16 December 2021
EMA/78746/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Kerendia

International non-proprietary name: finerenone

Procedure No. EMEA/H/C/005200/0000

Note

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

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Administrative information

Name of the medicinal product:	Kerendia
Applicant:	Bayer AG Kaiser-Wilhelm-Allee 1 51373 Leverkusen GERMANY
Active substance:	Finerenone
International Non-proprietary Name/Common Name:	finerenone
Pharmaco-therapeutic group (ATC Code):	C03DA05
Therapeutic indication(s):	Kerendia is indicated for the treatment of chronic kidney disease (stage 3 and 4 with albuminuria) associated with type 2 diabetes in adults.
Pharmaceutical form(s):	Film-coated tablet
Strength(s):	10 mg and 20 mg
Route(s) of administration:	Oral use
Packaging:	blister (PVC/PVDC/alu) and bottle (HDPE)
Package size(s):	100 x 1 tablets (unit dose), 14 tablets, 28 tablets, 98 tablets and 100 tablets

Table of contents

1. Background information on the procedure 7
1.1. Submission of the dossier 7
1.2. Legal basis, dossier content 7
1.3. Information on Paediatric requirements 7
1.4. Information relating to orphan market exclusivity 7
1.4.1. Similarity 7
1.5. Applicant's request(s) for consideration 8
1.5.1. Accelerated assessment 8
1.5.2. New active substance status 8
1.6. Scientific advice 8
1.7. Steps taken for the assessment of the product 9

2. Scientific discussion 10
2.1. Problem statement 10
2.1.1. Disease or condition 10
2.1.2. Epidemiology 10
2.1.3. Biologic features 10
2.1.4. Clinical presentation 11
2.1.5. Management 11
2.2. About the product 12
2.3. Type of application and aspects on development 13
2.4. Quality aspects 13
2.4.1. Introduction 13
2.4.2. Active Substance 14
2.4.3. Finished Medicinal Product 18
2.4.4. Discussion on chemical, pharmaceutical and biological aspects 23
2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects 24
2.4.6. Recommendation(s) for future quality development 24
2.5. Non-clinical aspects 24
2.5.1. Introduction 24
2.5.2. Pharmacology 24
2.5.3. Pharmacokinetics 28
2.5.4. Toxicology 31
2.5.5. Ecotoxicity/environmental risk assessment 44
2.5.6. Discussion on non-clinical aspects 46
2.5.7. Conclusion on the non-clinical aspects 52
2.6. Clinical aspects 53
2.6.1. Introduction 53
2.6.2. Clinical pharmacology 56
2.6.3. Discussion on clinical pharmacology 74
2.6.4. Conclusions on clinical pharmacology 77
2.6.5. Clinical efficacy 78
2.6.6. Discussion on clinical efficacy 114
2.6.7. Conclusions on the clinical efficacy 123

2.6.8. Clinical safety 123
2.6.9. Discussion on clinical safety 144
2.6.10. Conclusions on the clinical safety 147
2.7. Risk Management Plan 148
2.7.1. Safety concerns 148
2.7.2. Pharmacovigilance plan 148
2.7.3. Risk minimisation measures 149
2.7.4. Conclusion 149
2.8. Pharmacovigilance 149
2.8.1. Pharmacovigilance system 149
2.8.2. Periodic Safety Update Reports submission requirements 149
2.9. Product information 150
2.9.1. User consultation 150
2.9.2. Additional monitoring 150

3. Benefit-Risk Balance 150

3.1. Therapeutic Context 150
3.1.1. Disease or condition 150
3.1.2. Available therapies and unmet medical need 150
3.1.3. Main clinical studies 151
3.2. Favourable effects 151
3.3. Uncertainties and limitations about favourable effects 152
3.4. Unfavourable effects 152
3.5. Uncertainties and limitations about unfavourable effects 154
3.6. Effects table 154
3.7. Benefit-risk assessment and discussion 156
3.7.1. Importance of favourable and unfavourable effects 156
3.7.2. Balance of benefits and risks 157
3.7.3. Additional considerations on the benefit-risk balance 157
3.8. Conclusions 158

4. Recommendations 158

List of abbreviations

ACEI	angiotensin-converting enzyme inhibitor
ADA	American Diabetes Association
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
BCRP	breast cancer resistance protein
BID	bis in die (twice daily)
BMI	body mass index
BP	blood pressure
CHF	chronic heart failure
CI	confidence interval
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL	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)
CV	cardiovascular
CYP	cytochrome P450
DAPA-CKD	Dapagliflozin in Patients with Chronic Kidney Disease (clinical trial)
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)
ER	exposure / response
EASD	European Association for the Study of Diabetes
ESC	European Society of Cardiology
ESRD	end-stage renal disease
FAS	full analysis set
f_u	unbound fraction
GLP-1	glucagon-like peptide-1
HbA1c	glycated haemoglobin
HOPE	Heart Outcomes Prevention Evaluation (clinical trial)
HR	hazard ratio
IC_{50}	concentration to inhibit 50% of an enzyme activity
INN	international non-proprietary name
IR	immediate release
ITT	intent to treat (principle)

IV	intravenous
K^+	potassium
KDIGO	Kidney Disease: Improving Global Outcomes
K_i	inhibitory constant
LS means	least square means
M-1	finerenone metabolite M-1
M-2	finerenone metabolite M-2
M-3	finerenone metabolite M-3
M-4	finerenone metabolite M-4
M-5	finerenone metabolite M-5
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
pH	negative log of hydrogen ion concentration
PBPK	physiological based pharmacokinetic
PD	pharmacodynamic(s)
PEG	polyethylene glycol
P-gp	P (permeability)-glycoprotein
PK	pharmacokinetic(s)
pk_a	negative logarithm of the acid ionisation constant
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
SAE	serious adverse event
SAF	safety analysis set
SBP	systolic blood pressure
SD	standard deviation
SGLT2	sodium-glucose cotransporter-2
T2D(M)	Type 2 diabetes (mellitus)
TEAE	treatment-emergent adverse event
UACR	urinary albumin-to-creatinine ratio
UGT	uridine 5'-diphospho-glucuronosyltransferase
t_{max}	time to reach maximum drug concentration in plasma after single (first) dose
V/F	apparent volume of distribution
WCHF	worsening chronic heart failure

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Bayer AG submitted on 5 November 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Kerendia, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 18 October 2018.

The applicant applied for the following indication:

Kerendia is indicated to delay progression of kidney disease and to reduce the risk of cardiovascular mortality and morbidity in adults with chronic kidney disease (stage 3 and 4 with albuminuria) and type 2 diabetes.

The CHMP granted the following indication:

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

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0324/2019 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0324/2019 was not yet completed as some measures were deferred.

The PDCO issued an opinion on compliance for the PIP P/0324/2019.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant 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.

1.5. Applicant's request(s) for consideration

1.5.1. Accelerated assessment

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

1.5.2. New active substance status

The applicant requested the active substance finerenone contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. Scientific advice

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

SA received:

Date	Reference	SAWP co-ordinators
25 June 2015	EMEA/H/SA/3096/1/2015/III	Dr Peter Mol, Dr Kolbeinn Gudmundsson
14 December 2017	EMEA/H/SA/3096/1/FU/1/2017/II	Dr Karin Janssen van Doorn, Dr. Hrefna Gudmundsdottir

The applicant received scientific advice on two occasions as mentioned in the table above for the development of finerenone for treatment of diabetic kidney disease. The scientific advice pertained to the following quality, pre-clinical and clinical aspects:

- Designation of starting materials
- Overall non-clinical evidence generation strategy
- Non-clinical characterisation of metabolites
- Plans to characterise clinical pharmacology including PK/PD profile
- Plans for population PK modelling
- Phase 3 plans: number of studies, study populations to support targeted indication, primary and secondary efficacy endpoints, background therapy, visit frequency, treatment duration, observation period, dose justification, statistical analysis plan, predefined stratification and subgroup analysis strategy, minimisation and handling of missing data, sample size estimation, plans for interim analysis, safety assessment, management and stopping rules for hyperkalaemia, reporting for serious adverse events (SAEs) which are also study endpoints, inclusion of safety events narratives in CSRs.

1.7. 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

The application was received by the EMA on	5 November 2020
The procedure started on	26 November 2020
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	15 February 2021
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	22 February 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	1 March 2021
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	25 March 2021
The applicant submitted the responses to the CHMP consolidated List of Questions on	13 July 2021
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	26 August 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	02 September 2021
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	16 September 2021
The applicant submitted the responses to the CHMP List of Outstanding Issues on	11 October 2021
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	27 October 2021
The CHMP agreed on a 2nd list of outstanding issues in writing to be sent to the applicant on	11 November 2021
The applicant submitted the responses to the 2nd CHMP List of Outstanding Issues on	16 November 2021
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	01 December 2021
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Kerendia on	16 December 2021

Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	16 December 2021

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The approved therapeutic indication for finerenone is:

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

2.1.2. 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 characterised 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].

2.1.3. 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 haemodynamic, metabolic, inflammatory and fibrotic factors as interrelated pathophysiological drivers of CKD progression[7].

[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.
[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.

2.1.4. 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 utilisation 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.

2.1.5. Management

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

[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.
[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.

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]. Existing therapies for CKD in T2D primarily target metabolic and haemodynamic factors leaving MR overactivation and aldosterone upregulation untreated. Thus, 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.

2.2. 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 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.

[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.

The proposed clinical use of finerenone is to delay progression of kidney disease and to reduce the risk of cardiovascular mortality and morbidity in adults with chronic kidney disease (stage 3 and 4 with albuminuria) and type 2 diabetes.

