent discontinuation of study drug due to treatment-emergent worsening of renal function: number (%) of subjects (SAF)

	FIGARO-DKD		FIDELIO-DKD		FIDELIO+FIGARO	
Primary SOC **PT** MedDRA version 23.1	**Finerenone N=3683 (100%)**	**Placebo N=3658 (100%)**	**Finerenone N=2827 (100%)**	**Placebo N=2831 (100%)**	**Finerenone N=6510 (100%)**	**Placebo N=6489 (100%)**
Number (%) of subjects with at least 1 such AE	24 (0.7%)	10 (0.3%)	28 (1.0%)	32 (1.1%)	52 (0.8%)	42 (0.6%)
Investigations	11 (0.3%)	5 (0.1%)	12 (0.4%)	13 (0.5%)	23 (0.4%)	18 (0.3%)
Blood creatinine increased	2 (<0.1%)	1 (<0.1%)	5 (0.2%)	5 (0.2%)	7 (0.1%)	6 (<0.1%)
Glomerular filtration rate decreased	9 (0.2%)	4 (0.1%)	7 (0.2%)	8 (0.3%)	16 (0.2%)	12 (0.2%)
Renal and urinary disorders	13 (0.4%)	5 (0.1%)	16 (0.6%)	19 (0.7%)	29 (0.4%)	24 (0.4%)
Acute kidney injury	9 (0.2%)	3 (<0.1%)	5 (0.2%)	7 (0.2%)	14 (0.2%)	10 (0.2%)
Renal failure	2 (<0.1%)	1 (<0.1%)	3 (0.1%)	4 (0.1%)	5 (<0.1%)	5 (<0.1%)
Renal impairment	2 (<0.1%)	2 (<0.1%)	8 (0.3%)	8 (0.3%)	10 (0.2%)	10 (0.2%)

SMQ acute renal failure: narrow and broad search

Numbers of subjects with TEAEs and incidence rates using the narrow and broad search of the SMQ acute renal failure are provided in Table 53. In the narrow search of the SMQ acute renal failure, the percentage of subjects with TEAE is balanced between the treatment groups overall and for both, FIGARO-DKD and FIDELIO-DKD. However, the percentage of subjects with acute renal failure events is higher in FIDELIO-DKD than in FIGARO-DKD for both finerenone and placebo. In the broad search of the SMQ acute renal failure, the percentage of subjects with TEAE is higher in the finerenone arm than in the placebo arm. This result is driven by the results of FIDELIO-DKD, in which 17.8% of subjects in the finerenone arm and 16.3% of subjects in the placebo arm reported TEAEs related to acute renal failure. This difference is seen in the SOC investigations and mainly driven by the TEAE decreased GFR (6.3% of subjects in the finerenone arm vs 4.7% in the placebo arm).

Table 53 Number of subjects with TEAEs in SMQ acute renal failure (SAF)

	FIGARO-DKD		FIDELIO-DKD		FIDELIO+FIGARO	
Primary SOC **PT** MedDRA version23.1	**Finerenone N=3683 (100%)**	**Placebo N=3658 (100%)**	**Finerenone N=2827 (100%)**	**Placebo N=2831 (100%)**	**Finerenone N=6510 (100%)**	**Placebo N=6489 (100%)**
Number (%) of subjects with at least 1 such event	426 (11.6%)	369 (10.1%)	502 (17.8%)	461 (16.3%)	928 (14.3%)	830 (12.8%)
Number (%) of subjects with at least 1 event in narrow search	187 (5.1%)	167 (4.6%)	254 (9.0%)	254 (9.0%)	441 (6.8%)	421 (6.5%)
General disorders and administration site conditions	2 (<0.1%)	0	2 (<0.1%)	3 (0.1%)	4 (<0.1%)	3 (<0.1%)
Oedema due to renal disease	2 (<0.1%)	0	2 (<0.1%)	3 (0.1%)	4 (<0.1%)	3 (<0.1%)
Investigations	237 (6.4%)	203 (5.5%)	274 (9.7%)	219 (7.7%)	511 (7.8%)	422 (6.5%)
Blood creatinine increased	66 (1.8%)	64 (1.7%)	104 (3.7%)	87 (3.1%)	170 (2.6%)	151 (2.3%)
Blood urea increased	11 (0.3%)	8 (0.2%)	25 (0.9%)	11 (0.4%)	36 (0.6%)	19 (0.3%)
Glomerular filtration rate decreased	169 (4.6%)	141 (3.9%)	179 (6.3%)	133 (4.7%)	348 (5.3%)	274 (4.2%)
Protein urine present	2 (<0.1%)	1 (<0.1%)	1 (<0.1%)	4 (0.1%)	3 (<0.1%)	5 (<0.1%)
Renal function test abnormal	1 (<0.1%)	1 (<0.1%)	0	0	1 (<0.1%)	1 (<0.1%)
Urine output decreased	0	0	3 (0.1%)	1 (<0.1%)	3 (<0.1%)	1 (<0.1%)
Renal and urinary disorders	199 (5.4%)	185 (5.1%)	259 (9.2%)	268 (9.5%)	458 (7.0%)	453 (7.0%)
Acute kidney injury*	91 (2.5%)	98 (2.7%)	129 (4.6%)	136 (4.8%)	220 (3.4%)	234 (3.6%)
Albuminuria	4 (0.1%)	7 (0.2%)	3 (0.1%)	3 (0.1%)	7 (0.1%)	10 (0.2%)
Anuria*	0	1 (<0.1%)	0	1 (<0.1%)	0	2 (<0.1%)
Azotaemia *	1 (<0.1%)	2 (<0.1%)	4 (0.1%)	3 (0.1%)	5 (<0.1%)	5 (<0.1%)
Hyponatriuria	1 (<0.1%)	0	0	0	1 (<0.1%)	0
Nephritis	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Nephropathy toxic*	1 (<0.1%)	0	3 (0.1%)	1 (<0.1%)	4 (<0.1%)	1 (<0.1%)
Oliguria*	2 (<0.1%)	1 (<0.1%)	3 (0.1%)	1 (<0.1%)	5 (<0.1%)	2 (<0.1%)
Prerenal failure*	0	1 (<0.1%)	1 (<0.1%)	0	1 (<0.1%)	1 (<0.1%)
Proteinuria	7 (0.2%)	12 (0.3%)	9 (0.3%)	17 (0.6%)	16 (0.2%)	29 (0.4%)
Renal failure*	19 (0.5%)	13 (0.4%)	23 (0.8%)	23 (0.8%)	42 (0.6%)	36 (0.6%)
Renal impairment*	76 (2.1%)	61 (1.7%)	101 (3.6%)	98 (3.5%)	177 (2.7%)	159 (2.5%)
Renal tubular necrosis	1 (<0.1%)	0	0	0	1 (<0.1%)	0
Subacute kidney injury*	2 (<0.1%)	0	0	0	2 (<0.1%)	0
Tubulointerstitial nephritis	1 (<0.1%)	2 (<0.1%)	0	2 (<0.1%)	1 (<0.1%)	4 (<0.1%)
Surgical and medical procedures	0	1 (<0.1%)	4 (0.1%)	2 (<0.1%)	4 (<0.1%)	3 (<0.1%)
Dialysis*	0	0	2 (<0.1%)	0	2 (<0.1%)	0
Haemodialysis*	0	1 (<0.1%)	2 (<0.1%)	2 (<0.1%)	2 (<0.1%)	3 (<0.1%)

The incidence of 'eGFR decreased' for finerenone and placebo, respectively, was 4.6% and 3.9% in the FIGARO-DKD and 5.3% and 4.2% in the pooled analysis of FIGARO-DKD and FIDELIO-DKD. In FIGARO-DKD, more subjects in the finerenone group compared to placebo had a relative eGFR decrease of ≥30% (40.2% vs 32.0%) and ≥40% (19.4% vs 16.8%); however, the proportion of subjects with a decline in eGFR of ≥50% was balanced between finerenone and placebo (8.2% and 8.0%). The results of the pooled analysis were in general similar; although, a higher percentage of subjects in FIDELIO-DKD showed a relative eGFR decrease across all eGFR categories compared with FIGARO-DKD, for both finerenone and placebo.

There was an initial decrease in eGFR in the finerenone group compared with placebo group, with a mean difference between finerenone and placebo of approximately 2 mL/min/1.73 m^2 up to month 4. Over time, the eGFR declined more in the placebo group than in the finerenone group.

In FIGARO-DKD, the incidence of TEAEs in the SOC Renal and urinary disorders (source: Table 14.3.1.1/4, PH-42134) was slightly higher for placebo (15.0%) than for finerenone (13.4%), of which the incidence of 'acute kidney injury' (2.5% vs 2.7%) was balanced. However, the incidence of *drug-related* 'acute kidney injury' was increased for finerenone versus placebo (0.5% vs 0.2%).

The incidence of subjects with at least 1 event of 'acute renal failure' (SMQ broad search), was higher for finerenone than for placebo in both FIGARO-DKD (11.6% vs 10.1%) and FIDELIO-DKD (17.8% vs 16.3%); although more events of TEAEs in SMQ acute renal failure were reported in the FIDELO-DKD.

The incidence of SAEs in the SOC of Renal and urinary disorders (2.8% vs 3.4%), including 'acute kidney injury' (1.0% vs 1.3%) was slightly higher for placebo or balanced. The incidence of serious events of 'eGFR decreased' was low for finerenone (0.1%) and placebo (<0.1%).

The number of subjects with permanent discontinuation of study drug due to worsening of renal function was higher in the finerenone group (0.7%) compared with the placebo group (0.3%); however, treatment-emergent worsening of renal function requiring hospitalization was balanced for finerenone and placebo (1.1% vs 1.3%).

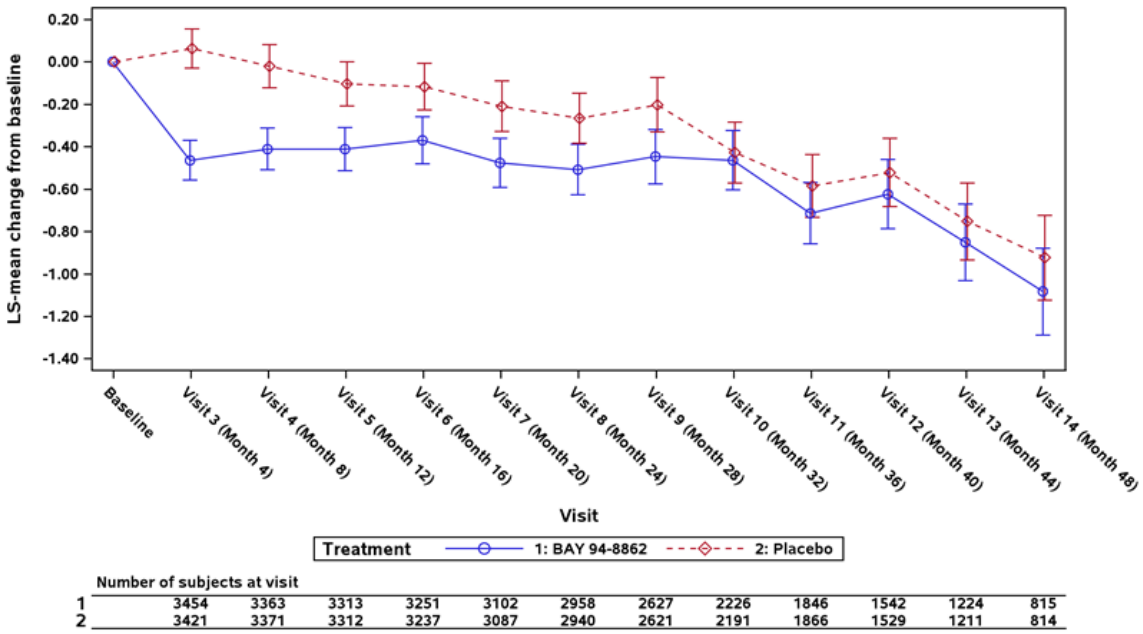
Laboratory findings

Laboratory findings

Haematology

In the FIGARO-DKD, a decrease in mean haemoglobin (<0.17 g/dL) and mean haematocrit (<0.85%) levels was observed in the first 4 months in the finerenone arm compared to placebo.

Figure 53 Line plot for least square means for hematocrit (%) in blood - absolute changes from baseline by visit (safety analysis set)



Least square means and 95% CIs result from a MIXED Model with factors treatment group, region, eGFR category at screening, type of albuminuria at screening, history of CVD, time, treatment*time, baseline value and baseline value*time as covariate.
Separate unstructured covariance patterns are estimated for each treatment group.
LS = Least squares, CI = Confidence intervals

In the FIGARO-DKD, a decrease in mean haemoglobin (<0.17 g/dL) and mean haematocrit (<0.85%) levels was observed in the first 4 months in the finerenone arm compared to placebo. The difference between finerenone and placebo became smaller over time. Data is consistent with data from the FIDELIO study.

"Decreased hemoglobin" is included in section 4.8 of the current SmPC for Kerendia.

Serum sodium

In the FIGARO-DKD, an initial decrease in mean serum sodium (approximately 0.8 mmol/L) was observed in the finerenone-treated subjects in the first month of treatment compared to placebo, followed thereafter by a progressive gradual increase over time in both treatment arms, although the increase observed was smaller in the finerenone arm.

In the FIGARO-DKD, an initial decrease in mean serum sodium (approximately 0.8 mmol/L) was observed for finerenone compared with placebo. This was in line with the decrease in mean serum sodium in the FIDELIO-DKD study (approximately 0.7 mmol/L).

“Hyponatremia” is included in section 4.8 of the current SmPC for Kerendia.

Serum potassium

In the FIGARO-DKD, an increase from baseline in mean serum potassium of approximately 0.15 mmol/L was observed in the finerenone arm compared to placebo over the course of the study. In the finerenone arm, the mean change in potassium was approximately 0.17 mmol/L (SD approx. 0.4) at Month 1 (compared to approx. 0.02 mmol/L (SD approx. 0.4) in the placebo arm), with generally stable measurements thereafter. The maximum mean increase in serum potassium with finerenone (0.19 mmol/L) was observed at Month 8.

In pooled data from FIDELIO-DKD and FIGARO-DKD, an increase from baseline in mean serum potassium of approximately 0.18 mmol/L was observed in the finerenone arm compared with placebo from Month 1 to Month 20 (range 0.17 to 0.19 mmol/L). A gradual increase of mean serum potassium values was observed in the finerenone arm until Month 20, with decreasing mean values thereafter, while the mean serum potassium values in the placebo arm were relatively stable throughout the observation period.

In the pooled analysis of data from FIDELIO-DKD and FIGARO-DKD, a change in potassium to >5.5 mmol/L at any time during treatment was reported for 16.8% of subjects in the finerenone arm and 7.4% of subject in the placebo arm. A change in potassium to >6.0 mmol/L at any time during treatment was reported for 3.3 % of subjects in the finerenone arm and 1.2 % in the placebo arm. The results for FIGARO-DKD and FIDELIO-DKD were comparable, considering that a higher percentage of subjects in both treatment arms reported elevated serum potassium levels in FIDELIO-DKD (Table 54).

Table 54 Number of subjects with treatment-emergent potassium value >5.5 mmol/L or >6.0 mmol/L (SAF)

	FIGARO-DKD		FIDELIO-DKD		FIGARO & FIDELIO	
Serum potassium value	Finerenone (N=3683) Num/Den (%)	Placebo (N=3658) Num/Den (%)	Finerenone (N=2827) Num/Den (%)	Placebo (N=2831) Num/Den (%)	Finerenone (N=6510) Num/Den (%)	Placebo (N=6489) Num/Den (%)
>5.5 mmol/L	478/3617 (13.2%)	214/3595 (6.0%)	597/2785 (21.4%)	256/2775 (9.2%)	1075/6402 (16.8%)	470/6370 (7.4%)
>6.0 mmol/L	85/3637 (2.3%)	42/3617 (1.2%)	126/2802 (4.5%)	38/2796 (1.4%)	211/6439 (3.3%)	80/6413 (1.2%)

In the FIGARO-DKD, an increase from baseline in mean serum potassium of approximately 0.15 mmol/L over observed in the finerenone arm compared to placebo over time, with a maximum value of 0.19 mmol/L at month 8. In pooled data from FIDELIO-DKD and FIGARO-DKD, the increase in mean serum potassium was approximately 0.18 mmol/L.

Information on the risk of hyperkalaemia is included in section 4.4 and 4.8 of the current SmPC for Kerendia.

Serum urea

In the FIGARO-DKD, an initial placebo-corrected increase in mean serum uric acid of approximately 0.25 to 0.3 mg/dL was observed in the finerenone arm from Month 1 to Month 16 compared to baseline. Thereafter, an attenuated increase compared to baseline in uric acid was observed in the finerenone arm compared to placebo. The highest mean value for uric acid in the finerenone arm was 6.779 mg/dL at Month 1 (excluding up-titration visits); the highest individual uric acid measurement in the finerenone arm was 17.16 mg/dL (Month 16). In the placebo arm, the highest mean value for uric acid was 6.561 mg/dL at Month 1 and the highest individual uric acid measurement was 18.44 mg/dL (Month 28). Hyperuricemia TEAEs (4.5% in the finerenone arm; 2.8% in the placebo arm) was noted in the FIGARO-DKD.

Treatment-emergent *gout* was reported in 104 subjects (2.8%) in the finerenone arm and 90 subjects (2.5%) in the placebo arm and was reported as serious in 2 subjects each in the finerenone and placebo arms. Treatment-emergent *gouty arthritis* was reported in 15 subjects (0.4%) in the finerenone arm and 18 subjects (0.5%) in the placebo arm and reported as serious in no subject in the finerenone arm and 2 subjects in the placebo arm. Treatment-emergent *nephrolithiasis* was reported in 50 subjects (1.4%) in the finerenone arm and 55 subjects (1.5%) in the placebo arm and was reported as serious in 12 subjects (0.3%) in the finerenone arm and 8 subjects (0.2%) in the placebo arm.

In summary, the incidence of hyperuricaemia was increased for finerenone compared with placebo (4.5% vs 2.8%). No imbalances of gout (2.8% vs 2.5%), gouty arthritis (0.4% vs 0.5%) or nephrolithiasis (1.4% vs 1.5%) were identified. “Hyperuricaemia” has been proposed to be included in section 4.8 of the proposed amended SmPC, which is accepted.

Vital signs

Blood pressure

In FIGARO-DKD, the mean SBP in the finerenone arm was reduced by approximately 2-3 mmHg compared to placebo at month 1, and the reduction remained generally stable thereafter. The mean DBP in the finerenone arm was reduced by approximately 1-2 mmHg compared to placebo in the first 36 months. No clinically relevant effect on heart rate, weight or BMI was observed during treatment with finerenone or placebo

In FIGARO-DKD, the mean SBP in the finerenone arm was reduced by approximately 2-3 mmHg compared to placebo at month 1, and the reduction remained generally stable thereafter. The mean DBP in the finerenone arm was reduced by approximately 1-2 mmHg compared to placebo in the first 36 months. Similar reductions in SBP and DBP was noted in the FIDELIO-DKD study (DBP: 2-3 mmHg; DBP: 1-2 mmHg).

Hypotension occurred more frequently in subjects in the finerenone group (4.2%) than in the placebo group (2.5%). Events associated with hypotension such as syncope (1.2% vs 1.4%) and fall (0.7% vs 0.7%) was balanced between the groups, but dizziness (5.3% vs 4.6%) was slightly increased for finerenone compared with placebo. The incidence of serious hypotension (<0.1% vs <0.1%) and serious dizziness was low and balanced (0.2% vs 0.2%).

Information on decreased SBP/DBP is included in section 4.4 of the current SmPC for Kerendia.

Heart rate

In the FIGARO-DKD, no clinically relevant effect on heart rate was observed based on mean and median changes during treatment. In both treatment arms, mean change from baseline fluctuated around 0 over the course of the study.

ECG

As in FIDELIO-DKD, standard 12-lead ECGs were performed in FIGARO-DKD with local investigator interpretation at specified times. A 12-lead ECG was also to be obtained if serum potassium levels exceeded 6.5 mmol/L. Clinically relevant abnormalities were reported either as an AE or outcome event (e.g., new onset atrial fibrillation).

In the FIDELIO-DKD, abnormal ECG findings were reported, of which the following were considered likely to be related to hyperkalaemia: e.g., peaked T-waves, bundle branch block, bradycardia, sinus bradycardia and 1st degree AV block. Overall, there were no unexpected ECG changes in the finerenone group.

Weight/BMI

The Applicant has clarified that no clinically relevant effect was observed on body weight or BMI with finerenone compared to placebo.

In the FIDELIO-DKD, the number of any AEs was slightly higher in finerenone group compared with placebo across all the BMI categories. However, SAEs were comparable between finerenone and placebo or slightly lower for finerenone in some subgroups. The slight difference between finerenone and placebo did not have any impact on safety across the BMI subgroups.

Safety in special populations

Integrated data from the FIDELIO-DKD and the FIGARO-DKD studies was provided for the subgroup analyses below:

Effect by age

In the pooled analysis of FIGARO-DKD and FIDELIO-DKD, the percentage of subjects with TEAEs, including drug-related TEAEs and serious TEAEs, was marginally higher in subjects ≥65 years compared to those <65 years. However, this was observed to a similar extent in both treatment arms (Table 55, Table 56).

Table 55 Overall summary of number of subjects with TEAE by age group (years) (SAF) – pooled analysis of FIGARO-DKD and FIDELIO-DKD

	Age <65 years		Age 65 - 74 years		Age ≥75 years	
Number (%) of subjects with TEAE	Finerenone N=2953 (100%)	Placebo N=2926 (100%)	Finerenone N=2631 (100%)	Placebo N=2578 (100%)	Finerenone N=926 (100%)	Placebo N=985 (100%)
Any AE	2494 (84.5%)	2523 (86.2%)	2301 (87.5%)	2225 (86.3%)	807 (87.1%)	859 (87.2%)
Maximum intensity for any AE						
Mild	911 (30.8%)	892 (30.5%)	735 (27.9%)	711 (27.6%)	248 (26.8%)	228 (23.1%)
Moderate	1126 (38.1%)	1114 (38.1%)	1079 (41.0%)	1002 (38.9%)	363 (39.2%)	399 (40.5%)
Severe	457 (15.5%)	517 (17.7%)	487 (18.5%)	512 (19.9%)	196 (21.2%)	232 (23.6%)
Any study drug-related AE	478 (16.2%)	384 (13.1%)	558 (21.2%)	337 (13.1%)	170 (18.4%)	141 (14.3%)
Maximum intensity for study drug-related AE						
Mild	287 (9.7%)	241 (8.2%)	302 (11.5%)	197 (7.6%)	93 (10.0%)	81 (8.2%)
Moderate	166 (5.6%)	124 (4.2%)	206 (7.8%)	121 (4.7%)	67 (7.2%)	48 (4.9%)
Severe	25 (0.8%)	19 (0.6%)	50 (1.9%)	19 (0.7%)	10 (1.1%)	12 (1.2%)
Any AE related to procedures required by the protocol	53 (1.8%)	44 (1.5%)	57 (2.2%)	32 (1.2%)	11 (1.2%)	12 (1.2%)
Any AE leading to discontinuation of study drug	128 (4.3%)	124 (4.2%)	212 (8.1%)	153 (5.9%)	74 (8.0%)	74 (7.5%)
Any SAE	856 (29.0%)	938 (32.1%)	871 (33.1%)	876 (34.0%)	333 (36.0%)	372 (37.8%)
Any study drug-related SAE	29 (1.0%)	27 (0.9%)	39 (1.5%)	17 (0.7%)	15 (1.6%)	17 (1.7%)
Any SAE related to procedures required by the protocol	1 (<0.1%)	1 (<0.1%)	3 (0.1%)	2 (<0.1%)	1 (0.1%)	1 (0.1%)
Any SAE leading to discontinuation of study drug	41 (1.4%)	48 (1.6%)	75 (2.9%)	71 (2.8%)	29 (3.1%)	35 (3.6%)
AE with outcome death	43 (1.5%)	55 (1.9%)	42 (1.6%)	62 (2.4%)	25 (2.7%)	34 (3.5%)

Table 56 Number of subjects with treatment-emergent hyperkalemia by age group (based on MLG hyperkalemia, SAF

	FIGARO-DKD		FIDELIO-DKD		FIGARO & FIDELIO	
Subgroup	Finerenone n/N (%)	Placebo n/N (%)	Finerenone n/N (%)	Placebo n/N (%)	Finerenone n/N (%)	Placebo n/N (%)
Overall	396 /3683 (10.8%)	193 /3658 (5.3%)	516 /2827 (18.3%)	255 /2831 (9.0%)	912 /6510 (14.0%)	448 /6489 (6.9%)
Any treatment-emergent hyperkalemia						
<65 years	136 /1752 (7.8%)	106 /1755 (6.0%)	224 /1201 (18.7%)	132 /1171 (11.3%)	360 /2953 (12.2%)	238 /2926 (8.1%)
65 - <75 years	192 /1436 (13.4%)	59 /1379 (4.3%)	228 /1195 (19.1%)	99 /1199 (8.3%)	420 /2631 (16.0%)	158 /2578 (6.1%)
75 - <85 years	64 /466 (13.7%)	26 /494 (5.3%)	63 /413 (15.3%)	24 /436 (5.5%)	127 /879 (14.4%)	50 /930 (5.4%)
≥85 years	4 /29 (13.8%)	2 /30 (6.7%)	1 /18 (5.6%)	0 /25 (0.0%)	5 /47 (10.6%)	2 /55 (3.6%)
Treatment-emergent hyperkalemia leading to hospitalization						
<65 years	7 /1752 (0.4%)	2 /1755 (0.1%)	19 /1201 (1.6%)	4 /1171 (0.3%)	26 /2953 (0.9%)	6 /2926 (0.2%)
65 - <75 years	9 /1436 (0.6%)	0 /1379 (0.0%)	16 /1195 (1.3%)	2 /1199 (0.2%)	25 /2631 (1.0%)	2 /2578 (<0.1%)
75 - <85 years	5 /466 (1.1%)	0 /494 (0.0%)	5 /413 (1.2%)	2 /436 (0.5%)	10 /879 (1.1%)	2 /930 (0.2%)
≥85 years	0 /29 (0.0%)	0 /30 (0.0%)	0 /18 (0.0%)	0 /25 (0.0%)	0 /47 (0.0%)	0 /55 (0.0%)
Treatment-emergent hyperkalemia leading to permanent discontinuation of study drug						
<65 years	11 /1752 (0.6%)	4 /1755 (0.2%)	20 /1201 (1.7%)	9 /1171 (0.8%)	31 /2953 (1.0%)	13 /2926 (0.4%)
65 - <75 years	26 /1436 (1.8%)	6 /1379 (0.4%)	28 /1195 (2.3%)	13 /1199 (1.1%)	54 /2631 (2.1%)	19 /2578 (0.7%)
75 - <85 years	9 /466 (1.9%)	2 /494 (0.4%)	16 /413 (3.9%)	3 /436 (0.7%)	25 /879 (2.8%)	5 /930 (0.5%)
≥85 years	0 /29 (0.0%)	1 /30 (3.3%)	0 /18 (0.0%)	0 /25 (0.0%)	0 /47 (0.0%)	1 /55 (1.8%)

The reporting rate was overall similar across the age groups. Slightly more TESAEs were reported in the age group ≥75 years (36.0% vs 37.8%) compared to subjects 65-74 years (33.1% vs 34.0%) and <65 years (29.0% vs 32.1%); however, the incidence of SAEs was higher for placebo than for finerenone in all age groups.

More subjects discontinued due to an AE in the finerenone group compared with placebo in the subgroups ≥75 years (8.0% vs 7.5%) and 65-74 years (8.1% vs 5.9%); however, the discontinuation rate due to AEs was balanced (4.3% vs 4.2%) in subjects <65 years.

Effect by sex

The pooled analysis of subjects with TEAE by sex is presented in Table 57.

Table 57 Overall summary of number of subjects with TEAE by sex (SAF) pooled analysis of FIGARO-DKD and FIDELIO-DKD

	Male		Female	
Number (%) of subjects with TEAE	**Finerenone N=4476 (100%)**	**Placebo N=4595 (100%)**	**Finerenone N=2034 (100%)**	**Placebo N=1894 (100%)**
Any AE	3899 (87.1%)	4011 (87.3%)	1703 (83.7%)	1596 (84.3%)
Maximum intensity for any AE				
Mild	1322 (29.5%)	1307 (28.4%)	572 (28.1%)	524 (27.7%)
Moderate	1763 (39.4%)	1783 (38.8%)	805 (39.6%)	732 (38.6%)
Severe	814 (18.2%)	921 (20.0%)	326 (16.0%)	340 (18.0%)
Any study drug-related AE	884 (19.7%)	612 (13.3%)	322 (15.8%)	250 (13.2%)
Maximum intensity for study drug-related AE				
Mild	507 (11.3%)	372 (8.1%)	175 (8.6%)	147 (7.8%)
Moderate	323 (7.2%)	202 (4.4%)	116 (5.7%)	91 (4.8%)
Severe	54 (1.2%)	38 (0.8%)	31 (1.5%)	12 (0.6%)
Any AE related to procedures required by the protocol	83 (1.9%)	64 (1.4%)	38 (1.9%)	24 (1.3%)
Any AE leading to discontinuation of study drug	313 (7.0%)	249 (5.4%)	101 (5.0%)	102 (5.4%)
Any SAE	1487 (33.2%)	1590 (34.6%)	573 (28.2%)	596 (31.5%)
Any study drug-related SAE	56 (1.3%)	46 (1.0%)	27 (1.3%)	15 (0.8%)
Any SAE related to procedures required by the protocol	3 (<0.1%)	3 (<0.1%)	2 (<0.1%)	1 (<0.1%)
Any SAE leading to discontinuation of study drug	115 (2.6%)	112 (2.4%)	30 (1.5%)	42 (2.2%)
AE with outcome death	73 (1.6%)	115 (2.5%)	37 (1.8%)	36 (1.9%)

Female subjects made up for approximately one third of the overall Phase 3 study population. No notable differences between males and females were noted, apart from that the incidence of subjects that discontinued due to an AE that was increased for finerenone compared with placebo (7.0% vs 5.4%) in males and was more balanced in females (5.0% than 5.4%).