The agreed during the IMA procedure indication is *Kerendia is indicated for the treatment of chronic kidney disease (stage 3 and 4 with albuminuria) associated with type 2 diabetes in adults.*

The starting dose of finerenone is 10 mg once daily. After 4 weeks of treatment, the dose can be increased to 20 mg once daily depending on serum potassium and the eGFR response.

2.3. Type of application and aspects on development

The CHMP did not agree to the applicant's request for an accelerated assessment as the product was not considered to be of major public health interest. This was based on the following:

In the FIDELIO-DKD trial, finerenone reduced the risk of the primary as well as key secondary composite endpoints, reaching formal statistical significance for both. However, the internal validity of the study needs to be carefully assessed, considering possible interactions between the treatment and relevant clinical variables. Moreover, the clinical relevance of an 18% reduced relative risk warrants further assessment. There was also a two-fold increase in treatment-emergent hyperkalaemia AEs observed for finerenone compared to placebo. According to the applicant, hyperkalaemia has been an important limiting factor for the use of the previously approved MRAs. In addition, the fact that the disease progresses slowly and that other treatments are available undermines the need of early availability of finerenone, bearing in mind that the approval of accelerated assessment would result in a reduction of 60 days in the MAA.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as film-coated tablets containing 10 mg or 20 mg of finerenone as active substance.

Other ingredients are:

Tablet core: microcrystalline cellulose, croscarmellose sodium, hypromellose 2910, lactose monohydrate, magnesium stearate and sodium laurilsulfate;

Tablet coating: hypromellose 2910, titanium dioxide, talc, iron oxide red (E172) (10 mg tablets) and iron oxide yellow (E172) (20 mg tablets).

The product is available in PVC/PVDC/Aluminium transparent calendarised or perforated unit dose blisters, and in white opaque HDPE bottle with white opaque polypropylene child-resistant screw cap with sealing insert as described in section 6.5 of the SmPC.

2.4.2. Active Substance

2.4.2.1. General information

The chemical name of finerenone is (4*S*)-4-(4-cyano-2-methoxyphenyl)-5-ethoxy-2,8-dimethyl-1,4-dihydro-1,6-naphthyridine-3-carboxamide corresponding to the molecular formula $C_{21}H_{22}N_4O_3$. It has a relative molecular weight of 378.2 and the following structure:

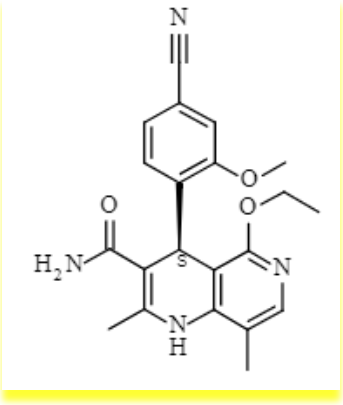


Figure 1: active substance structure

The chemical structure of finerenone was elucidated by a combination of IR, Raman, UV/Vis, ^{1}H-NMR, ^{13}C-NMR, MS, and elemental analysis. Single-crystal X-ray structural analysis was performed to confirm the absolute configuration.

Finerenone was examined for polymorphism and pseudo-polymorphism according to the ICH Q6A guideline by instrumental methods of analysis, crystallisation experiments from different solvents and from the melt. Finerenone was found to exist in one modification (modification I). The identity of Modification I is determined by XRPD. An amorphous form can exist at room temperature. In addition, existence of isomorphic solvates with different solvents was observed. The solvates are not stable at room temperature. Modification I is the thermodynamically stable polymorph and was used throughout the whole development for tablet manufacture and will also be used in the manufacture of proposed commercial product. The physical form has been controlled during development in all batches used in stability studies, and data presented show that the physical form does not change over time. Consequently the testing of the one modification is not included in the stability programme.

Polymorphic form is determined by the crystallisation. Only one form (Modification I) has been detected throughout development, validation, and stability studies.

The active substance is a white to yellow crystalline non-hygroscopic powder. It is soluble in methanol and sparingly soluble in ethanol, acetonitrile and acetone. Its solubility in aqueous media is strongly pH- dependent, being soluble at pH 1 and practically insoluble at pH above 4.5.

Finerenone has one stereocentre with S configuration. Enantiomeric purity is controlled routinely by chiral HPLC.

2.4.2.1. Manufacture, characterisation and process controls

Finerenone is synthesised at two different sites.

Two additional sites perform micronisation of the active substance.

Finerenone is manufactured by one synthetic route, in eight steps (five chemical transformations - although not all intermediates are isolated - leading to racemic finerenone, then resolution, crystallisation and physical treatment by micronisation) using four well defined starting materials with acceptable specifications. Adequate detailed description of the active substance synthesis process was provided in the dossier.

The choice of starting materials was discussed with the CHMP in a Scientific Advice in 2015. The CHMP expressed preliminary support for the proposed starting materials, but highlighted that the synthetic routes for two of the starting materials included compounds with potential structural alerts for genotoxicity, and concluded that these issues would have to be addressed in the dossier. The applicant has taken the advice and performed an in silico evaluation of potential mutagenic impurities in all four proposed starting materials. In the specification for one of the starting materials, limits are introduced on a mg/kg level. For the other starting materials, the applicant came to the conclusion that no routine controls are necessary. Justifications are in line with ICH Q11 and the EMA Guideline on the chemistry of active substances EMA/454576/2016. In conclusion, the proposed starting materials are acceptable.

Several suppliers were listed for each starting material, with differences in reagents, solvents and reaction conditions. All suppliers were listed with company names and addresses. Justifications for each starting material were presented, along with impurity profiles, batch data and specifications. Their respective impurity profiles were discussed, demonstrating an understanding on the active substance manufacturers part of the chemical properties of each.

The stereocentre of the active substance is formed during the synthesis. Two different methods for separation of the enantiomers are described, followed by a final purification and micronisation of the active substance. The acceptability of this approach has been discussed at pre-submission meetings with the EMA and the Rapporteurs prior to submission of the dossier. During validation, characterisation of batches made by both procedures were compared, including statistical evaluation of the results. The evaluation shows that the direct process product finerenone crude is highly pure and the statistical differences that were seen in some cases between the two processes are at a very low impurity levels and thus mainly related to the analytical methods. The batch to batch variation is in the same order as the process to process variation. No new impurities were found, and no change in quantitation of impurities was seen. Batch analysis data provided support that the two methods indeed are equivalent.

The enantiomeric control has been described, ensuring a complete purge of the R-enantiomer with the mother liquor, regardless the separation method used. The final steps do not affect stereochemistry. The presence of the undesired enantiomer (R) is controlled in the specification for the micronised active substance. No interconversion from S to R has been observed, even during forced degradation.

Following a Major Objection (MO) raised during the evaluation, critical process steps were identified based on their impact on critical quality attributes (CQAs). Identity, appearance and assay are defined as CQAs, although they cannot be linked to any specific step, but rather to the overall process design and control.

The following steps are considered critical:

- Enantiomeric separation
- Final crystallisation
- Micronisation of the active substance.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

All known potential mutagenic impurities in the active substance were evaluated in silico, using DEREK and Leadspace, supplemented by VITIC Nexus experimental data.

The potential formation of nitrosamines in the active substance was evaluated according to ICH M7. The entire manufacturing chain was included – all synthetic steps, including starting materials, reagents, raw materials, reaction conditions, re-use of solvents and active substance chemical structure, packaging, and storage conditions. No risks for nitrosamine formation were identified.

A risk assessment on the potential presence of elemental impurities was performed according to ICH Q3D. No metal catalysts are used in the active substance manufacturing. Six batches of the active substance were screened for elemental impurities. No elements were found above their respective thresholds.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development programme. The same overall route was used during pre-clinical and clinical development. Initially, five process steps were performed under cGMP, but in the MAA submission three additional steps were included in the GMP process as currently described. Changes introduced have been presented in sufficient detail and have been justified. For all pre-clinical and clinical batches up to phase 2, the separation of the enantiomers was achieved by one method; an alternative method was introduced at the time of clinical trials phase 3.

The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

Process parameters were evaluated by risk assessment, and those with potential influence on the quality attributes of micronised active substance were investigated by variation of one parameter at a time (OVAT), or, to investigate PARs, by variation multiple parameters simultaneously. PARs have been described for each process step. For PARs, the applicant compliance with the Q&A document EMA/CHMP/CVMP/QWP/354895/2017 "Questions and answers: Improving the understanding of NORs, PARs, DSp and normal variability of process parameters" has been declared in response to the MO.

The applicant claims two design spaces for the manufacturing process. Based on laboratory data from process understanding studies, simple design spaces have been defined and justified for non-critical process parameters.

For each proposed design space, the extremes were tested (data included in the dossier). Furthermore, in both cases no impact from reaction scale is expected as the amounts are calculated based on equivalents. No significant effects on output quality were found. Hence, the proposed design spaces are accepted.

The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed PARs and design spaces.

The active substance is packaged in LDPE foil bags. As secondary packaging, tightly closed containers for mechanical protection are used. The packaging material complies with Ph. Eur. 3.1.3 Polyolefins, EC Directives 1935/2004/EC, and Commission regulation (EU) 10/2011.

2.4.2.1. Specification

The active substance specification includes tests for appearance and colour, identity (IR, HPLC), PSD (laser diffraction), enantiomeric purity (RP-HPLC), water content (KF), residual solvents (HS-GC), related substances (RP-HPLC) and assay (RP-HPLC).

The specification comprises relevant tests for the intended use of the active substance.

The active substance is micronised prior to use in the finished product manufacture. Therefore, its particle size distribution is controlled by specification. The limits were set based on experience from finished product manufacture, e.g. that tablets manufactured with active substance particle size outside the specified limits displayed slower dissolution at 15 minutes, although compliance with specification at 30 minutes was observed. The proposed limits are considered adequate with respect to commercial content uniformity and dissolution, as well as comparability with development batches.

Enantiomeric purity limit is in line with ICH Q3A requirements.

Limits for the undesired R enantiomer, organic impurities/related substances, and residual solvents have been defined in line with ICH Q3A and Q3C, respectively, and the levels are acceptable.

Water is introduced in the crystallisation. It is purged with the mother liquor and by drying in that step. Finerenone is not hygroscopic, water is considered a non-critical attribute, but nonetheless it is controlled in the active substance specification with an acceptable limit.

Acceptable discussions and justifications for not including tests for elemental impurities, potentially mutagenic impurities other than already specified, microbiological purity, and polymorphic form in the active substance specification have been provided.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards of finerenone micronised and of impurities specified for the active substance have been provided.

Batch data for 10 commercial scale batches and representing the different combinations of enantiomer separation technique and micronisation site, are presented. All batches comply with current specification, and the inter-batch variation is very low. Thereby, the presented batch data is accepted as support for the comparability of active substance manufactured using one of the two different methods for separation of the enantiomers and being micronised at either site.

In addition, data from a number of development batches is presented. The analytical methods, and if there were any differences between them and those described in S.4.2, have not described or discussed. However, the presented results are generally in good agreement with those presented for the commercial batches, which is taken as an indication that the manufacturing procedure has remained consistent and robust over time.

2.4.2.1. Stability

Stability data from 10 commercial validation batches of micronised active substance from the proposed manufacturers (five batches were made by each method for enantiomeric separation, and both micronisation sites are represented) stored in the intended commercial package for up to 12 months under long term conditions (25ºC / 60% RH), 12 months at 30 °C/75 % RH and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided.

The following parameters were tested: appearance, identity, PSD, enantiomeric purity, water, specified impurities, any unspecified impurity, total impurities, and assay. The analytical methods used were the same as for release and were stability indicating.

All tested parameters were within the specifications. Analytical results remained essentially constant over the studied periods under all storage conditions. Results were also very similar between batches.

Additional supportive stability results from the 7 pilot-scale clinical batches stored for up to 24 months at 25ºC / 60% RH and for up to 12 months at 40ºC / 75% RH were presented. They showed that the active substance is very stable. There are only minor changes within those batches, and no clear trends in any parameters. Also, there is good agreement in results between batches and between long-term and accelerated conditions. The applicant states that all results met the current specifications at the time, but that most batches also would comply with the proposed commercial specification, which is agreed.

Photostability tests following the ICH guideline Q1B were performed in solid and in solution on a commercial scale batch. Based on the results obtained, solid finerenone was classified as not being photolabile in the solid state, and consequently no measures to protect it from light during handling or storage are proposed. In solution, finerenone should be protected from light by e.g. suitable packaging.

Results from stress testing under thermal, oxidative and hydrolytic conditions were also provided. Finerenone was found to be stable to thermal stress, stable to hydrolysis at neutral or moderately alkaline conditions, but somewhat susceptible to hydrolysis at higher pH and upon treatment with acid. The active substance is rapidly degraded if exposed to oxidative conditions in solution.

The stability results indicate that the micronised finerenone manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period of 24 months with no special storage instructions in the proposed container.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

Kerendia film-coated tablet 10 mg is presented as pink film-coated, oval oblong tablet with a length of 10 mm, a width of 5 mm, a radius of curvature of 3.4 mm, a height of 3.1 – 3.7 mm and a weight of 136.00 mg. The tablets are marked with "10" on the top side and "FI" on the bottom side.

Kerendia film-coated tablet 20 mg is presented as pale-yellow film-coated, oval oblong tablet with a length of 10 mm, a width of 5 mm, a radius of curvature of 3.4 mm, a height of 3.1 – 3.7 mm and a weight of 136.00 mg. The tablets are marked with "20" on the top side and "FI" on the bottom side.

The list of excipients is included in section 6.1 of the SmPC.

Finerenone tablets are film-coated in order to provide a homogeneous appearance, to add a colour for product identification and to facilitate swallowing. Commonly used coating excipients with worldwide acceptability have been selected. The coating is applied as an aqueous coating suspension, containing hypromellose 5 cP as film forming agent, talc as anti-tacking agent and depending on the dose strength inorganic pigments to achieve the desired respective colour.

The tablets have same shape and same weight, but different colour (10 mg tablets light pink and 20 mg tablets light yellow) and markings. Based on the posology it is likely that the patient has only one strength to handle. The risk for mix-up is considered satisfactorily addressed.

The tablet cores for the 10 mg and 20 mg strengths have identical qualitative and quantitative composition except for the amounts of finerenone, microcrystalline cellulose, lactose monohydrate and sodium laurilsulfate.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards, except the iron oxides used in the tablet-coatings (Iron oxide red and iron oxide yellow). The constituents of the lacquers comply with Ph. Eur. or the EU foodstuffs regulation. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

In the section 4.2. of SmPC it is reported that for patients who are unable to swallow whole tablets, Kerendia tablets may be crushed. The film-coating is not functional and it has been shown that it does not influence the drug dissolution. The purpose of the coating is cosmetical and better compliance. Thereby it is acceptable to crush the tablet.

The aim of the pharmaceutical development was to provide a safe and effective oral formulation containing finerenone micronised that is convenient for patients and ensures patient compliance according to the Quality Target Product Profile (QTPP). The QTPP describes the properties of the dosage form including route of administration (oral, immediate release tablet, format and colour) as well as the requirements which should be fulfilled to comply with the specification (identity, appearance, solid state form, assay, uniformity of dosage, degradation products, dissolution and microbial purity). Additionally, a minimum shelf life which should be achieved in a suitable container closure system, is included.

All these properties were evaluated and development led to immediate release easy to swallow tablets for a variety of strengths, which meet all ICH- and Ph.Eur. requirements and showed to be very stable, as detailed hereafter.

Immediate release (IR) tablet formulations of relatively small size were selected as dosage form.

Compatibility studies of finerenone active substance with common tablet excipients, such as cellulose microcrystalline, croscarmellose sodium, hypromellose 5 cP, lactose monohydrate, magnesium stearate, sodium laurilsulfate, talc, titanium dioxide and ferric oxides were performed. Binary drug excipient mixtures were investigated storing the mixtures at 40 °C/75 % relative humidity (RH), open storage and at 60 °C. Significant drug excipient incompatibilities could not be detected.

Due to the low solubility of finerenone, micronised substance is used in the tablets, as indicated in the active substance section.

From the QTPP a list of relevant quality attributes was initially identified. The criticality of each quality attribute was then evaluated based on its impact on the safety and efficacy to a patient if the product falls outside the acceptable range of that quality attribute. From the criticality analysis the following seven quality attributes (QAs) are defined as critical quality attributes (CQAs) for finerenone coated tablet: identity, appearance, uniformity of dosage, dissolution, degradation products, assay and microbial purity.

The start of Phase I dose finding studies was performed using an oral liquid formulation of finerenone. For clinical trials with radiolabelled active ingredient an aqueous oral solution or a macrogol-based solution was applied.

An intravenous solution for infusion with an active substance concentration of 0.005 % has also been developed and studied in an absolute bioavailability study for the evaluation of immediate release tablets 5 mg.

All other clinical trials were performed with immediate release tablet formulations of various dose strengths. The different dose strengths needed to supply clinical studies Phase I-IIa (1.25 mg + 10 mg), Phase IIb (1.25 mg – 20 mg) and Phase-III (10 mg – 20 mg) were based on the same qualitative core composition and manufacturing process.

The proposed commercial products are of the same core composition as the clinical Phase IIb/III formulations.

Alternative formulations are under development for paediatric use.

The comparison between the dissolution profiles of the tablets used for clinical studies and those intended for commercial use was performed on three buffers at pH 1.2-6.8 and they show comparable *in vitro* profiles for the two formulations.

The development of the dissolution method has been described by the applicant. A dissolution limit of Q = 80 % in 30 minutes was set first as a critical quality attribute and then a method was developed to achieve this limit instead of first developing a discriminative method and then setting the specification limit based on data from clinical batches. Based on the data provided the applicant was requested to revise the acceptance criteria in line with the reflection paper EMA/CHMP/CVMP/QWP/336031/2017. The limit was changed in line with the reflection paper. This is acceptable.

A standard manufacturing process is proposed for Kerendia film-coated tablets consisting of fluid-bed granulation (including drying and sieving) followed by post-blending, compression and film-coating.

During process development and scale up, the impact of manufacturing conditions on the quality attributes of the final dosage form as defined from the QTPP was investigated.

The applicant applied QbD principles in the development of the finished product and their manufacturing process. A comprehensive risk analysis was performed using the failure mode effect analysis (FMEA) method to define which functionality related characteristics of the excipients and which critical process steps and process parameters of each manufacturing steps may have an influence on the key quality attributes of the final finished product as derived from the QTPP. According to the risk analysis only the film-coating was identified as a critical manufacturing process step.

A total of 7 potential critical raw material attributes and of 15 potential critical process parameters had been identified. Most of them were further investigated by individual laboratory experiments and for process parameters carefully monitored during design of experiments (DoE) studies in laboratory scale as well as pilot and commercial scale. For those not included in further experiments appropriate explanation was given. Adequate process control (in-process testing) and release testing of the finished product have been established.