Effect by race

The pooled analysis of subjects with TEAE by race is presented in Table 58. In the pooled analysis of FIGARO-DKD and FIDELIO-DKD, the percentage of subjects with TEAEs was overall balanced between the treatment arms for all race groups.

Table 58 Overall summary of number of subjects with TEAE by race (SAF) - pooled analysis of FIGARO-DKD and FIDELIO-DKD

	White		Black		Asian		Other	
Number (%) of subjects with TEAE	Finerenone N=4441 (100%)	Placebo N=4410 (100%)	Finerenone N=252 (100%)	Placebo N=269 (100%)	Finerenone N=1433 (100%)	Placebo N=1457 (100%)	Finerenone N=384 (100%)	Placebo N=353 (100%)
Any AE	3714 (83.6%)	3689 (83.7%)	207 (82.1%)	229 (85.1%)	1335 (93.2%)	1370 (94.0%)	346 (90.1%)	319 (90.4%)
Maximum intensity for any AE								
Mild	1139 (25.6%)	1123 (25.5%)	55 (21.8%)	63 (23.4%)	603 (42.1%)	570 (39.1%)	97 (25.3%)	75 (21.2%)
Moderate	1776 (40.0%)	1655 (37.5%)	100 (39.7%)	103 (38.3%)	525 (36.6%)	583 (40.0%)	167 (43.5%)	174 (49.3%)
Severe	799 (18.0%)	911 (20.7%)	52 (20.6%)	63 (23.4%)	207 (14.4%)	217 (14.9%)	82 (21.4%)	70 (19.8%)
Any study drug-related AE	772 (17.4%)	532 (12.1%)	50 (19.8%)	35 (13.0%)	327 (22.8%)	246 (16.9%)	57 (14.8%)	49 (13.9%)
Maximum intensity for study drug-related AE								
Mild	403 (9.1%)	308 (7.0%)	21 (8.3%)	21 (7.8%)	227 (15.8%)	167 (11.5%)	31 (8.1%)	23 (6.5%)
Moderate	313 (7.0%)	193 (4.4%)	24 (9.5%)	14 (5.2%)	80 (5.6%)	65 (4.5%)	22 (5.7%)	21 (5.9%)
Severe	56 (1.3%)	31 (0.7%)	5 (2.0%)	0	20 (1.4%)	14 (1.0%)	4 (1.0%)	5 (1.4%)
Any AE related to procedures required by the protocol	71 (1.6%)	51 (1.2%)	3 (1.2%)	4 (1.5%)	37 (2.6%)	28 (1.9%)	10 (2.6%)	5 (1.4%)
Any AE leading to discontinuation of study drug	297 (6.7%)	234 (5.3%)	17 (6.7%)	15 (5.6%)	84 (5.9%)	83 (5.7%)	16 (4.2%)	19 (5.4%)
Any SAE	1366 (30.8%)	1427 (32.4%)	80 (31.7%)	88 (32.7%)	509 (35.5%)	577 (39.6%)	105 (27.3%)	94 (26.6%)
Any study drug-related SAE	57 (1.3%)	34 (0.8%)	5 (2.0%)	1 (0.4%)	19 (1.3%)	22 (1.5%)	2 (0.5%)	4 (1.1%)
Any SAE related to procedures required by the protocol	3 (<0.1%)	0	0	0	1 (<0.1%)	4 (0.3%)	1 (0.3%)	0
Any SAE leading to discontinuation of study drug	102 (2.3%)	98 (2.2%)	6 (2.4%)	5 (1.9%)	30 (2.1%)	43 (3.0%)	7 (1.8%)	8 (2.3%)
AE with outcome death	76 (1.7%)	115 (2.6%)	5 (2.0%)	4 (1.5%)	20 (1.4%)	25 (1.7%)	9 (2.3%)	7 (2.0%)

The incidence of AEs was about 82%-90% in White, Black and 'Other subjects' and was slightly higher in Asian subjects (93-94%). The difference was mainly driven by a higher number of subjects with AEs of mild intensity in the Asian race group (39%-42%) compared to the other race groups (21-26%).

Effect by hepatic impairment

Subjects with hepatic impairment were identified using 2 approaches: based on medical history findings and laboratory values. For the assessment based on medical history the SMQ hepatic disorders (excl. sub-SMQs liver-related investigations, signs and symptoms and liver-related coagulation and bleeding disturbances) was used. An approximation of the Child Pugh classification was calculated based on total bilirubin and albumin in serum at baseline.

A summary of number of subjects with TEAE by hepatic impairment in medical history is presented Table 59.

An overview of the number of subjects with TEAE by Child Pugh classification in the pooled analysis of FIGARO-DKD and FIDELIO-DKD is provided in Table 60.

Table 59 Overall summary of number of subjects with TEAE by hepatic impairment in medical history (SAF) - pooled analysis of FIGARO-DKD and FIDELIO-DKD

	No		Yes	
Number (%) of subjects with TEAE	**Finerenone N=5422 (100%)**	**Placebo N=5410 (100%)**	**Finerenone N=1088 (100%)**	**Placebo N=1079 (100%)**
Any AE	4621 (85.2%)	4633 (85.6%)	981 (90.2%)	974 (90.3%)
Maximum intensity for any AE				
Mild	1589 (29.3%)	1502 (27.8%)	305 (28.0%)	329 (30.5%)
Moderate	2110 (38.9%)	2089 (38.6%)	458 (42.1%)	426 (39.5%)
Severe	922 (17.0%)	1042 (19.3%)	218 (20.0%)	219 (20.3%)
Any study drug-related AE	990 (18.3%)	718 (13.3%)	216 (19.9%)	144 (13.3%)
Maximum intensity for study drug-related AE				
Mild	563 (10.4%)	429 (7.9%)	119 (10.9%)	90 (8.3%)
Moderate	357 (6.6%)	247 (4.6%)	82 (7.5%)	46 (4.3%)
Severe	70 (1.3%)	42 (0.8%)	15 (1.4%)	8 (0.7%)
Any AE related to procedures required by the protocol	96 (1.8%)	74 (1.4%)	25 (2.3%)	14 (1.3%)
Any AE leading to discontinuation of study drug	327 (6.0%)	286 (5.3%)	87 (8.0%)	65 (6.0%)
Any SAE	1650 (30.4%)	1770 (32.7%)	410 (37.7%)	416 (38.6%)
Any study drug-related SAE	69 (1.3%)	53 (1.0%)	14 (1.3%)	8 (0.7%)
Any SAE related to procedures required by the protocol	5 (<0.1%)	3 (<0.1%)	0	1 (<0.1%)
Any SAE leading to discontinuation of study drug	116 (2.1%)	126 (2.3%)	29 (2.7%)	28 (2.6%)
AE with outcome death	96 (1.8%)	123 (2.3%)	14 (1.3%)	28 (2.6%)

Table 60 Overall summary of number of subjects with TEAE by Child Pugh classification (SAF) - pooled analysis of FIGARO-DKD and FIDELIO-DKD

	Likely Child Pugh A		Likely Child Pugh B		Certain Child Pugh B	
Number (%) of subjects with TEAE	**Finerenone N= 6255 (100%)**	**Placebo N=6228 (100%)**	**Finerenone N=246 (100%)**	**Placebo N=252 (100%)**	**Finerenone N=6 (100%)**	**Placebo N=7 (100%)**
Any AE	5378 (86.0%)	5378 (86.4%)	217 (88.2%)	222 (88.1%)	4 (66.7%)	6 (85.7%)
Maximum intensity for any AE						
Mild	1836 (29.4%)	1772 (28.5%)	56 (22.8%)	58 (23.0%)	1 (16.7%)	0
Moderate	2457 (39.3%)	2412 (38.7%)	107 (43.5%)	101 (40.1%)	2 (33.3%)	2 (28.6%)
Severe	1085 (17.3%)	1194 (19.2%)	54 (22.0%)	63 (25.0%)	1 (16.7%)	4 (57.1%)
Any study drug-related AE	1158 (18.5%)	824 (13.2%)	44 (17.9%)	36 (14.3%)	2 (33.3%)	2 (28.6%)
Maximum intensity for study drug-related AE						
Mild	655 (10.5%)	497 (8.0%)	24 (9.8%)	21 (8.3%)	2 (33.3%)	1 (14.3%)
Moderate	421 (6.7%)	280 (4.5%)	17 (6.9%)	12 (4.8%)	0	1 (14.3%)
Severe	82 (1.3%)	47 (0.8%)	3 (1.2%)	3 (1.2%)	0	0
Any AE related to procedures required by the protocol	118 (1.9%)	83 (1.3%)	2 (0.8%)	4 (1.6%)	1 (16.7%)	1 (14.3%)
Any AE leading to discontinuation of study drug	392 (6.3%)	326 (5.2%)	22 (8.9%)	25 (9.9%)	0	0
Any SAE	1955 (31.3%)	2071 (33.3%)	101 (41.1%)	111 (44.0%)	2 (33.3%)	4 (57.1%)
Any study drug-related SAE	78 (1.2%)	58 (0.9%)	4 (1.6%)	3 (1.2%)	0	0
Any SAE related to procedures required by the protocol	5 (<0.1%)	3 (<0.1%)	0	1 (0.4%)	0	0
Any SAE leading to discontinuation of study drug	135 (2.2%)	142 (2.3%)	10 (4.1%)	12 (4.8%)	0	0
AE with outcome death	105 (1.7%)	144 (2.3%)	5 (2.0%)	7 (2.8%)	0	0

The Applicant presented overall summary by hepatic impairment: “subjects with no hepatic impairment” (n=10,832) and “subjects with hepatic impairment” (n=2,167). The incidence of subjects with any TEAE and any TESAE, respectively, was slightly higher in subjects with hepatic impairment (TEAEs:90%; TESAEs:38%-39%) compared to those without hepatic impairment in the medical history (TEAEs:85%-86%; TESAEs:30%-33%), in both treatment groups. The Applicant also presented an overview of subjects with AE by Child Pugh classification: “likely Child Pugh A” (n=12,483), “likely Child Pugh B” (n=498) and “certain Child Pugh B” (n=13). However, the Child-Pugh score system is mainly used for assessing the prognosis of chronic liver disease, primarily cirrhosis. Since prothrombin time or INR were not analysed in the study and, therefore, a proper Child-Pugh classification could not be done. Therefore,

the severity classification “mild”, “moderate” and severe” hepatic impairment should be used in the wording in the SmPC instead of the Child-Pugh classification.

Effect by renal impairment

An overall summary of number of subjects with TEAE by baseline eGFR category, in the pooled analysis of FIGARO-DKD and FIDELIO-DKD, have been presented in Table 61.

The number of subjects with treatment-emergent worsening of renal function leading to hospitalization for selected subgroups, in the pooled analysis of FIGARO-DKD and FIDELIO-DKD, have been presented in Table 62.

An overall summary of number of subjects with TEAE by baseline albuminuria category is presented in the pooled analysis of FIGARO-DKD and FIDELIO-DKD, have been presented in Table 63, Table 64, Table 65.

Table 61 Overall summary of number of subjects with TEAE by baseline eGFR category (CKD-EPI, SAF) - pooled analysis of FIGARO-DKD and FIDELIO-DKD

	<25 mL/min/1.73m²		25 - <45 mL/min/1.73m²		45 - <60 mL/min/1.73m²		≥60 mL/min/1.73m²	
Number (%) of subjects with TEAE	Finerenone N=81 (100%)	Placebo N=81 (100%)	Finerenone N=2112 (100%)	Placebo N=2106 (100%)	Finerenone N=1715 (100%)	Placebo N=1713 (100%)	Finerenone N=2602 (100%)	Placebo N=2588 (100%)
Any AE	74 (91.4%)	76 (93.8%)	1860 (88.1%)	1862 (88.4%)	1495 (87.2%)	1495 (87.3%)	2173 (83.5%)	2174 (84.0%)
Maximum intensity for any AE								
Mild	21 (25.9%)	15 (18.5%)	584 (27.7%)	550 (26.1%)	496 (28.9%)	478 (27.9%)	793 (30.5%)	788 (30.4%)
Moderate	34 (42.0%)	40 (49.4%)	852 (40.3%)	863 (41.0%)	691 (40.3%)	684 (39.9%)	991 (38.1%)	928 (35.9%)
Severe	19 (23.5%)	21 (25.9%)	424 (20.1%)	449 (21.3%)	308 (18.0%)	333 (19.4%)	389 (15.0%)	458 (17.7%)
Any study drug-related AE	25 (30.9%)	13 (16.0%)	534 (25.3%)	367 (17.4%)	316 (18.4%)	237 (13.8%)	331 (12.7%)	245 (9.5%)
Maximum intensity for study drug-related AE								
Mild	9 (11.1%)	8 (9.9%)	295 (14.0%)	205 (9.7%)	179 (10.4%)	155 (9.0%)	199 (7.6%)	151 (5.8%)
Moderate	11 (13.6%)	4 (4.9%)	196 (9.3%)	136 (6.5%)	113 (6.6%)	72 (4.2%)	119 (4.6%)	81 (3.1%)
Severe	5 (6.2%)	1 (1.2%)	43 (2.0%)	26 (1.2%)	24 (1.4%)	10 (0.6%)	13 (0.5%)	13 (0.5%)
Any AE related to procedures required by the protocol	1 (1.2%)	1 (1.2%)	50 (2.4%)	45 (2.1%)	28 (1.6%)	20 (1.2%)	42 (1.6%)	22 (0.9%)
Any AE leading to discontinuation of study drug	14 (17.3%)	8 (9.9%)	183 (8.7%)	141 (6.7%)	117 (6.8%)	90 (5.3%)	100 (3.8%)	112 (4.3%)
Any SAE	28 (34.6%)	42 (51.9%)	711 (33.7%)	761 (36.1%)	570 (33.2%)	604 (35.3%)	751 (28.9%)	779 (30.1%)
Any study drug-related SAE	2 (2.5%)	2 (2.5%)	47 (2.2%)	30 (1.4%)	20 (1.2%)	14 (0.8%)	14 (0.5%)	15 (0.6%)
Any SAE related to procedures required by the protocol	0	0	3 (0.1%)	4 (0.2%)	2 (0.1%)	0	0	0
Any SAE leading to discontinuation of study drug	7 (8.6%)	6 (7.4%)	68 (3.2%)	66 (3.1%)	36 (2.1%)	32 (1.9%)	34 (1.3%)	50 (1.9%)
AE with outcome death	3 (3.7%)	3 (3.7%)	34 (1.6%)	44 (2.1%)	31 (1.8%)	41 (2.4%)	42 (1.6%)	63 (2.4%)