On the basis of the knowledge gained from the DoE studies in laboratory and pilot scale it was decided to focus the DoE study in commercial scale on the granulation process (spray rate, spray pressure and product temperature) and film coating (spray rate, outlet air temperature and drum rotation speed). A full 2-level factorial design with three factors and four centre points was carried out for each of them.

These experiments have been used to set the parameter ranges for the in-process controls.

The applicant claimed design space for the granulation and film-coating steps. However, data provided was not sufficient to support them. They were withdrawn and replaced by acceptable NORs and PARs.

The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed PARs.

The tablets are either packaged in PVC/PVDC/Al transparent calendarised or perforated unit dose blisters or HDPE bottles with opaque polypropylene child-resistant screw cap with sealing insert, as described in section 6.5 of the SmPC. The materials comply with Ph.Eur., EU food regulation and/or EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.4.3.1. Manufacture of the product and process controls

The tablets are manufactured and released by Bayer AG, Germany. The manufacturing process is a standard process consisting of mixing, wet granulation, drying, sieving, blending, tablet compression and film-coating as outlined in Scheme 2. To manufacture the aqueous coating suspension, the individual components or a ready-to-use film-coat can be used.

The manufacturing process has been adequately described.

Some data derived from pilot scale batches for 10 and 20 mg tablets to support the proposed holding times of intermediate products have been provided. The findings are considered acceptable. The applicant has started studies to confirm the proposed holding times on commercial batches. Control of assay and impurities will be included in these studies in order to assure that there is no change of the active substance during the holding times. The CHMP recommended the applicant to provide the confirmatory data from the on-going holding times study on commercial scale 10 and 20 mg tablets to support the proposed holding times of intermediate products (REC).

It has been confirmed that the start of shelf-life is calculated in accordance with "Note for Guidance on the start of shelf-life of the finished dosage form".

Adequate in-process controls (loss on drying, uniformity of mass, breaking load, disintegration and friability) with limits justified during pharmaceutical development have been described.

The only critical step is the film-coating step that is appropriately controlled.

Process validation has been performed on three production scale batches of each strength. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

2.4.3.1. Product specification

The finished product release and shelf life specifications include: appearance, identity (HPLC/UPLC, retention time and UV spectrum), uniformity of dosage units (Ph. Eur), dissolution (Ph. Eur), degradation products (HPLC/UPLC), assay (HPLC/UPLC), microbial purity, TAMC, TYMC and *E. coli* (Ph. Eur.).

The specification includes relevant and appropriate tests for this kind of dosage form.

Rac-Amido-naphthyridine is the only specified degradation product of the active substance. It is also the major metabolite in animals and humans and thus can be considered toxicologically qualified.

The limits for related substances at both release and shelf-life are in accordance with ICH Q3B and are considered acceptable. All other limits have also been satisfactorily justified.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on six batches using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity control. The information on the control of elemental impurities is satisfactory.

Following a MO raised by the CHMP, the applicant presented a risk evaluation concerning the presence of nitrosamine impurities in the finished product considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information presented and the responses to the questions raised with regards to the presence of nitrocellulose print primer, printing inks and over-lacquer on the outside of the lidding foil of the blisters, it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product, since neither the foil nor the printing ink contain any components with known amine groups. Therefore, no additional control measures are deemed necessary on the proposed product. The applicant is reminded that future changes to materials or supplier of any material need to be reassessed regarding the risk of nitrosamines presence in the product and that the MAH is responsible for the evaluation and conclusions regarding presence of nitrosamine impurities in their products.

Acceptable justifications for the omission of tests for enantiomeric purity, residual solvents, water content, tablet breaking load and disintegration were also provided.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided from three pilot scale batches of each strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Furthermore batch analysis data from clinical batches and additional data from batches using active substance manufactured with each of the applied enantiomer separation methods followed by micronisation at the relevant sites were provided. No differences were observed.

2.4.3.1. Stability of the product

Stability data from six pilot scale batches of finished product (three batches per strength) stored for up to 24 months under long term conditions (25ºC / 60% RH and 30ºC / 75% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The batches of Kerendia are identical to those proposed for marketing and were packed in the primary packagings proposed for marketing (i.e. both blister and bottles).

The stability study samples were tested for appearance, assay, degradation products, dissolution and microbial purity. The analytical procedures used are stability indicating.

All results were within the specification limits and no trends were seen. The tablets are very stable. There are no differences between the results for tablets stored in blister or bottle.

Additional stability data on 10 mg and 20 mg tablet batches which were manufactured using active substance with each of the applied enantiomer separation methods followed by micronisation at the relevant sites were provided. All were stable under normal and accelerated conditions.

Bulk stability studies were conducted in long-term conditions of 25°C/60 % RH and 30°C/75 % RH for two finished product batches of each strength covering a storage period of up to 12 months. The tablets were packed in PE bags in a tightly closed tin cans. The specified degradation product rac-amido-naphthyridine showed a slight increase during storage but the results are well-within the specification limit. All other tested parameters are stable under the tested conditions and show no discernible trend during storage. The bulk stability data confirmed that the tablets are stable for 12 months when stored in PE bags in tightly closed tin cans.

The tablets complied with the specification also after stress storage at 80°C for 3 months, open air storage at 45°C for 3 months after light exposure.

Photostability studies were performed on three commercial scale batches from each tablet strength in accordance with the requirements of the ICH guideline Q1B, "Photo stability Testing of New Drug Substances and Products". Samples were tested for appearance, assay, degradation products and dissolution. The analytical procedures used are stability indicating. All results of the directly exposed samples met the acceptance criteria and no differences to the unexposed samples were observed. Based on the data obtained, the tablets are stable upon exposure to light. No light protection is required.

Based on available stability data, the proposed shelf-life of 3 years and with no special precautions for storage as stated in the SmPC (section 6.3 and 6.4) are acceptable. The tablets are very stable and no in-use shelf-life is necessary for opened bottles. The proposed bulk storage for 12 months is also acceptable.

2.4.3.1. Adventitious agents

Magnesium stearate is of vegetable origin.

It is confirmed that the lactose monohydrate is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. Two Major Objections (MO) were raised during the evaluation relating to absence of critical steps in the active substance manufacturing process and nitrosamines risk assessment in the finished product. In response, critical steps in the active substance manufacturing process were identified based on their impact on critical quality attributes (CQAs) and the applicant presented a risk evaluation concerning the presence of nitrosamine impurities in the finished product considering all suspected and actual root causes in line with EMA guidelines. Both MOs were considered to be resolved.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. The applicant has applied QbD principles in the development of the

active substance and the finished product and their manufacturing process. The two design spaces claimed in the active substance synthesis are accepted.

At the time of the CHMP opinion, there was minor unresolved quality issue having no impact on the Benefit/Risk ratio of the product, which pertain to the confirmation of the holding times for the manufacture of the tablets on commercial batches. This point is put forward and agreed as recommendation for future quality development.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.4.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

The applicant is recommended to provide the confirmatory data from the on-going holding times study on commercial scale 10 and 20 mg tablets to support the proposed holding times of intermediate products.

2.5. Non-clinical aspects

2.5.1. Introduction

The mineralocorticoid receptor (MR) is expressed in many tissues including the kidneys, heart and blood vessels. The receptor is activated by mineralocorticoids such as aldosterone as well as glucocorticosteroids like cortisol. Chronic overactivation of the MR, has been demonstrated in chronic pathophysiological states, where it contributes to organ damage and dysfunction in heart failure, myocardial infarction, chronic kidney disease and hypertension. Finerenone is a nonsteroidal antagonist of the MR and it can thereby attenuate the inflammation and fibrosis mediated by the overactivation of the MR.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

Primary pharmacodynamics in vitro

The pharmacological *in vitro* characterisation of finerenone was conducted in a series of experiments. A cell-based transactivation assay using the ligand binding domains of human mineralocorticoid, androgen, progesterone and oestrogen receptors were used to compare finerenone with the other MR antagonists spironolactone and eplerenone. Finerenone had an IC50 of 17 nM in the MR, but no activity up to 10 µM in the other steroid hormone receptors. Spironolactone had similar activity on the MR (IC50 of 28 nM), and also activity in the other receptors (IC50 GR-2430 nM, AR-160 nM, PR-1500 nM, ERα – 5970 nM, ERβ – 4940 nM).

Similar results were obtained when using ligand binding domains of rat and dog MR in the cell-based transactivation assay. No information was presented on the binding of finerenone to the MR in mouse or rabbit. No data or discussion on the binding capacity of finerenone towards other steroid hormone receptors in the common experimental animals was presented.

Experiments with the full-length MR and radioactive binding assays confirmed finerenone to be a potent antagonist.

No agonistic activity of BAY 94-8862 at any of the tested human steroid hormone receptors (up to 10 µM) was observed.

In an experiment with MR and the agonists aldosterone, cortisol, corticosterone and DOCA, the blocking with BAY 94-8862 was more potent than spironolactone and eplerenone, as demonstrated with lower IC50 values.

The cell-based transactivation assay using the ligand binding domains of human mineralocorticoid receptor was also used to characterize 6 atropisomers of the human plasma metabolites of finerenone (M-1a, M-1b, M-2a, M-2b, M-3a, and M-3b). No activity up to 9 µM of the atropisomers was detected.

The *in vitro* characterisation of finerenone was further characterised and the x-ray structure of the wild typ MR presented. The gain-of-function S810L MR mutant is said to be the cause for early-onset hypertension in men and gestational hypertension in women. In a functional cell-based *in vitro* experiment finerenone was capable of inhibiting aldosterone induced activity.

Primary pharmacodynamics in vivo

Finerenone has been evaluated in several *in vivo* models covering different aspects of cardiorenal disease. The presented studies were conducted by the applicant, but several studies were submitted as scientific publications. The models included genetical, surgical and chemically induced disease in mice, rats and dogs.

Finerenone induced natriuresis in conscious rats at 0.3 mg/kg after a single dose administration. The urinary Na+/K+ ratio was also increased after a single dose in conscious dogs. The dogs had been pretreated with a metabolically stable aldosterone analogue. The increase in Na+/K+ ratio was observed at doses from 10 µg/kg.

The protective effects of finerenone were investigated in the DOCA-salt model in rat. Desoxycorticosterone acetate (DOCA) is a potent MR agonist and when uninephrectomised rats on 1% NaCl drinking water are administered DOCA once weekly for 10 weeks, they end up with heart failure and severe end organ damages. In the study, urine was collected and blood pressure measured weekly. At the end of the experiment, haemodynamics and histopathology was evaluated. Finerenone was administered at 0.1, 1 and 10 mg/kg once daily. Finerenone showed pronounced end-organ protection of heart and kidneys by a dose-dependent decrease in blood pressure, plasma prohormone of brain natriuretic peptide (proBNP), proteinuria, cardiac and renal hypertrophy. The renal expression of several pro-inflammatory and pro-fibrotic biomarker genes was also reduced. The histopathological analysis of heart and kidney lesions, showed antifibrotic activity of finerenone.

The effect of finerenone in a model of myocardial infarction was investigated in rat. Finerenone treatment started one week after surgery were the left anterior descending coronary artery was permanently ligated. Several of the haemodynamic parameters were improved by finerenone, however not statistically significant.

The effect of finerenone 10 mg/kg once daily for 45 days was investigated in the stroke prone spontaneous hypertensive model in rat. The model is a high renin model of hypertension-induced end-organ damages. Morbidity and mortality are increased due to renal, myocardial and cerebrovascular

lesions. Before start of treatment the animals were pretreated with high salt diet for 7 weeks. Finerenone showed protection from morbidity and mortality. Administration of finerenone also reduced protein excretion and pro-fibrotic markers (OPN, TIMP1, and PAI-1) in serum and urine. The semiquantitative histopathological analysis of the heart (vasculopathies, focal myocardial degeneration and fibrosis) and kidney lesions (tubular degeneration and atrophy of adipose tissue in kidneys), revealed significant improvement with finerenone.

The protective effects of finerenone was also evaluated in a cardiac hypertrophy model and a cardiac fibrosis model in mice. Cardiac hypertrophy is induced by a surgical intervention in which transverse aortic constriction is induced causing a left ventricular pressure overload. Treatment with finerenone in this model significantly lowered the left ventricular mass compared with vehicle treated animals. In the cardiac fibrosis model, fibrosis is induced by a isoproterenol injection. Pretreatment with finerenone blocked the induced cardiac fibrosis and macrophage invasion.

In a rat model of type-2 diabetes mellitus, administration of finerenone reduced left ventricular end-diastolic pressure. A decrease in proteinuria and renal neutrophil gelatinase associated to lipocalin (NGAL) expression was also observed.

The effects of pretreatment with finerenone in an ischemia/reperfusion induced kidney injury model in mice and rats were investigated. In mice, the analysis was done 4 weeks after the I/R. Increases by I/R in plasma creatinine, plasma urea and TGF-beta expression were prevented by finerenone.

In the I/R study in rats, effects were analysed both acutely (24 h after I/R, AKI) and as chronic kidney disease (4 months, CKD). Finerenone 10 mg/kg was administered before the ischemia. In the AKI setting, pretreatment with finerenone blunted increases of plasma creatinine and urea. In the finerenone treated animals the presence of tubular lesions and infiltrates of macrophages were reduced in comparison with vehicle treated AKI animals. In the animals 4 months after the I/R induction, renal dysfunction and modified renal haemodynamics were observed. These effects were not observed in the animals pretreated with finerenone.

A study was conducted in a genetic CKD model in rat. The rats develops spontaneously albuminuria and exhibits endothelial dysfunction associated to low NO availability. In this study, animals were administered finerenone 10 mg/kg for 4 weeks. The treatment lowered albuminuria and reduced systolic blood pressure.

Overall, administration of finerenone in the different studies resulted in MR-antagonising effects with a beneficial/ protective effect on heart and kidneys in rodents.

2.5.2.2. Secondary pharmacodynamic studies

Finerenone and its major human plasma metabolites were assessed for its off-target activity in screening assays (65-67 receptors, transporters and ion channels). These radioligand binding assays included mostly human off-targets from various (neuro)transmitter systems e.g. adenosine (A1, A2A, A3), adrenergic (α1a, α1b, α1d, α2a, β1, β2, NET), cannabinoid (CB1), dopamine (D1, D2s, D3, D4.4, DAT), GABA (A, B1A, GABA-T), glutamate (kainate, NMDA, glycine), histamine (H1, H2, H3), muscarinergic (M1, M2, M3), opioid (δ1, κ, μ), serotoninergic (5-HT1a, 5-HT2b, 5-HT3, SERT). There were no interactions at 10 μM in any of these assays.

Finerenone and the selectivity on the mineralocorticoid receptor vs other steroid hormone receptors was also investigated. The results are presented primarily in the primary pharmacodynamic section.

Finerenone and the major metabolites were also investigated in *in vitro* patch clamp studies assessing different human cardiac ion channels. These experiments did not show interference with cardiac ion

channels *in vitro* including the hERG K^+ current, the hNav1.5 Na^+ current, and the hCav1.2 Ca^{2+} current.

2.5.2.3. Safety pharmacology programme

Safety pharmacology studies addressed the impact of finerenone on vital organ functions (CNS, cardiovascular system including ECG, respiratory system).

Cardiovascular

Voltage clamp studies were conducted in human embryonic kidney (HEK) cells transfected with hERG. The hERG IC50 was 86 µmol/L (33 mg/L), which is approximately 200 times the total clinical Cmax (161 µg/L), and 2400 times the free fraction (Cmax, unbound 13.4 µg/L; fu 8.3%). The human metabolites M-1a, M-2a or M-3a did not inhibit the hERG potassium channel current at the tested concentrations.

ECG was analysed in conscious dogs after a single oral dose. No effects of finerenone was observed on QRS complex duration and on QT/QTc intervals. PQ intervals were shortened by 5-10 %. The effect continued for several hours. The clinical relevance is not known. The maximum dose tested in the study (10 mg/kg) corresponds to a Cmax of 13.9 mg/L, which is approximately 86 times the clinical Cmax (161 µg/L). The Cmax unbound at 10 mg/kg was 764.5 µg/L, which corresponds to 57 times the free fraction (Cmax, unbound 13.4 µg/L; fu 8.3%).

According to the SmPC, a dedicated QT study in 57 healthy participants has been conducted. There was no indication of a QT/QTc prolonging effect of finerenone after single doses of 20 mg (therapeutic) or 80 mg (supratherapeutic).

Respiratory

An *in vivo* study in rats were conducted to investigate the effect of finerenone on respiratory function. No effects were observed on respiration rate, tidal volume or minute volume.

Systemic exposure was not measured in Sprague Dawley rats after a single dose. However, the same maximum dose (30 mg/kg), resulted in a total Cmax of 94.5 mg/L in Wistar rats, which is 587 times the Cmax observed in patients (161 µg/L). If comparing the unbound Cmax values, the rat Cmax unbound was 44.4 µg/L, to be compared with the human Cmax, unbound of 13.4 µg/L, which renders an exposure margin of 3. Thus, based on the total exposure it is reasonable to conclude that the exposure margin in the SD rat is sufficiently high to conclude that no effects on respiratory function can be expected in humans. When comparing the unbound fractions the exposure margin is significantly lower. There are however no indications from the clinical trials of any adverse effects on respiratory function.

CNS

No behavioural or physiological changes were observed after a single dose of finerenone in male rats. No interference with phentylenetetrazole induced convulsions as a model of pro- or anticonvulsive activity was observed after administration of finerenone. Furthermore, no impairment of motorcoordination was observed in a RotaRod experiment.

Systemic exposure was measured in satellite animals. The highest dose tested in the modified Irwin study (30 mg/kg), resulted in a Cmax of 94.5 mg/L, which is 587 times the Cmax observed in patients (161 µg/L). If comparing the unbound Cmax values, the rat Cmax unbound was 44.4 µg/L, to be compared with the human Cmax, unbound of 13.4 µg/L, which renders an exposure margin of 3.

Thus, based on the total exposure it is reasonable to conclude that the exposure margin in the SD rat is sufficiently high to conclude that no behavioural or physiological changes can be expected in humans. When comparing the unbound fractions the exposure margin is significantly lower. There are however no indications from the clinical trials of any adverse effects on CNS.

2.5.2.4. Pharmacodynamic drug interactions

No non-clinical pharmacodynamic drug interaction studies were performed which is considered acceptable.

2.5.3. Pharmacokinetics

Pharmacokinetics of finerenone was investigated *in vivo* after single administration in CD 1 mouse, Wistar rat, Beagle dog and Cynomolgus monkey. In addition, *in vitro* studies were performed to investigate permeability in Caco-2 cells, plasma protein binding, blood cell/plasma partitioning and drug metabolism in several species (mouse, rat, rabbit, dog, monkey, and human). Drug-drug interaction potential in terms of various metabolizing enzymes and transporters were also analysed and is evaluated as part of the clinical assessment. Pharmacokinetics after repeated administration were performed as part of the toxicology studies.