Table 62 Number of subjects with treatment-emergent hyperkalaemia for selected subgroups (safety analysis set))

	FIGARO-DKD		FIDELIO-DKD		FIGARO & FIDELIO	
Subgroup	Finerenone n/N (%)	Placebo n/N (%)	Finerenone n/N (%)	Placebo n/N (%)	Finerenone n/N (%)	Placebo n/N (%)
Baseline eGFR category						
<25 mL/min/1.73m²	4 /15 (26.7%)	2 /12 (16.7%)	14 /66 (21.2%)	9 /69 (13.0%)	18 /81 (22.2%)	11 /81 (13.6%)
25 - <45 mL/min/1.73m²	132 /639 (20.7%)	56 /607 (9.2%)	325 /1473 (22.1%)	159 /1499 (10.6%)	457 /2112 (21.6%)	215 /2106 (10.2%)
45 - <60 mL/min/1.73m²	96 /744 (12.9%)	49 /787 (6.2%)	143 /971 (14.7%)	58 /926 (6.3%)	239 /1715 (13.9%)	107 /1713 (6.2%)
≥60 mL/min/1.73m²	164 /2285 (7.2%)	86 /2251 (3.8%)	34 /317 (10.7%)	29 /337 (8.6%)	198 /2602 (7.6%)	115 /2588 (4.4%)
Baseline eGFR (KDIGO) category						
<30 mL/min/1.73m²	30 /97 (30.9%)	14 /96 (14.6%)	85 /341 (24.9%)	42 /352 (11.9%)	115 /438 (26.3%)	56 /448 (12.5%)
30 - <60 mL/min/1.73m²	202 /1301 (15.5%)	93 /1310 (7.1%)	397 /2169 (18.3%)	184 /2142 (8.6%)	599 /3470 (17.3%)	277 /3452 (8.0%)
60 - <90 mL/min/1.73m²	143 /1631 (8.8%)	70 /1598 (4.4%)	34 /312 (10.9%)	29 /331 (8.8%)	177 /1943 (9.1%)	99 /1929 (5.1%)
≥90 mL/min/1.73m²	21 /654 (3.2%)	16 /653 (2.5%)	0 /5 (0.0%)	0 /6 (0.0%)	21 /659 (3.2%)	16 /659 (2.4%)

Table 63 Overall summary of number of subjects with TEAE by baseline albuminuria (mg/g) category (SAF) - pooled analysis of FIGARO-DKD and FIDELIO-DKD

	Normalbuminuria (UACR <30 mg/g)		High albuminuria (UACR 30 mg/g - <300 mg/g)		Very high albuminuria (UACR ≥300 mg/g)	
Number (%) of subjects with TEAE	Finerenone N= 120 (100%)	Placebo N= 109 (100%)	Finerenone N= 2073 (100%)	Placebo N= 2017 (100%)	Finerenone N= 4316 (100%)	Placebo N= 4361 (100%)
Any AE	103 (85.8%)	92 (84.4%)	1808 (87.2%)	1775 (88.0%)	3690 (85.5%)	3739 (85.7%)
Maximum intensity for any AE						
Mild	35 (29.2%)	31 (28.4%)	560 (27.0%)	541 (26.8%)	1299 (30.1%)	1258 (28.8%)
Moderate	53 (44.2%)	45 (41.3%)	831 (40.1%)	793 (39.3%)	1684 (39.0%)	1677 (38.5%)
Severe	15 (12.5%)	16 (14.7%)	417 (20.1%)	441 (21.9%)	707 (16.4%)	804 (18.4%)
Any study drug-related AE	23 (19.2%)	12 (11.0%)	416 (20.1%)	279 (13.8%)	766 (17.7%)	571 (13.1%)
Maximum intensity for study drug-related AE						
Mild	9 (7.5%)	8 (7.3%)	227 (11.0%)	176 (8.7%)	446 (10.3%)	335 (7.7%)
Moderate	14 (11.7%)	4 (3.7%)	159 (7.7%)	89 (4.4%)	265 (6.1%)	200 (4.6%)
Severe	0	0	30 (1.4%)	14 (0.7%)	55 (1.3%)	36 (0.8%)
Any AE related to procedures required by the protocol	1 (0.8%)	2 (1.8%)	44 (2.1%)	26 (1.3%)	76 (1.8%)	60 (1.4%)
Any AE leading to discontinuation of study drug	5 (4.2%)	8 (7.3%)	162 (7.8%)	115 (5.7%)	247 (5.7%)	228 (5.2%)
Any SAE	36 (30.0%)	32 (29.4%)	705 (34.0%)	723 (35.8%)	1318 (30.5%)	1431 (32.8%)
Any study drug-related SAE	2 (1.7%)	0	31 (1.5%)	22 (1.1%)	50 (1.2%)	39 (0.9%)
Any SAE related to procedures required by the protocol	0	0	3 (0.1%)	2 (<0.1%)	2 (<0.1%)	2 (<0.1%)
Any SAE leading to discontinuation of study drug	2 (1.7%)	2 (1.8%)	58 (2.8%)	48 (2.4%)	85 (2.0%)	104 (2.4%)
AE with outcome death	2 (1.7%)	3 (2.8%)	48 (2.3%)	53 (2.6%)	60 (1.4%)	95 (2.2%)

Table 64 Overall summary of number of subjects with TEAE in subjects with high albuminuria

Baseline albuminuria (mg/g) category: High albuminuria (30 mg/g - < 300 mg/g)

	FIGARO-DKD		FIDELIO-DKD		FIGARO-DKD & FIDELIO-DKD	
	Finerenone N=1724 (100%)	Placebo N=1682 (100%)	Finerenone N=349 (100%)	Placebo N=335 (100%)	Finerenone N=2073 (100%)	Placebo N=2017 (100%)
Number (%) of subjects with adverse events						
Any AE	1507 (87.4%)	1483 (88.2%)	301 (86.2%)	292 (87.2%)	1808 (87.2%)	1775 (88.0%)
Maximum intensity for any AE						
MILD	460 (26.7%)	462 (27.5%)	100 (28.7%)	79 (23.6%)	560 (27.0%)	541 (26.8%)
MODERATE	689 (40.0%)	652 (38.8%)	142 (40.7%)	141 (42.1%)	831 (40.1%)	793 (39.3%)
SEVERE	358 (20.8%)	369 (21.9%)	59 (16.9%)	72 (21.5%)	417 (20.1%)	441 (21.9%)
Any study drug-related AE	327 (19.0%)	241 (14.3%)	89 (25.5%)	38 (11.3%)	416 (20.1%)	279 (13.8%)
Maximum intensity for study drug-related AE						
MILD	181 (10.5%)	150 (8.9%)	46 (13.2%)	26 (7.8%)	227 (11.0%)	176 (8.7%)
MODERATE	124 (7.2%)	79 (4.7%)	35 (10.0%)	10 (3.0%)	159 (7.7%)	89 (4.4%)
SEVERE	22 (1.3%)	12 (0.7%)	8 (2.3%)	2 (0.6%)	30 (1.4%)	14 (0.7%)
Any AE related to procedures required by the protocol	40 (2.3%)	20 (1.2%)	4 (1.1%)	6 (1.8%)	44 (2.1%)	26 (1.3%)
Any AE leading to discontinuation of study drug	133 (7.7%)	104 (6.2%)	29 (8.3%)	11 (3.3%)	162 (7.8%)	115 (5.7%)
Any SAE	607 (35.2%)	616 (36.6%)	98 (28.1%)	107 (31.9%)	705 (34.0%)	723 (35.8%)
Any study drug-related SAE	23 (1.3%)	20 (1.2%)	8 (2.3%)	2 (0.6%)	31 (1.5%)	22 (1.1%)
Any SAE related to procedures required by the protocol	3 (0.2%)	0	0	2 (0.6%)	3 (0.1%)	2 (<0.1%)
Any SAE leading to discontinuation of study drug	48 (2.8%)	44 (2.6%)	10 (2.9%)	4 (1.2%)	58 (2.8%)	48 (2.4%)
AE with outcome death	46 (2.7%)	49 (2.9%)	2 (0.6%)	4 (1.2%)	48 (2.3%)	53 (2.6%)

Table 65 Overall summary of number of subjects with TEAE in subjects with very high albuminuria

Baseline albuminuria (mg/g) category: Very high albuminuria (>= 300 mg/g)

	FIGARO-DKD		FIDELIO-DKD		FIGARO-DKD & FIDELIO-DKD	
	Finerenone N=1850 (100%)	Placebo N=1877 (100%)	Finerenone N=2466 (100%)	Placebo N=2484 (100%)	Finerenone N=4316 (100%)	Placebo N=4361 (100%)
Number (%) of subjects with adverse events						
Any AE	1532 (82.8%)	1562 (83.2%)	2158 (87.5%)	2177 (87.6%)	3690 (85.5%)	3739 (85.7%)
Maximum intensity for any AE						
MILD	581 (31.4%)	574 (30.6%)	718 (29.1%)	684 (27.5%)	1299 (30.1%)	1258 (28.8%)
MODERATE	684 (37.0%)	664 (35.4%)	1000 (40.6%)	1013 (40.8%)	1684 (39.0%)	1677 (38.5%)
SEVERE	267 (14.4%)	324 (17.3%)	440 (17.8%)	480 (19.3%)	707 (16.4%)	804 (18.4%)
Any study drug-related AE	210 (11.4%)	161 (8.6%)	556 (22.5%)	410 (16.5%)	766 (17.7%)	571 (13.1%)
Maximum intensity for study drug-related AE						
MILD	124 (6.7%)	104 (5.5%)	322 (13.1%)	231 (9.3%)	446 (10.3%)	335 (7.7%)
MODERATE	75 (4.1%)	47 (2.5%)	190 (7.7%)	153 (6.2%)	265 (6.1%)	200 (4.6%)
SEVERE	11 (0.6%)	10 (0.5%)	44 (1.8%)	26 (1.0%)	55 (1.3%)	36 (0.8%)
Any AE related to procedures required by the protocol	28 (1.5%)	13 (0.7%)	48 (1.9%)	47 (1.9%)	76 (1.8%)	60 (1.4%)
Any AE leading to discontinuation of study drug	69 (3.7%)	72 (3.8%)	178 (7.2%)	156 (6.3%)	247 (5.7%)	228 (5.2%)
Any SAE	516 (27.9%)	571 (30.4%)	802 (32.5%)	860 (34.6%)	1318 (30.5%)	1431 (32.8%)
Any study drug-related SAE	10 (0.5%)	7 (0.4%)	40 (1.6%)	32 (1.3%)	50 (1.2%)	39 (0.9%)
Any SAE related to procedures required by the protocol	0	0	2 (<0.1%)	2 (<0.1%)	2 (<0.1%)	2 (<0.1%)
Any SAE leading to discontinuation of study drug	20 (1.1%)	30 (1.6%)	65 (2.6%)	74 (3.0%)	85 (2.0%)	104 (2.4%)
AE with outcome death	31 (1.7%)	48 (2.6%)	29 (1.2%)	47 (1.9%)	60 (1.4%)	95 (2.2%)

In the pooled analysis of FIDELIO-DKD and FIGARO-DKD, approximately 1.2 % of the subjects had baseline eGFR<25 mL/min/1.73m^2, 32 % eGFR 25 -<45 mL/min/1.73m^2, 26 % eGFR 45 - <60 mL/min/1.73m^2 and 40 % eGFR eGFR>60 mL/min/1.73m^2. The number of subjects with eGFR<25 mL/min/1.73m^2 was too limited to draw any firm conclusions.

Subjects with lower eGFR at baseline reported overall more TEAEs and TESAEs compared to subjects with higher eGFR at baseline although the incidences were balanced for finerenone and placebo, or higher for placebo, across the eGFR strata: eGFR 25 -<45 mL/min/1.73m^2 (TEAEs:88.1% vs 88.4% and TESAEs:33.7% vs 36.1%), eGFR 45 - <60 mL/min/1.73m^2 (TEAEs:87.2% vs 87.3% and TESAEs:33.2% and 35.3%) and eGFR >60 mL/min/1.73m^2(TEAEs: 83.5% vs 84.0% and TESAEs: 28.9% and 30.1%).

However, the incidence of *study-drug related* AEs was increased for finerenone compared with placebo across the subgroups: eGFR 25 -<45 mL/min/1.73m^2 (25.3% vs 17.4%), eGFR 45 - <60 mL/min/1.73m^2 (18.4% vs 13.8%) and eGFR>60 mL/min/1.73m^2 (12.7% vs 9.5%). *Study-drug related* SAEs was increased for finerenone compared with placebo in subjects with eGFR 25 -<45 mL/min/1.73m^2 (2.2% vs 1.4%) and eGFR 45 - <60 mL/min/1.73m^2 (1.2% vs 0.8%) and was balanced in subjects with eGFR>60 mL/min/1.73m^2 (0.5% vs 0.6%).

The incidence of subjects with any AE leading to discontinuation of study drug was increased for finerenone compared with placebo in subjects with eGFR 25 -<45 mL/min/1.73m^2 (8.7% vs 6.7%) and eGFR 45 - <60 mL/min/1.73m^2 (6.8% vs 5.3%) and was slightly higher for placebo in subjects with eGFR>60 mL/min/1.73m^2 (3.8% vs 4.3%).

The risk of hyperkalaemia increased with decreasing renal function across eGFR strata: ≥60 mL/min/1.73m^2 (7.6% vs 4.4%), 45 -<60 mL/min/1.73m^2 (13.9% vs 6.2%) and 25-45 mL/min/1.73m^2 (21.6% vs 10.2%).

Finerenone is not recommended in subjects with eGFR <25 mL/min/1.73m^2 due to limited data.

Effect by albuminuria

In the FIGARO study, subjects with high albuminuria (AEs:87.4% vs 88.2%; SAEs:35.2% vs 36.6%) reported overall more AEs and SAEs compared to subjects with very high albuminuria (AEs:82.8% vs 83.2%; SAEs:27.9% vs 30.4%) at baseline although the incidences were higher for placebo. The incidences of *drug-related* AEs were more increased in subjects with high albuminuria (19.0% vs 14.3%) compared with subjects with very high albuminuria (11.4% vs 8.6%). Moreover, the incidence of *any AE leading to study drug discontinuation* was more increased for finerenone than for placebo in subjects with high albuminuria (7.7% vs 6.2%) compared with subjects with very high albuminuria (3.7% vs 3.8%). The data was similar for the pooled analysis of data from FIDELIO-DKD and FIGARO-DKD.

Table 66 Overall summary of number of subjects with TEAE by baseline UACR and by baseline UACR and baseline eGFR category (safety analysis set) - FIGARO-DKD & FIDELIO-DKD

	FIGARO-DKD		FIDELIO-DKD		FIGARO & FIDELIO	
Number (%) of subjects with TEAEs	**Finerenone**	**Placebo**	**Finerenone**	**Placebo**	**Finerenone**	**Placebo**
Baseline UACR: <300 mg/g	**N=1833 (100%)**	**N=1779 (100%)**	**N=360 (100%)**	**N=347 (100%)**	**N=2193 (100%)**	**N=2126 (100%)**
Any AE	1602 (87.4%)	1566 (88.0%)	309 (85.8%)	301 (86.7%)	1911 (87.1%)	1867 (87.8%)
Any study drug-related AE	350 (19.1%)	252 (14.2%)	89 (24.7%)	39 (11.2%)	439 (20.0%)	291 (13.7%)
Any AE leading to discontinuation of study drug	138 (7.5%)	111 (6.2%)	29 (8.1%)	12 (3.5%)	167 (7.6%)	123 (5.8%)
Baseline UACR: ≥300 mg/g	**N=1850 (100%)**	**N=1877 (100%)**	**N=2466 (100%)**	**N=2484 (100%)**	**N=4316 (100%)**	**N=4361 (100%)**
Any AE	1532 (82.8%)	1562 (83.2%)	2158 (87.5%)	2177 (87.6%)	3690 (85.5%)	3739 (85.7%)
Any study drug-related AE	210 (11.4%)	161 (8.6%)	556 (22.5%)	410 (16.5%)	766 (17.7%)	571 (13.1%)
Any AE leading to discontinuation of study drug	69 (3.7%)	72 (3.8%)	178 (7.2%)	156 (6.3%)	247 (5.7%)	228 (5.2%)
Baseline UACR * eGFR: UACR <300 mg/g and eGFR <60 mL/min/1.73m²	**N=1179 (100%)**	**N=1189 (100%)**	**N=330 (100%)**	**N=317 (100%)**	**N=1509 (100%)**	**N=1506 (100%)**
Any AE	1046 (88.7%)	1060 (89.2%)	287 (87.0%)	278 (87.7%)	1333 (88.3%)	1338 (88.8%)
Any study drug-related AE	255 (21.6%)	192 (16.1%)	84 (25.5%)	37 (11.7%)	339 (22.5%)	229 (15.2%)
Any AE leading to discontinuation of study drug	111 (9.4%)	81 (6.8%)	27 (8.2%)	11 (3.5%)	138 (9.1%)	92 (6.1%)
Baseline UACR * eGFR: UACR <300 mg/g and eGFR ≥60 mL/min/1.73m²	**N=654 (100%)**	**N=590 (100%)**	**N=30 (100%)**	**N=30 (100%)**	**N=684 (100%)**	**N=620 (100%)**
Any AE	556 (85.0%)	506 (85.8%)	22 (73.3%)	23 (76.7%)	578 (84.5%)	529 (85.3%)
Any study drug-related AE	95 (14.5%)	60 (10.2%)	5 (16.7%)	2 (6.7%)	100 (14.6%)	62 (10.0%)
Any AE leading to discontinuation of study drug	27 (4.1%)	30 (5.1%)	2 (6.7%)	1 (3.3%)	29 (4.2%)	31 (5.0%)
Baseline UACR * eGFR: UACR ≥300 mg/g and eGFR <60 mL/min/1.73m²	**N=219 (100%)**	**N=217 (100%)**	**N=2179 (100%)**	**N=2177 (100%)**	**N=2398 (100%)**	**N=2394 (100%)**
Any AE	181 (82.6%)	177 (81.6%)	1914 (87.8%)	1918 (88.1%)	2095 (87.4%)	2095 (87.5%)
Any study drug-related AE	34 (15.5%)	24 (11.1%)	501 (23.0%)	364 (16.7%)	535 (22.3%)	388 (16.2%)
Any AE leading to discontinuation of study drug	12 (5.5%)	9 (4.1%)	164 (7.5%)	138 (6.3%)	176 (7.3%)	147 (6.1%)
Baseline UACR * eGFR: UACR ≥300 mg/g and eGFR ≥60 mL/min/1.73m²	**N=1631 (100%)**	**N=1659 (100%)**	**N=287 (100%)**	**N=307 (100%)**	**N=1918 (100%)**	**N=1966 (100%)**
Any AE	1351 (82.8%)	1385 (83.5%)	244 (85.0%)	259 (84.4%)	1595 (83.2%)	1644 (83.6%)
Any study drug-related AE	176 (10.8%)	137 (8.3%)	55 (19.2%)	46 (15.0%)	231 (12.0%)	183 (9.3%)
Any AE leading to discontinuation of study drug	57 (3.5%)	63 (3.8%)	14 (4.9%)	18 (5.9%)	71 (3.7%)	81 (4.1%)

All interruptions are excluded from the person-time at risk, i.e. for subjects with an interruption, events in the period from interruption start + 3 days until end of interruption are not considered.
eGFR = estimated glomerular filtration rate, MLG = Bayer MedDRA Labeling Grouping, N = number of subjects, TEAE = treatment emergent adverse event, UACR = urinary albumin-to-creatinine ratio
Source: bay948862 ia ema fidelio figaro, Tables 2.2/4 and 2.2/5

Table 67 Number of subjects with MLG: Hyperkalemia by Baseline UACR (safety analysis set) - FIGARO-DKD & FIDELIO-DKD

	FIGARO-DKD		FIDELIO-DKD		FIGARO & FIDELIO	
Number (%) of subjects with TEAE	**Finerenone**	**Placebo**	**Finerenone**	**Placebo**	**Finerenone**	**Placebo**
Baseline UACR: <300 mg/g	**N=1833 (100%)**	**N=1779 (100%)**	**N=360 (100%)**	**N=347(100%)**	**N=2193(100%)**	**N=2126 (100%)**
Any treatment-emergent event	248 (13.5%)	110 (6.2%)	62 (17.2%)	26 (7.5%)	310 (14.1%)	136 (6.4%)
Drug-related	151 (8.2%)	66 (3.7%)	42 (11.7%)	15 (4.3%)	193 (8.8%)	81 (3.8%)
Leading to permanent discontinuation	34 (1.9%)	9 (0.5%)	7 (1.9%)	4 (1.2%)	41 (1.9%)	13 (0.6%)
Baseline UACR: ≥300 mg/g	**N=1850 (100%)**	**N=1877 (100%)**	**N=2466 (100%)**	**N=2484 (100%)**	**N=4316 (100%)**	**N=4361 (100%)**
Any treatment-emergent event	148 (8.0%)	83 (4.4%)	454 (18.4%)	229 (9.2%)	602 (3.9%)	312 (7.2%)
Drug-related	89 (4.8%)	48 (2.6%)	291 (11.8%)	120 (4.8%)	380 (8.8%)	168 (3.9%)
Leading to permanent discontinuation	12 (0.6%)	4 (0.2%)	57 (2.3%)	21 (0.8%)	69 (1.6%)	25 (0.6%)
Baseline UACR * eGFR: UACR <300 mg/g and eGFR <60 mL/min/1.73m²	**N=1179 (100%)**	**N=1189 (100%)**	**N=330 (100%)**	**N=317 (100%)**	**N=1509 (100%)**	**N=1506 (100%)**
Any treatment-emergent event	199 (16.9%)	92 (7.7%)	61 (18.5%)	22 (6.9%)	260 (17.2%)	114 (7.6%)
Drug-related	121 (10.3%)	55 (4.6%)	41 (12.4%)	13 (4.1%)	162 (10.7%)	68 (4.5%)
Leading to permanent discontinuation	32 (2.7%)	8 (0.7%)	7 (2.1%)	4 (1.3%)	39 (2.6%)	12 (0.8%)
Baseline UACR * eGFR: UACR <300 mg/g and eGFR ≥60 mL/min/1.73m²	**N=654 (100%)**	**N=590 (100%)**	**N=30 (100%)**	**N=30 (100%)**	**N=684 (100%)**	**N=620 (100%)**
Any treatment-emergent event	49 (7.5%)	18 (3.1%)	1 (3.3%)	4 (13.3%)	50 (7.3%)	22 (3.5%)
Drug-related	30 (4.6%)	11 (1.9%)	1 (3.3%)	2 (6.7%)	31 (4.5%)	13 (2.1%)
Leading to permanent discontinuation	2 (0.3%)	1 (0.2%)	0	0	2 (0.3%)	1 (0.2%)
Baseline UACR * eGFR: UACR ≥300 mg/g and eGFR <60 mL/min/1.73m²	**N=219 (100%)**	**N=217 (100%)**	**N=2179 (100%)**	**N=2177 (100%)**	**N=2398 (100%)**	**N=2394 (100%)**
Any treatment-emergent event	33 (15.1%)	15 (6.9%)	421 (19.3%)	204 (9.4%)	454 (18.9%)	219 (9.1%)
Drug-related	21 (9.6%)	8 (3.7%)	266 (12.2%)	105 (4.8%)	287 (12.0%)	113 (4.7%)
Leading to permanent discontinuation	4 (1.8%)	0	51 (2.3%)	19 (0.9%)	55 (2.3%)	19 (0.8%)
Baseline UACR * eGFR: UACR ≥300 mg/g and eGFR ≥60 mL/min/1.73m²	**N=1631 (100%)**	**N=1659 (100%)**	**N=287 (100%)**	**N=307 (100%)**	**N=1918 (100%)**	**N=1966 (100%)**
Any treatment-emergent event	115 (7.1%)	68 (4.1%)	33 (11.5%)	25 (8.1%)	148 (7.7%)	93 (4.7%)
Drug-related	68 (4.2%)	40 (2.4%)	25 (8.7%)	15 (4.9%)	93 (4.8%)	55 (2.8%)
Leading to permanent discontinuation	8 (0.5%)	4 (0.2%)	6 (2.1%)	2 (0.7%)	14 (0.7%)	6 (0.3%)

Except 'Any event', all event types displayed are treatment-emergent.
For treatment-emergent events all interruptions are excluded from the person-time at risk, i.e. for subjects with an interruption, events in the period from interruption start + 3 days until end of interruption are not considered.
MLG hyperkalemia includes "hyperkalaemia" and "blood potassium increased".
eGFR = estimated glomerular filtration rate, MLG = Bayer MedDRA Labeling Grouping, N = number of subjects, TEAE = treatment-emergent adverse event, UACR = urinary albumin-to-creatinine ratio
Source: bay948862 ia ema fidelio figaro, Tables 2.2/7 and 2.2/8

In the subgroup with UACR <300 mg/g, the majority of patients (66%) had a baseline eGFR <60 mL/min/1.73m^2 in the FIGARO study. However, in the subgroup with UACR ≥300 mg/g, most subjects (88%) had a baseline eGFR ≥60 mL/min/1.73m^2. Thus, the incidence of drug-related AEs and for AEs leading to study drug discontinuation is most likely driven by the worsening of kidney function, rather than the degree of albuminuria. The same trend is seen with treatment-emergent hyperkalaemia, where

the number of subjects with hyperkalaemia events increased with decreasing renal function, independent of the degree of albuminuria.

Safety related to drug-drug interactions and other interactions

Concomitant use of finerenone with medications that impair potassium excretion and increase serum potassium, may increase the risk of hyperkalaemia. See product information of the current SmPC for Kerendia.

Discontinuation due to adverse events

TEAEs resulting in permanent discontinuation of study drug were reported more frequently in the finerenone arm: 207 subjects (5.6%) in the finerenone arm and 183 subjects (5.0%) in the placebo arm. This difference is driven by the higher number of subjects permanently discontinuing study drug due to hyperkalaemia events (i.e. hyperkalaemia and increased blood potassium; Table 68).

The numbers of subjects with serious TEAEs resulting in permanent discontinuation of study drug was low in both treatment arms (1.9% vs 2.1%). The most frequent serious TEAEs resulting in permanent discontinuation of study drug in the finerenone arm were acute kidney injury (6 subjects, 0.2%) and hyperkalaemia (5 subjects, 0.1%). All other serious TEAEs resulting in permanent discontinuation of study drug in the finerenone arm and all events in the placebo arm were reported in <0.1% of the subjects.

Table 68 Most common (>0.1%) TEAEs leading to permanent discontinuation of study drug by SOC and PT: number (%) of subjects and incidence rates (SAF)