Finerenone contains one asymmetric carbon atom, and the drug is the pure S-enantiomer. The potential for racemisation/conversion of the S-enantiomer to its pharmacologically inactive R-enantiomer under *in vivo* conditions has been performed in humans, no racemisation in human plasma was seen. In addition, the predominant human plasma metabolites of finerenone M-1, M-2, and M-3 exhibit axial chirality forming the atropisomers M-1a, M-1b, M-2a, M-2b, M-3a, and M-3b, respectively and analysis of the atropisomer ratios of M-1, M-2, and M-3 in human plasma and plasma from rats and dogs (used in the toxicological studies) have been performed. No conversion of the atropisomers was seen *in vitro*.

Analytical methods
Different achiral LC MS/MS assays were developed and validated for the determination of finerenone and its predominant metabolites in plasma of mouse, rat, rabbit, dog, monkey and human. When [^{14}C]-finerenone or radiolabeled metabolised were used, radioactivity concentration in body fluids, organs and tissues, and in excreta was determined by liquid scintillation counting (LSC). For quantitative whole-body autoradiography (QWBA) studies a phosphor imaging method (radioluminography) was used to determine radioactivity concentrations in tissues. The methods used are considered adequate.

Absorption
In vitro permeability of finerenone was investigated using Caco-2 cell monolayers and finerenone was shown to be highly permeable. Efflux with ratios of 2.3 (2 µM) to 0.9 (210 µM) was observed indicating active transport of finerenone (see "Pharmacokinetic drug interactions" evaluated in the Clinical PK AR).

Absorption of total radioactivity from the gastrointestinal tract was high or complete in rats and bioavailability of finerenone was high (83 to 120%). In dogs, bioavailability of finerenone was between 57% and 100%. However, the higher bioavailability was determined in dogs after oral administration of 3 mg/kg finerenone which exceeded the linear range of pharmacokinetics. In dogs, the pharmacokinetics were dose-proportional up to 0.3 mg/kg after po administration of finerenone and in the dose range from 0.3 to 3 mg/kg AUC and C_{max} increased more than dose-proportionally. In male

rats the pharmacokinetics of finerenone were almost linear within the investigated dose range after iv (0.3 and 1 mg/kg) and po (0.3 to 3 mg/kg) administration. Bioavailability in humans was ~44%.

Plasma clearance was very low in mice (0.0062 L/(kg·h)) and rats (0.011-0.014 L/(kg·h)), and low in dogs (0.16 L/(kg·h)) and monkeys (0.39 L/(kg·h)). Volume of distribution was low in mice (0.10 L/kg) and rats (0.11-0.14 L/kg), and moderate in dogs (0.39 L/kg) and monkeys (0.25 L/kg). In humans Vss of finerenone was approximately 0.65 to 0.87 L/kg (~similar to total body water), indicating low tissue binding.

The terminal elimination half-life of finerenone from plasma was long in mice with 12 h (interval up to 72 h) after iv administration. In rats, long half-lives with 8.1 to 8.6 h (iv) and 7.8 to 9.1 h (po) were calculated in the interval up to 72 h. In contrast, the corresponding terminal half-lives were short with approximately 1.7 h (iv) and 1.5 to 2.4 h (po) in dogs (interval up to 32 h) and 1.3 h (iv) in monkeys (interval up to 10 h).

A higher exposure of up to 8-9-fold was determined in female rats compared to male rats within the repeated dose studies (possibly due to generally lower activity of the cytochrome P450 system of the female rat liver).

Plasma protein binding and blood cell/plasma partitioning
Plasma protein binding of finerenone was high in rodents (rat fu 0.05% and mouse fu 0.1%) and rabbit (fu 0.2%), whereas moderate protein binding was determined in most non-rodent species (monkey fu ~3%, dog fu 6% and human fu 8%). The major binding protein fraction of finerenone in human plasma was shown to be albumin with lower binding to α1-acidic glycoprotein, LDL and γ-globulins. Saturation of plasma protein binding was seen at high and not clinically relevant concentrations. The large species difference in the free fraction in plasma, with higher levels in humans, suggests that fu should be considered when exposure margins are calculated.

Plasma protein binding and blood to plasma concentration ratio were also determined *in vitro* for the major human metabolites M-1a, M-1b, M-2a, and M-3a. Species differences were less pronounced compared to finerenone. For human, rat, dog, rabbit and mouse unbound fractions of metabolites M-1a/M-1b were 5.8/3.9, 6.0/11, 11/6.4, 2.1/1.3 and 15/12%, respectively. For the metabolite M-2a the unbound fractions ranged between ~38 to 58% in rabbit, rat, dog and mouse while a somewhat lower unbound fraction was seen in human plasma (17%). The unbound fractions of M-3a were between ~68 and 82% across all tested species.

Finerenone was mainly distributed to plasma in whole blood with blood-to-plasma ratios of 0.55 and 0.72 for rat and dog, respectively and a ratio of 0.94 seen in human whole blood at clinically relevant concentrations. Metabolites M-1a, M-2a and M-3a were also mainly distributed to plasma in whole blood of rat, dog and human

Organ and tissue distribution
Organ and tissue distribution were studied by quantitative whole-body autoradiography after administration of a single dose of [14C]-finerenone to male and female albino rats (Wistar) and male pigmented rats (Long Evans), as well as pregnant albino rats (Wistar, Day 18 of gestation).

Maximum concentrations (Ceq,max) of radioactivity were reached in most organs and tissues at 1 h post-dosing (tmax). Highest concentrations were found in blood followed by lung, liver, kidney papilla and adrenal medulla. High radioactivity concentration was also present in the interstitial spaces throughout the whole animal body. Highest exposure in terms of AUC was determined in the bile duct and gastrointestinal tract contents indicating biliary/faecal excretion of [14C]-finerenone radioactivity. The AUC(0-24) was high in blood as well as in well perfused organs and tissues, such as liver, lungs, kidney papilla and adrenal medulla. The AUC and the radioactivity concentrations in brain were less than 2% of those in blood. Which might rather reflect the radioactivity in residual blood, than

penetration across the blood/brain barrier. Similar distribution patterns were seen after oral and iv administration and between male and female rats. Female rats had a ~2-fold higher concentration in organs and tissues at 2 h and residual concentrations after 24 h between 9-fold (liver) and 27-fold (adrenal medulla) higher than in males (blood 17-fold higher). This suggests a significantly slower elimination of radioactivity in female rats.

No irreversible binding or retention was indicated. At 7 days post-oral administration, residual radioactivity in the animal body (excluding gastrointestinal tract) amounted to less than 0.1% of the administered dose. Similar results were obtained in pigmented Long Evans rats and there was no indication of any specific affinity of substance-associated radioactivity to melanin bearing tissues such as eye wall or skin.

Organ and tissue distribution in pregnant rats
The maximum radioactivity concentrations were reached at 4 h post-dose in most maternal organs, tissues and blood. Later maximum concentrations were observed, i.e., after 8 h in skin and submandibulary glands and after 24 h in kidney cortex. In all foetal organs and tissues, increasing concentrations were observed between 8 and 48 hours. 49% of the dose was still available systemically at 48h (last time point analyzed). Even though the maximum concentration in maternal blood was seen at 4h, the level at 48h was still 4.5 times higher compared to the level seen in foetal blood.

Based on maximum concentrations, the highest systemic exposure occurred in maternal blood and placenta. All investigated maternal and foetal organs showed lower maximum levels than maternal blood. The average foetal concentration was about 14-fold lower than the maternal blood concentration. The highest exposure was detected for foetal blood, skeletal muscles and skin. The AUC(0-tn) ratios for the average foetus exposure/maternal blood and foetal blood/maternal blood were 0.088 and 0.13, respectively. The estimated terminal elimination half-lives were between 25h (ovaries, maternal skin) and 59h (maternal skeletal muscles). Due to terminally increasing concentrations in foetal organs and tissues calculation of elimination half-lives was not applicable. After 24h and 48h, 49 to 48.6% of the dose was still systemically available, mainly located in maternal blood and 1.6 and 2.1% of the dose was located in foetuses.

Metabolism
Two major biotransformation pathways were identified: (a) oxidation of the dihydronaphthyridine to the naphthyridine derivative M-1 followed by hydroxylation leading to the hydroxymethyl naphthyridine metabolite M-2 with subsequent oxidation leading to the carboxylic acid M-3; (b) a presumably intermediate epoxidation with subsequent hydrolysis leading to the dihydrodiol M-4 and further hydroxylation giving M-5. Hydroxylated metabolite M-7 was also formed in most species. No significant species differences were observed. The same biotransformation pathways were found in both liver microsomes and hepatocytes from rat, dog, monkey, and human, with the predominant naphthyridine oxidation pathway (M-1/M-2/M-3) favoured over the dihydrodiol pathway (M-4/M-5) in all species investigated.

Following oral administration of [14C]-finerenone, parent compound was by far the major component in mouse and rat plasma (>96% of total radioactivity AUC) with 3 minor metabolites (M-1, M-4, and M-7) present in plasma of these species. In dog and human, finerenone accounted for 28% and 7.1%, respectively, of total radioactivity AUC. In human plasma, the naphthyridine metabolites M-1, M-2, and M-3 were the predominant metabolites covering 49%, 22%, and 9.0% of total radioactivity AUC. The dihydrodiol metabolites M-4 and M-5 were present in plasma only to minor amounts (<3% of total radioactivity AUC). Similar total levels of excreted dihydrodiol derivatives were seen across species (sum of M-4, M-5, M-8: rat, 17%; dog, 17%; human, 22% of the administered dose). Considering the similar excretion levels and low human plasma levels, the possible formation of an epoxide

intermediate during the formation of M-4 and M-5 is not considered to be of any concern. No additional studies are thought to be needed.

Finerenone is administered as a pure S-enantiomer and only this isomer was found in human plasma, i.e. there was no racemisation. Detailed investigations revealed that the predominant human plasma metabolites M-1, M-2, and M-3 exhibited axial chirality forming the atropisomers M-1a, M-1b, M-2a, M-2b, M-3a and M-3b, respectively and the predominant appearance of one atropisomer (a-series, >80%) of each metabolite across all species. Based on human mass balance study and data from renally impaired patients, metabolites M-1a, M-1b, M-2a, and M-3a (M-3a identified in renally impaired patients) were concluded to be major human plasma metabolites (accounting for >10% of AUC of total drug related components). This is agreed.

Excretion
Finerenone was mainly excreted via the biliary/fecal route in rats (20% in urine and 75.7% in feces). While similar levels of excretion into urine and feces were seen in dogs (53%/42%) and mainly urinary exretion was seen in humans (80%/21%).

Finerenone derived radioactivity were excreted into milk of lactating rats and ~20% of the dose was found in milk within the observation period up to 48 h after administration.

Nonclinical pharmacokinetics is considered sufficiently characterised and show that the toxicological species used are acceptable and relevant to use.

2.5.4. Toxicology

The applicant has developed finerenone, selective non-steroidal mineralocorticoid receptor (MR) antagonist indicated for the treatment of chronic kidney disease (CKD) in adults. The maximum recommended human dose (MRHD) for treatment of kidney disease is 20 mg once daily by the oral route. A full programme of toxicity studies has been performed to evaluate the toxicity profile of the substance. The programme was comprised of general toxicology studies and studies of genotoxicity, carcinogenicity, reproductive toxicity and phototoxicity. The study programme also included three studies in juvenile animals (one single-dose TK study, one systemic toxicity study and one juvenile toxicity study focused on female fertility). While these studies have been included and assessed in this assessment report, they are outside the scope of the present application.

The oral route (oral gavage) has been used throughout the study programme, as this route is the intended clinical route. According to the applicant, the carcinogenicity studies were originally planned with administration in the diet. Therefore, studies in rats and mice using this route of administration have been included in the Application. As it became clear during course of the 13-week studies in mice and rats that the toxicokinetic profile did not match the human kinetic profile, the studies were discontinued and the diet exposure plans were not pursued further. Therefore, the studies using oral exposure via diet have not been included in this assessment report. Even so, general toxicity studies using oral gavage exposure are available for mouse, rat and dog, where rat and dog are considered main general toxicology species and have been used for studies of up to 26- and 39-weeks duration respectively. Both species are considered pharmacologically relevant based on appropriate binding data and formation of metabolites. However, as pointed out in the pharmacology section, no binding-data is available for the rabbit (used in the EFD-study) why the pharmacological relevance of the rabbit is currently unclear.

The vehicle varied across the study programme, with different vehicles used in mouse-, rat- and dog studies. While the reason for this has not been discussed in the overview documents, the vehicles used have overall been well-tolerated (except perhaps in the FEED study where extensive salivation was

noted). Finerenone is metabolised to give metabolites M-1, M-2 and M-3. These metabolites exhibited axial chirality forming the atropisomers M-1a, M-1b, M-2a, M-2b, M-3a and M-3b of which the a-atropisomers seems dominant across all species. 4 major human metabolites were identified, M-1a, M-1b, M-2a and M-3a. They were all sufficiently covered in the rat, why further metabolite-studies have not been performed.

The toxicity profile of finerenone is mostly reflective of the aldosterone inhibitory pharmacological action of the substance, with effects mainly on the on water and electrolyte balance and adaptive findings in adrenals. However, adverse toxicities have been identified in the programme, and issues have been identified below which should be further discussed by the applicant.

2.5.4.1. Single dose toxicity

A single-dose toxicity study in mouse and rat was performed with finerenone in which LD_{50}-cut-offs and MNLDs were generated. It is strongly stressed that these study endpoints have no regulatory value and such studies should not be performed for animal welfare reasons. Further, relevant single-dose data can be generated within repeated-dose toxicity studies. Based on the data provided, the rat seems more sensitive than the mouse as the oral MNLDs differ by a factor of 40.

2.5.4.2. Repeat dose toxicity

Repeat-dose toxicity studies have been performed in rat and dog using oral (gavage) administration. In the rat studies, the Wistar HsdCpb:WU strain was used. However, for the 26-week study the strain was changed to HsdRCCHan:Wist. While the underlying reason for this change is unclear, the change is not considered to be of importance for the study evaluations. Doses between 0.5 and 30mg/kg/day were used in the rat. As exposures were higher in female rats than in males, female rats were treated at lower dose levels than males in the 26-week study to get similar exposure across sexes. Recovery animals were only included in the 4-week study. In the dog, doses up to 15mg/kg/day were used, and recovery animals were only included in the 4-week study. Finally, to support dose-selection in the carcinogenicity study, studies of up to 13-weeks were also performed in mice (in accordance with ICH S1C).

Mortality

No mortalities were noted in the mouse or dog studies. In the rat, three females died in the 4-week study none of which was considered treatment related. Two died from gavage error, and one from sampling procedures. In the 13-week study, no data on mortalities had been disclosed except for a comment that no effects were noted on survival. However, according to the study data animals died during the study. Therefore, the applicant was asked to provide with data on animals found dead and euthanised during the study, including clinical signs and necropsy findings supporting reasons for their deaths. In the response, the applicant explained that no deaths occurred, and that aspects of the documentation system may have caused a misunderstanding. The provided explanation was reasonable, and the issue was thus considered resolved. In the 26-week study, one female at 15mg/kg/day) was sacrificed on SD 96. The animal showed poor general condition, bloody nose, paleness and piloerection prior to death. No cause of death could be established at histopathological examinations. In the absence of similar clinical signs in surviving animals, it was concluded that the treatment did not affect the survival of the animals. This is agreed.

Clinical signs and body weights

Clinical signs which appeared repeatedly in the studies include soft/mushy faeces, paleness and piloerection. The signs were noted already from 5 mg/kg/day in the rat, whereas higher exposures (30mg/kg/day) decreased motility, sunken flanks and skinny appearance were noted. The clinical signs are overall considered signs of general toxicity.

Reduced body weights were noted across all species used in the general toxicity studies. However, in the mouse, body weights were fluctuating in the 13-week study without clear dose-response. It should be noted that the dosing in the mouse study was aiming at supporting a carcinogenicity study based on a clinical exposure of 10mg, why the doses used in the study were generally lower. In the rat, reduced bodyweights were noted from 5mg/kg/day in females and 10mg/kg/day in males. In the 13-week-study, females body weight gains were severely reduced at 30mg/kg/day reaching an MTD. Correlation with food-consumption was seen in some studies. In the dog, effects on bodyweight were noted from 15mg/kg/day in the 4-week study with correlating effects on food consumption. No effects were noted on body weight in the chronic studies.

Water and electrolyte balance

In line with the pharmacological action of finerenone as an aldosterone antagonist, effects on water and electrolytes were seen across the studies in rat. Overall, increased urination and water intake was seen, with increases in K/Na ratio. In the dog, small or no effects were reported. In the 13-week study, only minimal electrolyte changes were noted at 10mg/kg/day. It is to this end surprising that so mild effects on pharmacology-related parameters are noted considering the relatively high exposure margins achieved.

Liver

Liver effects (mild) were seen in the mouse 4-week study and rat 4- and 13-week studies. They were mostly periportally or diffusely condensed hepatocytes (minimal-moderate) with reduced fat deposits and correlated with increased liver weights in the 13-week rat study. In the mouse, cobble-stone shaped cells without cell-cell adhesion was noted, but at very high exposure (150mg/kg/day) , The findings recovered in the rat 4-week study which was the only rat study with recovery animals. Importantly, no liver findings were seen in the 26-week rat study, in dog or in the cancer studies suggesting adaptive findings in the rat and related to high exposure in the mouse 4-week study.

Adrenals

As a consequence of the mineralocorticoid receptor blockade MoA of finerenone, a compensatory hypertrophy of the zona glomerulosa (the site of aldosterone synthesis in the adrenal cortex) was prominently seen in all species (graded minimal-extensive) from the lowest doses. In the 4-week study in rats, vacuoles in the zona fasciculata are reported only in the recovery animals. It was unclear what these vacuoles are composed of, and the applicant is asked to clarify the intracellular accumulation and deposition that resulted in the vacuoles and reflect on the clinical relevance of the vacuoles. In the response, the applicant described that fat droplets in stained FFPE sections of adrenocortical cells appear as round and empty vacuoles of variable size without any signs of degeneration like intravacuolar eosinophilic material. Therefore, based on the described morphology of the discussed findings in the report, the vacuoles are by the applicant considered composed of lipids. Further, the applicant suggests that a possible mechanism for the increase of vacuoles in the zona fasciculata could be extensive activation of the zona glomerulosa resulting in an increased production of corticosterone and aldosterone. Collectively, the explanations and suggestions seem reasonable. Regarding clinical relevance, it is agreed that the effects were mainly noted at concentrations considered in excess of human clinical exposure.