	FIGARO-DKD		FIDELIO-DKD		FIDELIO & FIGARO	
Primary SOC **PT** MedDRA version 23.1	**Finerenone** **N=3683 (100%) /** **IR per 100 p-yrs**	**Placebo** **N=3658 (100%) /** **IR per 100 p-yrs**	**Finerenone** **N=2827 (100%) /** **IR per 100 p-yrs**	**Placebo** **N=2831 (100%) /** **IR per 100 p-yrs**	**Finerenone** **N=6510 (100%) /** **IR per 100 p-yrs**	**Placebo** **N=6489 (100%) /** **IR per 100 p-yrs**
Number (%) of subjects with at least 1 such AE	**207 (5.6%)/ 1.97**	**183 (5.0%)/ 1.73**	**207 (7.3%)/ 3.36**	**168 (5.9%)/ 2.66**	**414 (6.4%)/ 2.48**	**351 (5.4%)/ 2.08**
Gastrointestinal disorders	**24 (0.7%)/ 0.23**	**26 (0.7%)/ 0.25**	**14 (0.5%)/ 0.23**	**16 (0.6%)/ 0.25**	**38 (0.6%)/ 0.23**	**42 (0.6%)/ 0.25**
Diarrhoea	10 (0.3%)/ **0.09**	4 (0.1%)/ **0.04**	4 (0.1%)/ **0.06**	9 (0.3%)/ **0.14**	14 (0.2%)/ **0.08**	13 (0.2%)/ **0.08**
Nausea	3 (<0.1%)/ **0.03**	10 (0.3%)/ **0.09**	2 (<0.1%)/ **0.03**	4 (0.1%)/ **0.06**	5 (<0.1%)/ **0.03**	14 (0.2%)/ **0.08**
Investigations	**24 (0.7%)/ 0.23**	**10 (0.3%)/ 0.09**	**26 (0.9%)/ 0.42**	**20 (0.7%)/ 0.32**	**50 (0.8%)/ 0.30**	**30 (0.5%)/ 0.18**
Blood creatinine increased	2 (<0.1%)/ **0.02**	1 (<0.1%)/ **0.01**	5 (0.2%)/ **0.08**	5 (0.2%)/ **0.08**	7 (0.1%)/ **0.04**	6 (<0.1%)/ **0.04**
Blood potassium increased	10 (0.3%)/ **0.09**	1 (<0.1%)/ **0.01**	13 (0.5%)/ **0.21**	6 (0.2%)/ **0.09**	23 (0.4%)/ **0.14**	7 (0.1%)/ **0.04**
Glomerular filtration rate decreased	9 (0.2%)/ **0.09**	4 (0.1%)/ **0.04**	7 (0.2%)/ **0.11**	8 (0.3%) / **0.13**	16 (0.2%)/ **0.10**	12 (0.2%)/ **0.07**
Metabolism and nutrition disorders	**43 (1.2%)/ 0.41**	**20 (0.5%)/ 0.19**	**52 (1.8%)/ 0.84**	**22 (0.8%)/ 0.35**	**95 (1.5%)/ 0.57**	**42 (0.6%)/ 0.25**
Hyperkalaemia	36 (1.0%)/ **0.34**	12 (0.3%)/ **0.11**	51 (1.8%)/ **0.83**	19 (0.7%)/ **0.30**	87 (1.3%)/ **0.52**	31 (0.5%)/ **0.18**
Renal and urinary disorders	**15 (0.4%)/ 0.14**	**10 (0.3%)/ 0.09**	**27 (1.0%)/ 0.44**	**34 (1.2%)/ 0.54**	**42 (0.6%)/ 0.25**	**44 (0.7%)/ 0.26**
Acute kidney injury	9 (0.2%)/ **0.09**	3 (<0.1%)/ **0.03**	5 (0.2%)/ **0.08**	7 (0.2%)/ **0.11**	14 (0.2%)/ **0.08**	10 (0.2%)/ **0.06**
Chronic kidney disease	0	0	2 (<0.1%)/ **0.03**	8 (0.3%)/ **0.13**	2 (<0.1%)/ **0.01**	8 (0.1%)/ **0.05**
Renal impairment	2 (<0.1%)/ **0.02**	2 (<0.1%)/ **0.02**	8 (0.3%)/ **0.13**	8 (0.3%)/ **0.13**	10 (0.2%)/ **0.06**	10 (0.2%)/ **0.06**
Skin and subcutaneous tissue disorders	**8 (0.2%)/ 0.08**	**12 (0.3%)/ 0.11**	**12 (0.4%)/ 0.19**	**7 (0.2%)/ 0.11**	**20 (0.3%)/ 0.12**	**19 (0.3%)/ 0.11**
Pruritus	0	2 (<0.1%)/ **0.02**	5 (0.2%)/ **0.08**	1 (<0.1%)/ **0.02**	5 (<0.1%)/ **0.03**	3 (<0.1%)/ **0.02**

In FIGARO-DKD, TEAEs resulting in permanent discontinuation of study drug were reported slightly more frequently for finerenone (5.6%) than for placebo (5.0%), driven mostly by hyperkalaemia (1.0% vs 0.3% for finerenone vs placebo).

Post marketing experience

N/A

2.5.1. Discussion on clinical safety

The safety result of FIGARO-DKD was presented individually followed by a summary of the pooled analysis of FIGARO-DKD and FIDELIO-DKD. Similar safety data was overall seen from the pooled analysis of data from the FIGARO-DKD and FIDELIO-DKD studies.

In FIGARO-DKD, the overall exposure was 17,149 PY for finerenone and 17,221 PY for placebo. Mean duration of exposure was about 35 months; 90% of the subjects were exposed for at least 52 weeks, 81% for at least 2 years, 50% for at least 3 years and 22% for at least 4 years.

The number of TEAEs was balanced for finerenone (85.1%) and placebo (85.5%); however, the incidence of drug-related TEAEs was increased for finerenone (15.2%) compared with placebo (11.3%). The maximum intensity for any AE in most subjects (about 67%) was mild or moderate. The most reported TEAE was hyperkalaemia (10.8% vs 5.3%).

The incidence of serious TEAEs was slightly higher in the placebo group (33.2%) than in the finerenone group (31.4%). The most frequently reported serious TEAE was “pneumonia”, which occurred less frequently in finerenone-treated subjects (2.0%) than in placebo (3.1% placebo). The number of fatal outcomes or adverse events was lower in the finerenone group (9.2%) compared with the placebo group (10.4%). Overall, 4.9% in the finerenone arm and 6.0% in the placebo arm died due to treatment-emergent adverse or outcome event.

Discontinuation rate due to TEAE was slightly higher for finerenone (5.6%) than for placebo (5.0%). The most frequently reported TEAE leading to study drug discontinuation for finerenone vs placebo was hyperkalaemia (1.2% vs 0.4%).

Hyperkalaemia

The incidence of hyperkalaemia was 2 times increased for finerenone versus placebo (10.8% vs 5.3%). Drug-related hyperkalaemia were reported in 6.5% of the subjects in the finerenone group compared with 3.1% in the placebo group. Serious events of hyperkalaemia were reported more frequently for finerenone (0.7%) than for placebo (0.1%). Moreover, a higher incidence of hyperkalaemia leading to discontinuation (1.2% vs 0.4%) and hospitalization (0.6% vs <0.1%) was reported for finerenone compared with placebo.

In total, 580 events of hyperkalaemia were reported among 396 finerenone-treated subjects, of which 71%, 17% and 8%, respectively, experienced 1,2 and 3 events, respectively, of hyperkalaemia.

A higher incidence for finerenone, than for placebo, had changes in serum potassium to >5.5 mmol/L (13.2% vs 6.0%) and to >6.0 mmol/L (2.3% vs 1.2%), respectively, at any time during treatment.

Decreased eGFR and renal events

The incidence of ‘eGFR decreased’ was increased for finerenone (4.6%) compared with placebo (3.9%). The incidence of renal AEs was slightly higher for placebo (15.0%) than for finerenone (13.4%), of which the incidence of ‘acute kidney injury’ was balanced (2.5% vs 2.7%). However, the incidence of *drug-related* ‘acute kidney injury’ was increased for finerenone (0.5%) versus placebo (0.2%).

The incidence of SAEs in the SOC of Renal and urinary disorders (2.8% vs 3.4%), including ‘acute kidney injury’ (1.0% vs 1.3%) was slightly higher for placebo or balanced. The incidence of serious events of ‘eGFR decreased’ was low for finerenone (0.1%) and placebo (<0.1%)

Laboratory findings, vital signs

Haematocrit

A decrease in mean haemoglobin (<0.17g/dL) and mean haematocrit (<0.85%) levels was observed in the first 4 months in the finerenone arm compared to placebo. Further analysis on changes in haemoglobin and haematocrit in the FIGARO-DKD study over time are consistent with previous data from the FIDELIO study. Changes in haemoglobin are already covered in section 4,8 of the SmPC.

Blood pressure

The mean SBP in the finerenone arm was reduced by approximately 2-3 mmHg compared to placebo at month 1, and the reduction remained generally stable thereafter. The mean DBP in the finerenone arm was reduced by approximately 1-2 mmHg compared to placebo in the first 36 months.

Hypotension occurred more frequently in subjects in the finerenone group (4.2%) than in the placebo group (2.5%). Events associated with hypotension such as syncope (1.2% vs 1.4%) and fall (0.7% vs 0.7%) was balanced between the groups, but dizziness (5.3% vs 4.6%) was slightly increased for finerenone compared with placebo. The incidence of serious hypotension (<0.1% vs <0.1%) and serious dizziness was low and balanced (0.2% vs 0.2%).

Serum urea

The incidence of hyperuricaemia was increased for finerenone compared with placebo (4.5% vs 2.8%). No imbalances of gout (2.8% vs 2.5%), gouty arthritis (0.4% vs 0.5%) or nephrolithiasis (1.4% vs 1.5%) were identified.

Serum sodium

An initial decrease in mean serum sodium (approximately 0.8 mmol/L) was observed in the finerenone-treated subjects in the first month of treatment compared to placebo, followed thereafter by a progressive gradual increase over time in both treatment arms, although the increase observed was smaller in the finerenone arm

Subgroups

Integrated data from the FIDELIO-DKD and the FIGARO-DKD studies was provided for the subgroup analyses below:

Effect by age

In the pooled analysis of FIDELIO-DKD and FIGARO-DKD, the reporting rate was overall similar across the age groups. Slightly more SAEs were reported in the age group ≥75 years (36.0% vs 37.8%) compared to subjects 65-74 years (33.1% vs 34.0%) and <65 years (29.0% vs 32.1%); however, the incidence of SAEs was higher for placebo than for finerenone in all age groups.

More subjects discontinued due to an AE in the finerenone group compared with placebo in the subgroups ≥75 years (8.0% vs 7.5%) and 65-74 years (8.1% vs 5.9%); however, the discontinuation rate due to AEs was balanced (4.3% vs 4.2%) in subjects <65 years.

Effect by sex

In the pooled analysis of FIDELIO-DKD and FIGARO-DKD, female subjects made up for approximately one third of the overall Phase 3 study population. No notable differences between males and females were noted, apart from that the incidence of subjects that discontinued due to an AE that was increased for finerenone compared with placebo (7.0% vs 5.4%) in males and was more balanced in females (5.0% than 5.4%).

Effect by race

In the pooled analysis of FIDELIO-DKD and FIGARO-DKD, the incidence of AEs was about 82%-90% in White, Black and 'Other subjects' and was slightly higher in Asian subjects (93-94%). The difference was

mainly driven by a higher number of subjects with AEs of mild intensity in the Asian race group (39%-42%) compared to the other race groups (21-26%).

Effect by hepatic impairment

In the pooled analysis of FIGARO-DKD and FIDELIO-DKD, the incidence of subjects with any AE and any SAE, respectively, was slightly higher in subjects with hepatic impairment (AEs:90%; SAEs:38%-39%) compared to those without hepatic impairment in the medical history (AEs:85%-86%; SAEs:30%-33%), in both treatment groups.

Effect by renal function

In the pooled analysis of FIDELIO-DKD and FIGARO-DKD, approximately 32% of the subjects had baseline eGFR 25 -<45 mL/min/1.73m^2, 26% eGFR 45 - <60 mL/min/1.73m^2 and 40% eGFR eGFR>60 mL/min/1.73m^2. The number of subjects with eGFR<25 mL/min/1.73m^2 (1.2%) was too limited to draw any firm conclusions. Finerenone is not recommended in subjects with eGFR <25 mL/min/1.73m^2 due to limited data.

Subjects with lower eGFR at baseline reported overall more AEs and SAEs compared to subjects with higher eGFR at baseline although the incidences were balanced for finerenone and placebo, or higher for placebo, across the eGFR strata: eGFR 25 -<45 mL/min/1.73m^2 (AEs:88.1% vs 88.4% and SAEs:33.7% vs 36.1%), eGFR 45 - <60 mL/min/1.73m^2 (AEs:87.2% vs 87.3% and SAEs:33.2% and 35.3%) and eGFR >60 mL/min/1.73m^2(AEs: 83.5% vs 84.0% and SAEs: 28.9% and 30.1%).

However, the incidence of *study-drug related* AEs was increased for finerenone compared with placebo across the subgroups: eGFR 25 -<45 mL/min/1.73m^2 (25.3% vs 17.4%), eGFR 45 - <60 mL/min/1.73m^2 (18.4% vs 13.8%) and eGFR>60 mL/min/1.73m^2 (12.7% vs 9.5%). *Study-drug related* SAEs was increased for finerenone compared with placebo in subjects with eGFR 25 -<45 mL/min/1.73m^2 (2.2% vs 1.4%) and eGFR 45 - <60 mL/min/1.73m^2 (1.2% vs 0.8%) and was balanced in subjects with eGFR>60 mL/min/1.73m^2 (0.5% vs 0.6%).

The incidence of subjects with any AE leading to discontinuation of study drug was increased for finerenone compared with placebo in subjects with eGFR 25 -<45 mL/min/1.73m^2 (8.7% vs 6.7%) and eGFR 45 - <60 mL/min/1.73m^2 (6.8% vs 5.3%) and was slightly higher for placebo in subjects with eGFR>60 mL/min/1.73m^2 (3.8% vs 4.3%).

The risk of hyperkalaemia increased with decreasing renal function across eGFR strata: ≥60 mL/min/1.73m^2 (7.6% vs 4.4%), 45 -<60 mL/min/1.73m^2 (13.9% vs 6.2%) and 25-45 mL/min/1.73m^2 (21.6% vs 10.2%).

Effect by albuminuria

In the FIGARO study, subjects with high albuminuria (AEs:87.4% vs 88.2%; SAEs:35.2% vs 36.6%) reported overall more AEs and SAEs compared to subjects with very high albuminuria (AEs:82.8% vs 83.2%; SAEs:27.9% vs 30.4%) at baseline although the incidences were higher for placebo. The incidences of *drug-related* AEs were more increased in subjects with high albuminuria (19.0% vs 14.3%) compared with subjects with very high albuminuria (11.4% vs 8.6%). Moreover, the incidence of *any AE leading to study drug discontinuation* was more increased for finerenone than for placebo in subjects with high albuminuria (7.7% vs 6.2%) compared with subjects with very high albuminuria (3.7% vs 3.8%). The data was similar for the pooled analysis of data from FIDELIO-DKD and FIGARO-DKD.

In the subgroup with UACR <300 mg/g, the majority of patients (66%) had a baseline eGFR <60 mL/min/1.73m^2 in the FIGARO study. However, in the subgroup with UACR ≥300 mg/g, most subjects (88%) had a baseline eGFR ≥60 mL/min/1.73m^2. Thus, the incidence of drug-related AEs and for AEs leading to study drug discontinuation is most likely driven by the worsening of kidney function, rather

than the degree of albuminuria. The same trend is seen with treatment-emergent hyperkalaemia, where the number of subjects with hyperkalaemia events increased with decreasing renal function, independent of the degree of albuminuria.

2.5.2. Conclusions on clinical safety

Kerendia is indicated for the treatment of CKD (stage 3 and 4 with albuminuria) associated with type 2 diabetes in adults. The main evidence of efficacy submitted to support the indication was the FIDELIO-DKD study in T2DM patients with CKD (mean eGFR 44 mL/min/1.73 m^2) and albuminuria (mean UACR 806 mg/g). The FIGARO-DKD study included T2DM patients with CKD (mean eGFR 68 mL/min/1.73 m^2) and albuminuria (mean UACR 287 mg/g). The cumulative exposure was lower in FIDELIO-DKD compared with FIGARO-DKD, due to the overall shorter observation time in FIDELIO-DKD. Mean duration of exposure in FIGARO-DKD was about 35 months and in FIDELIO-DKD about 27.5 months.

The major safety concern in the FIDELIO-DKD study was hyperkalaemia that increased with decreasing renal function. SAEs of hyperkalaemia were reported more frequently for finerenone than for placebo and a higher incidence of hyperkalaemia leading to discontinuation and to hospitalisation was reported for finerenone compared with placebo. The risk for serious events of hyperkalaemia for Kerendia is handled with routine risk minimisation.

The safety profile for finerenone in the FIGARO-DKD study was overall similar compared with previously identified adverse drug reactions for finerenone in the FIDELIO-DKD study, with hyperkalaemia as the main safety concern. The incidence of hyperkalaemia was two-fold increased for finerenone compared with placebo in the FIGARO-DKD and FIDELIO-DKD studies, respectively; although, the incidences were overall lower in the FIGARO-DKD with a population that had a better-preserved kidney function.

In the FIGARO-DKD study, the incidence of hyperuricaemia was increased for finerenone compared with placebo (4.5% vs 2.8%). No imbalances of gout (2.8% vs 2.5%), gouty arthritis (0.4% vs 0.5%) or nephrolithiasis (1.4% vs 1.5%) were identified.

In the FIGARO-DKD study, 46% of the subjects had high albuminuria at baseline (UACR 30 mg/g ≤300 mg) and about 51% had very high albuminuria (UACR ≥300 mg/g). The incidences of *drug-related AEs* (high albuminuria: 19.0% vs 14.3%; very high albuminuria:11.4% vs 8.6%) and *AEs leading to study drug discontinuation* (high albuminuria: 7.7% vs 6.2%; very high albuminuria: 3.7% vs 3.8%) were higher in subjects with high albuminuria compared with subjects with very high albuminuria. The data was similar for the pooled analysis of data from FIDELIO-DKD and FIGARO-DKD and is most likely driven by the worsening of kidney function rather than the degree of albuminuria. In the subgroup with UACR <300 mg/g, the majority of patients (66%) had a baseline eGFR <60 mL/min/1.73m^2; however, in the subgroup with UACR ≥300 mg/g, most subjects (88%) had a baseline eGFR ≥60 mL/min/1.73m^2.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 2.2 (with DLP 14 OCT 2021 and date of final sign off: 14 Dec 2022) is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 2.2 with the following content:

Safety concerns

Table SVIII.1: Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	Hyperkalemia
Important potential risks	Embryo-foetal toxicity
Missing information	Use in pregnancy and lactation

Considering the data in the safety specification, the safety concerns listed above are appropriate.

Pharmacovigilance plan

No changes are applied to the pharmacovigilance plan.

Routine pharmacovigilance activities are in place for the important identified risk “Hyperkalemia”, important potential risk “Embryo-foetal toxicity” and missing information “Use in pregnancy and lactation”.

There are no additional pharmacovigilance activities proposed beyond adverse reactions reporting and signal detection in Part III.1 of the RMP. Routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

Risk minimisation measures

Routine risk minimisation measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important identified risk	
Hyperkalaemia	*Routine risk communication:*

	• SmPC section 4.2 Posology and method of administration • SmPC section 4.4 Special warnings and precautions for use • SmPC section 4.5 Interaction with other medicinal products and other forms of interaction • SmPC section 4.8 Undesirable effects *Routine risk minimisation activities recommending specific clinical measures to address the risk:* • SmPC section 4.2 Posology and method of administration • SmPC section 4.4 Special warnings and precautions for use • SmPC section 4.5 Interaction with other medicinal products and other forms of interaction *Other routine risk minimisation measures beyond the Product Information:* Kerendia is a prescription-only medicine
Important potential risk	
Embryo-foetal toxicity	*Routine risk communication* • SmPC section 4.4 Special warnings and precautions for use • SmPC section 4.6 Fertility, pregnancy and lactation • SmPC section 5.3 Preclinical safety data *Routine risk minimisation activities recommending specific clinical measures to address the risk:* • SmPC section 4.4 Special warnings and precautions for use • SmPC section 4.6 Fertility, pregnancy and lactation • SmPC section 5.3 Preclinical safety data *Other routine risk minimisation measures beyond the Product Information:* • Kerendia® is a prescription-only medicine
Missing information	
Use in pregnancy and lactation	*Routine risk communication* • SmPC section 4.4 Special warnings and precautions for use • SmPC section 4.6 Fertility, pregnancy and lactation • SmPC section 5.3 Preclinical safety data *Routine risk minimisation activities recommending specific clinical measures to address the risk:* • SmPC section 4.4 Special warnings and precautions for use • SmPC section 4.6 Fertility, pregnancy and lactation • SmPC section 5.3 Preclinical safety data *Other routine risk minimisation measures beyond the Product Information:* • Kerendia is a prescription-only medicine

Abbreviations: SmPC=Summary of Product Characteristics.

Additional risk minimisation measures

No additional risk minimisation measures beyond routine are considered necessary for Kerendia.

Only routine risk minimisation measures are in place for all risks included in the safety specification. This did not change and is considered acceptable.

Overall conclusions on risk minimisation measures

The proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

The MAH confirms that since the approval of user tested package leaflet within the initial MAA

- the content of the proposed package leaflet is almost identical
- the key safety information is the same
- the size, format and layout of the printed package leaflet will be the same.

2.7.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Kerendia (finerenone) is included in the additional monitoring list as new active substance.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Initially proposed new indication for finerenone:

Kerendia is indicated for the treatment of chronic kidney disease *(CKD) and for the prevention of cardiovascular (CV) events in adults with CKD* (~~stage 3 and 4~~ with albuminuria) associated with type 2 diabetes~~ in adults~~.

For study results with respect to renal and CV events in the population studied, see section 5.1.

Applicant's updated proposed indication:

Kerendia is indicated for the treatment of chronic kidney disease (~~stage 3 and 4~~ with albuminuria) associated with type 2 diabetes in adults.
For study results with respect to renal and cardiovascular events, see section 5.1.

Compared to the previous round, the applicant has agreed to modify the reference to 5.1 and replace "cardiovascular protection" with "renal and cardiovascular events".

3.1.2. Available therapies and unmet medical need

For the treatment of chronic kidney disease and type 2 diabetes, ACEis and ARBs constitute the current standard of care. SGLT2-inhibitors, initially approved in 2013 for improving glycaemic control in T2D, have recently been shown to provide additional kidney and cardiovascular benefits in patients with CKD and T2D. CKD in T2D is progressive and irreversible with a close connection to ESRD and cardiovascular disease, leading to the need for renal replacement therapy.

The pathophysiology of CKD in T2D is multifactorial and there is a need for further effective therapies to address the complex and numerous underlying disease mechanisms.

3.1.3. Main clinical studies

The application for variation is based on efficacy data from the FIGARO-DKD study encompassing 7334 patients with CKD and T2D treated with the individual maximum tolerated labelled dose of either an ACEI or an ARB. The study was event driven and the primary objective was to demonstrate whether, in addition to standard of care, finerenone is superior to placebo in delaying the time to first occurrence of CV mortality and morbidity. The secondary objective was to determine whether finerenone was superior to placebo in delaying the progression of kidney disease. Thus, the first secondary endpoint in the FIGARO-DKD study was the primary endpoint in FIDELIO-DKD study and vice versa.

3.2. Favourable effects

Primary endpoint

Treatment with finerenone resulted in a 13% relative risk reduction compared with placebo for the CV composite endpoint of CV death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for heart failure (HR 0.87 [95% CI 0.76; 0.98]; p=0.0264). The primary endpoint of the FIGARO-DKD study was thus met. The effect is driven by hospitalizations due to heart failure (HR 0.71 [95% CI 0.56; 0.90]; p=0.0043). The components non-fatal stroke and non-fatal MI were unchanged by the treatment whereas CV death was numerically slightly lower in the finerenone compared to the placebo arm.

The Kaplan-Meier curves did separate starting 6 months after treatment initiation, which indicates a sustained effect. The absolute risk reduction based on Kaplan-Meier cumulative incidences for the primary CV endpoint was 2.0% at Month 36 and 2.1% at Month 42, corresponding to NNTs to prevent one primary endpoint event of 51 and 47 subjects, respectively.

Secondary endpoints

Treatment with finerenone resulted in a 13% relative hazard reduction compared with placebo of the first secondary endpoint time to the first occurrence of onset of kidney failure, a sustained decrease of eGFR ≥ 40% from baseline over at least 4 weeks, or renal death (HR 0.87 [95% CI 0.76; 1.01] p=0.0689]) but the result did however not reach statistical significance and the remaining secondary endpoints were not tested formally, but in an exploratory manner.

Finerenone had no effect on all-cause hospitalisation (HR = 0.97 [95% CI 0.90;1.04]; logrank test nominal p=0.3558) but had an effect on the component hospitalization due to heart failure (that was also the main contributor to the effect on the primary endpoint).

All-cause mortality was numerically reduced in the finerenone arm (HR = 0.89 [95% CI 0.77;1.04]; logrank test nominal p=0.1337).

Treatment with finerenone resulted in a reduced UACR from baseline to month 4 (ratio of LS-means=0.676 [95% CI 0.650; 0.704]; nominal p-value of F-test <0.0001). Additional explorative long-term data support a sustained suppression of UACR. Furthermore, the secondary 57% renal composite defined a more pronounced eGFR decrease that corresponds to a doubling of serum creatinine. Treatment with finerenone resulted in a 23% relative hazard reduction compared with placebo (HR 0.77 [95% CI 0.60;0.99]; logrank test nominal p=0.0406) i.e. a similar risk reduction as seen in the previous FIDELIO-DKD study, providing support for renoprotection.

3.3. Uncertainties and limitations about favourable effects

For the 40% and 57% renal endpoints, the treatment effect was reduced in subjects with 'high' albuminuria (<300 mg/g) compared to 'very high' albuminuria (>300 mg/g). Data on UACR however suggest a similar and sustained response in both subgroups. Also, for the exploratory analysis of the chronic eGFR slope there was a positive effect on the slope in both subgroups compared to placebo, but the magnitude was reduced in patients in the "high" compared to the "very high" subgroup which may be expected given the lower progression rate of renal dysfunction in these patients. Thus, data suggest no treatment effect on renal clinical endpoints during the follow up time but the effect on GFR slope and UACR indicate a future beneficial effect not yet seen in clinical endpoints.

3.4. Unfavourable effects

Kerendia is indicated for the treatment of CKD (stage 3 and 4 with albuminuria) associated with type 2 diabetes in adults. The main evidence of efficacy submitted to support the indication was the FIDELIO-DKD study in T2DM patients with CKD (mean eGFR 44 mL/min/1.73 m^2) and albuminuria (mean UACR 806 mg/g).

The FIGARO-DKD study included T2DM patients with CKD (mean eGFR 68 mL/min/1.73 m^2) and albuminuria (mean UACR 287 mg/g). The cumulative exposure was lower in FIDELIO-DKD compared with FIGARO-DKD, due to the overall shorter observation time in FIDELIO-DKD. Mean duration of exposure in FIGARO-DKD was about 35 months and in FIDELIO-DKD about 27.5 months.

The safety profile for finerenone in the FIGARO-DKD study was overall similar compared with previously identified adverse drug reactions for finerenone in the FIDELIO-DKD study, with hyperkalaemia as the main safety concern. The incidence of hyperkalaemia was two-fold increased for finerenone compared with placebo in FIGARO-DKD and FIDELIO-DKD; although, the incidences overall were lower in the FIGARO-DKD with a population that had a better-preserved kidney function. The risk for hyperkalaemia increases with decreasing renal function. The risk for serious events of hyperkalaemia for Kerendia is handled with routine risk minimisation.

The safety result of FIGARO-DKD was presented individually followed by a summary of the pooled analysis of FIGARO-DKD and FIDELIO-DKD. Similar safety data was overall seen from the pooled analysis of data from the FIGARO-DKD and FIDELIO-DKD studies.

In FIGARO-DKD, the overall exposure was 17,149 PY for finerenone and 17,221 PY for placebo. Mean duration of exposure was about 35 months; 90% of the subjects were exposed for at least 52 weeks, 81% for at least 2 years, 50% for at least 3 years and 22% for at least 4 years.

The number of TEAEs was balanced for finerenone (85.1%) and placebo (85.5%); however, the incidence of drug-related TEAEs was increased for finerenone (15.2%) compared with placebo (11.3%). Most of the TEAEs (about 67%) were mild or moderate in intensity.

The incidence of serious TEAEs was slightly higher in the placebo group (33.2%) than in the finerenone group (31.4%). The number of fatal outcomes or adverse events was lower in the finerenone group (9.2%) compared with the placebo group (10.4%).

Discontinuation rate due to TEAE was slightly higher for finerenone (5.6%) than for placebo (5.0%). The most frequently reported TEAE leading to study drug discontinuation for finerenone vs placebo was hyperkalaemia (1.2% vs 0.4%).

The incidence of *hyperkalaemia* was 2 times increased for finerenone versus placebo (10.8% vs 5.3%). Drug-related hyperkalaemia were reported in 6.5% of the subjects in the finerenone group compared with 3.1% in the placebo group. Serious events of hyperkalaemia were reported more frequently for finerenone (0.7%) than for placebo (0.1%).

More subjects in the finerenone group (4.6%) reported '*eGFR decreased*' compared with the placebo group (3.9%); however, *renal events* were more common for placebo (15.0%) than for finerenone (13.4%), of which the incidence of 'acute kidney injury' was balanced (2.5% vs 2.7%). The incidence of drug-related *'acute kidney injury*' was increased for finerenone (0.5%) versus placebo (0.2%)

Laboratory findings, vital signs

A *decrease in mean haematocrit* (<0.85%) levels was observed in the first 4 months in the finerenone arm compared to placebo.

The *mean SBP* in the finerenone arm was reduced by approximately 2-3 mmHg compared to placebo at month 1, and the reduction remained generally stable thereafter. The *mean DBP* in the finerenone arm was reduced by approximately 1-2 mmHg compared to placebo in the first 36 months.

Hypotension occurred more frequently in subjects in the finerenone group (4.2%) than in the placebo group (2.5%).

The incidence of *hyperuricaemia* was increased for finerenone compared with placebo (4.5% vs 2.8%). Hyperuricaemia is now included in section 4.8 of the SmPC. No imbalances of gout (2.8% vs 2.5%), gouty arthritis (0.4% vs 0.5%) or nephrolithiasis (1.4% vs 1.5%) were identified

Subgroups

Integrated data from the FIDELIO-DKD and the FIGARO-DKD studies was provided for the subgroup analyses below:

<u>Effect by age</u>

The reporting rate was overall similar across the age groups. Slightly more SAEs were reported in the age group ≥75 years (36.0% vs 37.8%) compared to subjects 65-74 years (33.1% vs 34.0%) and <65 years (29.0% vs 32.1%); however, the incidence of SAEs was higher for placebo than for finerenone in all age

groups. More subjects discontinued due to an AE in the finerenone group compared with placebo in the subgroups ≥75 years and 65-74 years.

Effect by sex

No notable differences between males and females were noted.

Effect by race

The incidence of AEs was about 82%-90% in White, Black and 'Other subjects' and was slightly higher in Asian subjects (93-94%).

Effect by hepatic impairment

The incidence of subjects with any AE and any SAE, respectively, was slightly higher in subjects with *hepatic impairment* (AEs:90%; SAEs:38%-39%) compared to those without hepatic impairment in the medical history (AEs:85%-86%; SAEs:30%-33%), in both treatment groups.

Effect by renal function

Subjects with lower eGFR at baseline reported overall more AEs and SAEs compared to subjects with higher eGFR at baseline although the incidences were balanced for finerenone and placebo, or higher for placebo, across the eGFR strata: eGFR 25 -<45 mL/min/1.73m^2 (AEs:88.1% vs 88.4% and SAEs:33.7% vs 36.1%), eGFR 45 - <60 mL/min/1.73m^2 (AEs:87.2% vs 87.3% and SAEs:33.2% and 35.3%) and eGFR >60 mL/min/1.73m^2(AEs: 83.5% vs 84.0% and SAEs: 28.9% and 30.1%). However, the incidence of *study-drug related* AEs was increased for finerenone compared with placebo across the subgroups: eGFR 25 -<45 mL/min/1.73m^2 (25.3% vs 17.4%), eGFR 45 - <60 mL/min/1.73m^2 (18.4% vs 13.8%) and eGFR>60 mL/min/1.73m^2 (12.7% vs 9.5%).

The risk of hyperkalaemia increased with decreasing renal function across eGFR strata: ≥60 mL/min/1.73m^2 (7.6% vs 4.4%), 45 -<60 mL/min/1.73m^2 (13.9% vs 6.2%) and 25-45 mL/min/1.73m^2 (21.6% vs 10.2%).

Effect by albuminuria

In the FIGARO-DKD study, 46% of the subjects had high albuminuria at baseline (UACR 30 mg/g ≤300 mg) and about 51% had very high albuminuria (UACR ≥300 mg/g). The incidences of *drug-related AEs* (high albuminuria: 19.0% vs 14.3%; very high albuminuria:11.4% vs 8.6%) and *AEs leading to study drug discontinuation* (high albuminuria: 7.7% vs 6.2%; very high albuminuria:3.7% vs 3.8%) were more increased in subjects with high albuminuria compared with subjects with very high albuminuria. The data is most likely driven by the worsening of kidney function rather than the degree of albuminuria. In the subgroup with UACR <300 mg/g, the majority of patients (66%) had a baseline eGFR <60 mL/min/1.73m^2; however, in the subgroup with UACR ≥300 mg/g, most subjects (88%) had a baseline eGFR ≥60 mL/min/1.73m^2

3.5. Uncertainties and limitations about unfavourable effects

In the FIGARO-DKD study, the incidences of *drug-related AEs* and *AEs leading to study drug discontinuation* were more increased in subjects with high albuminuria compared with subjects with very high albuminuria. The data was similar for the pooled analysis of data from FIDELIO-DKD and FIGARO-DKD. This is explained by the fact that mean eGFR at baseline was higher in the subgroup of patients with baseline UACR ≥300 mg/g, as compared to those with UACR <300 mg/g.

3.6. Effects Table

Table 1. Effects Table for finerenone in patients with CKD and T2D (FIGARO-DKD study)

Effect	Short description	Unit	Finerenone	Placebo	Uncertainties / Strength of evidence	References
Favourable Effects						
Primary endpoint	Composite of CV death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for heart failure	n/N(%)	458/3686 (12.4%)	519/3666 (14.2%)	HR 0.87 [95% CI 0.76; 0.98] p=0.0264	
Secondary endpoints	Composite of onset of kidney failure, a sustained decrease of eGFR ⩾40% from baseline over at least 4 weeks, or renal death	n/N(%)	350/3686 (9.5%)	395/3666 (10.8%)	HR 0.87 [95% CI 0.76;1.01] p=0.0689) Unc: Reduced effect in patients with albuminuria in the lower range.	
	All-cause hospitalization	n/N(%)	1573/3686 (42.7%)	1605/3666 (43.8%)	HR 0.97 [95% CI 0.90;1.04] p=0.3558) explorative	
	All-cause mortality	n/N(%)	333/3686 (9.0%)	370/3666 (10.1%)	HR 0.89 [95% CI 0.77;1.04] p=0.1337) explorative	
	Change in UACR (Ratio to baseline at Month 4)	Geom. mean (geom. SD)	0.6239 (2.4618)	0.9223 (2.3622)	Ratio of LS-means 0.676 [95% CI 0.650; 0.704] p<0.0001 explorative	
	Composite of onset of kidney failure, a sustained decrease of eGFR ⩾57% from baseline over at least 4 weeks, or renal death	n/N(%)	108/3686 (2.9%)	139/3666 (3.8%)	HR 0.77 [95% CI 0.60;0.99] p=0.0406 explorative	
Unfavourable Effects						
Any TEAE		n (%)	3134 (85.1%)	3219 (85.5%)		
Any TESAE		n (%)	1158 (31.4%)	1215 (33.2%)		
Hyperkalaemia		n (%)	396 (10.8%)	193 (5.3%)		

Effect	Short description	Unit	Finerenone	Placebo	Uncertainties / Strength of evidence	References
Decreased eGFR		n (%)	169 (4.6%)	141 (3.9%)		
Effect of renal function						
Any AE						
eGFR 25 -<45		n (%)	561 (87.8%)	529 (87.1%)		
eGFR 45 - <60		n (%)	652 (87.6%)	697 (88.6%)		
eGFR ≥60		n (%)	1907 (83.5%)	1892 (84.1%)		
Any SAE						
eGFR 25 -<45		n (%)	243 (38.0%)	232 (38.2%)		
eGFR 45 - <60		n (%)	253 (34.0%)	297 (37.7%)		
eGFR ≥60		n (%)	657 (28.8%)	680 (30.2%)		
Hyperkalaemia						
eGFR 25 -<45		n (%)	132 (20.7%)	56 (9.2%)		
eGFR 45 - <60		n (%)	96 (12.9%)	49 (6.2%)		
eGFR ≥60		n (%)	164 (7.2%)	86 (3.8%)		
Effect by albuminuria						
High albuminuria (UACR 30 mg/g **≤300** mg)						
Any AE		n (%)	1507 (87.4%)	1483 (88.2%)		
Any SAE		n (%)	607 (35.2%)	616 (36.6%)		
Any drug-related AE		n (%)	327 (19.0%)	241 (14.3%)		
AEs leading to study drug discontinuation		n (%)	133 (7.7%)	104 (6.2%)		
Very high albuminuria (UACR **≥300** mg/g)						
Any AE		n (%)	1532 (82.8%)	2158 (87.5%)		
Any SAE		n (%)	516 (27.9%)	571 (30.4%)		
Any drug-related AE		n (%)	210 (11.4%)	161 (8.6%)		
AEs leading to study drug discontinuation		n (%)	69 (3.7%)	72 (3.8%)		

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

CKD and T2D are each independently major global health concerns. An estimated 20 to 40% of T2D patients develop CKD, which is characterized by progressive damage and irreversible loss of function in the kidney eventually leading to kidney failure.

For the treatment of CKD and T2D, ACEis and ARBs constitute the current standard of care. SGLT2-inhibitors, initially approved in 2013 for improving glycaemic control in T2D, have recently been shown to provide additional kidney and cardiovascular benefits in patients with CKD and T2D.

Finerenone was approved in 2022 for the treatment of patients with CKD stage 3 and 4 with albuminuria associated with type 2 diabetes in adults. The market authorisation was supported by the pivotal FIDELIO-DKD study that showed a 17.5% relative risk reduction compared with placebo for the composite endpoint of time to first occurrence of kidney failure, a sustained decrease of eGFR ≥40% from baseline

over at least 4 weeks, or renal death. The treatment effect was obtained on top of current standard of care (ACEi or ARB).

The current application for variation is based on efficacy data from the FIGARO-DKD study encompassing 7334 patients with CKD and T2D treated with the individual maximum tolerated labelled dose of either an ACEI or an ARB. With the variation, the indication is proposed to be broadened to encompass all stages of CKD (with albuminuria) associated with type 2 diabetes (i.e. deletion of “stage 3 and 4” from the currently approved indication). Initially, the MAH also applied for the indication “prevention of cardiovascular (CV) events in adults with CKD”, but this request has subsequently been withdrawn.

In the FIGARO-DKD study, treatment with finerenone resulted in a 13% relative risk reduction compared with placebo for the primary composite endpoint of CV death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for heart failure. Thus, a statistically significant effect has been shown in line with data from the previous FIDELIO-DKD study. The effect was driven by hospitalizations for heart failure but observed in a population without previous symptomatic heart failure (NYHA II-IV). There was no effect on nonfatal myocardial infarction and stroke. The applicant proposed a reference to section 5.1 with respect to “cardiovascular protection” but has agreed to change the reference to “renal and CV events” in order to align the SmPC with other recently approved products.

The key secondary renal endpoint intends to support a broadening of the indication to encompass all stages of CKD (with albuminuria) associated with type 2 diabetes (i.e. deletion of “stage 3 and 4” from the currently approved indication). Treatment with finerenone resulted in a 13% relative hazard reduction compared with placebo of the first secondary endpoint time to the first occurrence of onset of kidney failure, a sustained decrease of eGFR $\geqslant$40% from baseline over at least 4 weeks, or renal death. The results did not reach statistical significance, but, in line with the CHMP’s opinion given in the SA, lack of statistical significance in the FIGARO results is not considered a main limiting factor to the pursued extension of indication, considering that a positive trend favouring finerenone over placebo has been demonstrated in the study population including Stage 1 and 2 of CKD. Data is thus in general in support for an effect across the different KDIGO categories, including CKD stage 1 and 2 for which extension of indication is sought.

However, for the key secondary renal endpoint, the treatment effect was reduced in subjects with ‘high’ albuminuria (HR=1.16 [95% CI 0.91; 1.47]) compared to ‘very high’ albuminuria (HR=0.74 [95% CI 0.62; 0.90]). Data on change in UACR however suggest a similar and sustained response in both subgroups. Also, for the exploratory analysis of the chronic eGFR slope there was a positive effect on the slope in both subgroups compared to placebo, but the magnitude was reduced in patients in the “high” compared to the “very high” subgroup which may be expected given the lower progression rate of renal dysfunction in these patients. Thus, data suggest no treatment effect on the key secondary renal endpoint during the follow up time, but the effect on GFR slope and UACR indicate a future beneficial effect not yet seen in clinical endpoints. In addition, finerenone had a beneficial effect on the primary CV endpoint in the FIGARO-DKD study, regardless of baseline albuminuria status. Thus, the totality of data, including findings from post hoc analyses, support that patients with both “high” and “very high” albuminuria benefit from the treatment.

No new safety concerns arise from the data provided compared to what is previously known concerning the safety profile for finerenone. The main safety concern is hyperkalaemia that increases with decreasing renal function. SAEs of hyperkalaemia are reported more frequently for finerenone than for placebo and more subjects discontinued treatment due to hyperkalaemia in the finerenone group compared with the placebo group. The incidence of hyperkalaemia was two-fold increased for finerenone compared with placebo in the FIGARO-DKD and FIDELIO-DKD studies, respectively; however, the incidences were overall lower in the FIGARO-DKD with a population that had a better-preserved kidney function. The risk of hyperkalaemia for Kerendia is handled with routine risk minimisation.

3.7.2. Balance of benefits and risks

The primary CV endpoint from the FIGARO-DKD is in line with the CV findings from the previous FIDELIO-DKD study and provides additional data for a population encompassing patients with CKD stage 1-2. The results for the key secondary renal endpoint were not significant, but in line with previous CHMP advice, lack of statistical significance is not considered a main limiting factor to the pursued extension of indication, considering that a positive trend favouring finerenone over placebo has been demonstrated in the study population including CKD stage 1-2. The response in the key secondary endpoint display heterogeneity concerning albuminuria while the beneficial CV effect was observed regardless of baseline albuminuria status. Patients with “high” albuminuria has a lower progression rate of renal dysfunction and explorative data suggest possible future beneficial renal effects not yet seen during the follow up time. Thus, the FIGARO-DKD study provides support for a positive B/R balance also for patients with CKD stage 1-2 and it is not considered that the data support a restriction of the indication to patients with very high albuminuria (>300 mg/g). The benefit-risk balance is considered positive.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of Kerendia is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following group of variations acceptable and therefore recommends, by a majority of 29 out of 30 votes, the variations to the terms of the Marketing Authorisation, concerning the following changes:

Variations accepted		Type	Annexes affected
C.I.13	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	Type II	None
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I

Extension of indication to include the treatment of chronic kidney disease (CKD) associated with type 2 diabetes in adults with CKD regardless of the stage of albuminuria, based on results from Study 17530 (FIGARO-DKD); a randomized, double-blind, placebo-controlled, parallel-group, multicenter, event-driven Phase III study to investigate the efficacy and safety of finerenone on the reduction of cardiovascular morbidity and mortality in subjects with type 2 diabetes mellitus and the clinical diagnosis of diabetic kidney disease in addition to standard of care. As a consequence, sections 4.1, 4.8, 5.1, 5.2 of the SmPC

is being updated and the Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to make editorial changes in the SmPC. The updated RMP version 2.2 has also been accepted.

Update of the SmPC section 5.2 based on the results of Study 21429, a phase 1 drug interaction study of finerenone with rosuvastatin.

Submission of the results of Study 21325, a phase 1 bioequivalence study assessing BE between finerenone 2 x 10 mg tablets and 20 mg tablet in Japanese healthy male adult participants (required by the Japanese PMDA).

The group of variations leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the group of variations, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

Divergent position to the majority recommendation is appended to this report.

5. EPAR changes

The EPAR will be updated following Commission Decision for this group of variations. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion Kerendia-H-C-5200-II-0001/G

Attachments

1. SmPC, Annex II, Labelling, Package Leaflet (changes highlighted).

APPENDIX

DIVERGENT POSITION DATED 15 DECEMBER 2022

DIVERGENT POSITION DATED 15 DECEMBER 2022

KERENDIA EMEA/H/C/005200/II/0001/G

The undersigned member of the CHMP did not agree with the CHMP's positive opinion recommending the variation to the terms of the marketing authorisation of Kerendia.

The reason for divergent opinion was the following:

The FIGARO study showed a benefit in the "very high" albuminuria" group but failed to convincingly demonstrate a benefit in the "high" albuminuria group as:

- the renal composite endpoints, which are recommended as primary outcomes in confirmatory trials by EMA guidelines, failed to show efficacy [HR=1.16 (95% CI 0.91; 1.47) in 40% renal composite].

-The chronic eGFR slope over a 36 month-follow-up period showed a difference from placebo which is below clinical relevance (between-treatment difference of 0.702 [95% CI 0.143;1.261]).

- the positive effect observed in the Urine Albumin-to-Creatinine Ratio (UACR) end-point alone is unable to support a benefit. This is supported by the dissociation between the trend in the composite renal endpoints and albuminuria changes over a 4-year follow-up period.

The lack of demonstrated efficacy, together with a slightly unfavorable renal safety profile in this sub-group, does not allow to conclude on a positive B/R in patients with <300 mg/g albuminuria.

Armando Genazzani