In the 4-week study in dog, eosinophilic cytoplasmic change of the zona glomerulosa was noted. The finding did not fully recover in the 4-week study (the only dog study with recovery animals). Overall, in

the absence of degenerative or inflammatory findings in the adrenals, the adrenals findings are not considered to be of concern, and are known compensatory effects of aldosterone inhibition.

Urinary tract and kidneys

In the rat 4- and 13-week studies, hyperplasia of the transitional epithelium of the urinary bladder were noted, occasionally with inflammatory infiltrates. The finding did not recover in the 4-week study. In both studies, necrotic findings were evident in the kidney with increased mineralisation at the corticomedullary border with tubulopathy of the proximal tubule P3 segment associated with basophilic tubules. This correlated with increased kidney weights, increased urea levels and an increased urinary excretion of µ-GST (with increased excreted µ-GST/Crea levels). According to the applicant, the focal mineralisation in the kidney may be associated with the increase in serum calcium levels and urinary pH, which is supported by the lack of such effects (and mineralisation) in the chronic studies in rat. While this may be agreed, it does not explain the tubulopathy of the P3 segments. Still, as no findings were noted in the chronic studies (or in the dog studies) the long-term relevance of the finding is unclear. The bladder effects were also not seen in the chronic studies or in dogs, perhaps suggestive of adaption with time in rat. Regardless, the kidney findings are related to the MoA and are not considered unexpected.

Reproductive organs

In the rat 4-week study, reversible changes were evident in the female genital tract at 30mg/kg/day which were composed of foamy corpus luteum cells in the ovary, atrophy of myo-/endometrium and cervical epithelium in the uterus. Further, atrophy with mucification of the vagina was evident. Similar findings were also seen int the 13-week study but here there were also findings of diffuse atrophy of the mammary glands. According to the applicant, these changes are considered secondary pharmacological effects, possibly due to a cross-reactivity with other steroid receptors at the higher doses. Further, as MRs are expressed in the ovary and other female gonadal tissues, it is possible that high levels of finerenone might interfere with ovarian regulation. While it is possible, no hormone levels have been made available, and it is rather speculative. In any case, no similar findings are reported from the 26-week study, which is somewhat surprising given that the ovary findings in the 13-week study were evident already at 10 mg/kg/day.

In the mouse 13-week study, increased testes weights were recorded from 3mg/kg/day which correlated with increased germinal epithelium debris (incidence 1/2/2/6 and graded minimal) at 10mg/kg/day. No similar findings were recorded in rat or dog, or in the carcinogenicity studies in rat and mice why the finding is of unclear relevance. However, In male dogs, chronic administration (up to 39-weeks) of finerenone resulted in reduced prostate size and weight starting at 1.5 mg/kg/day which correlated with reduced size of prostate at necropsy in one male at 1.5mg/kg/day and 2 males at 5mg/kg/day. The prostate had not been a target organ of toxicity in the 4- and 13-week studies, suggesting that longer-term exposures are required for the development. While no supporting histopathology findings were noted this is still considered treatment related and possibly clinically relevant as the MoE is only 10. Accordingly, as an OC the applicant was asked to include these data in section 5.3 of the SmPC. According to the applicant, the overall effect of finerenone on prostate weight was mild and only the animals with reduced prostate size had weights below the lowest control animal. While it is agreed that the lowest control weight was low, another way of putting it is that the lowest control prostate weight was lower than only one prostate weight at ≥1.5 mg/kg/day. While it is agreed that prostate weight was not statistically significantly different in the treated group, a sample size of n=4 gives low power to detect small (but possibly biologically relevant) differences. It is agreed that the lack of effect noted in the 4- and 13-week dog studies may be related to the sexual immaturity of the dogs in those studies. If sexually mature dogs had been used, lower prostate weights may have been obvious earlier than 39-weeks, further supporting the influence of finerenone on prostate size

and weight. While the comparison with eplenerone is interesting (for eplerenone, a mild hormonal imbalance was identified as the most likely cause for the changes, why it is possible that a similar explanation holds true also for finerenone), the effects on prostate weight and size was more severe after eplenerone exposure, possibly related to the slight anti-androgenic effect of the substance. While no anti-androgenic effects have been reported for finerenone, the finerenone induced effects on prostate weight/size may be related to hormonal imbalance via the MR. Thus, given the relatively low MoE (LOAEL=10, NOAEL=2) and no reason to assume lower human susceptibility, the applicant was asked to include the findings in SmPC section 5.3 along with relevant margins of exposure to clinical exposure. In the response, the applicant agreed that the low margin of exposure for the prostate finding in the dog to human clinical exposure may suggest a clinical relevance. However, it was the applicant's view that the limited effect size (in terms of absolute prostate weight change), the lack of clear progression with increased dose and the identification of the prostate finding in only a subset of the animals suggests limited clinical relevance. While it was agreed that the effect size was not great, the lack of dose-response is not a valid argument in this case. The finding was only identified in the 39-week study, was considered adverse by the study pathologist and had limited margins to clinical exposure at NOAEL and LOAEL. Further, as no recovery group was used in the study, the potential for recovery is not known. As finerenone treatment is a chronic treatment it was also not clear if the effects would progress with longer treatment.

The applicant agreed to include the finding in section 5.3 of the SmPC and proposed an update of the repeated dose toxicity paragraph. This text was edited by the Assessor to reflect that the relevance of the finding is unclear. Further clinical development of the product may clarify to what extent the prostate is a target of toxicity also in human.

2.5.4.3. Genotoxicity

A full programme of genotoxicity studies has been performed by the applicant. The Ames test performed in the Salmonella strains TA98, TA100, TA102, TA1535, and TA1537 was negative up to 5000 µg finerenone per plate, suggesting no mutagenic activity of finerenone. Based on the data presented from the *in vitro* micronucleus test, finerenone is not considered to be a clastogen. An *in vivo* micronucleus assay in male where bone marrow smears were evaluated. Exposures up to 1000mg/kg/day did not find evidence of increased fractions of micronucleated polychromatic erythrocytes. However, from 250 mg/kg/day, signs of toxicity were evident with an altered fraction of NCE to PCE. Collectively, finerenone is not considered clastogenic. In summary, the genotoxicity studies presented do not indicate a genotoxic risk for finerenone.

2.5.4.4. Carcinogenicity

The carcinogenic potential of firenenone was evaluated in a programme which included two 104-week carcinogenicity studies. While the applicant was advised by the CHMP to consider using a short or medium-term *in vivo* rodent test system or alternative methods in combination with a 2-year carcinogenicity study, the programme as presented is in accordance with ICH S1B and is thus acceptable.

<u>Mouse 104-week carcinogenicity study</u>

Based on recommendations from FDA and a single-dose TK study in the mouse strain used for the carcinogenicity study, the high doses in the study were set at 30mg/kg/day for males and 7.5mg/kg/day for females. Mortality and survival rates were similar across dose-groups. Further, macroscopic and microscopic findings did not differ between early terminated animals and those

surviving the full 104 weeks. It was however noted that only 24/60, 26/60 and 26/60 females survived in the control, 2.5 and 7.5 mg/kg/day dose-groups. While this is considered low, it is acceptable.

Macroscopic examinations revealed enlargement and/or a pale area of the testes in several male mice from 3mg/kg/day. This correlated microscopically with increased incidence of Leydig cell adenoma in males administered 30 mg/kg/day when compared to both study control groups and the Covance historical control data in mice of this strain. The adenomas were present unilaterally in all animals, and (except in one case) only in animals surviving to terminal sacrifice suggesting a late occurrence. In combination with the lack of genotoxic effects of finerenone, this supports that the finding is likely an indirect effect perhaps related to hormonal perturbation. However, the applicant was asked to further support this issue. As MR are expressed in rat testes (selectively localised to Leydig cells) and aldosterone increases testosterone production in Leydig cells, the applicant suggests that blocking of the MR by finerenone may reduce testosterone production in Leydig cells. This blocking may then increase LH secretion (from the pituitary) to increase testosterone production. While this sequence of events is possible, available data do not support reduced hormone levels in the carcinogenicity studies. Therefore, the applicant suggests that the findings were only an enhancement of spontaneous age-related changes. While the findings in the control group may represent background findings, the clear increase in pale area and/or macroscopic enlargement of the testis in males administered 3, 10, or 30 mg/kg/day, and a statistically significant increased incidence of Leydig cell adenoma in the testis of males administered 30 mg/kg/day are considered finerenone-induced effects. However, given the known susceptibility of rodents to develop adenomas, differences in the number of LH and LH-related aging changes and the fact that the increase in adenoma findings were only noted with a MoE of 22x to human clinical exposure the clinical relevance is uncertain. Still, the findings should (and are) included in section 5.3 of the SmPC. Females given 2.5mg/kg/day finerenone had significantly increased incidences of combined haemolymphoreticular tumours, whereas females given 0.75mg/kg/day finerenone showed significantly increased combined uterine stromal tumours. According to the historical control database, these tumours are common and were not increased in the high-dose group. While lack of dose-response is not a sufficient argument on its own, the fact that the incidences were included in the historical control database supports that they are not likely toxicologically significant.

Rat 104-week carcinogenicity study

In the rat, the dose-levels used in the study were based on the 13-week and 26-week studies in male and female rats. As pointed out in the repeated-dose toxicity section, different strains were used in these studies. In the carcinogenicity study, the same strains as used in the 26-week study was used (RccHan:WIST), but the origin of the animals differed. Overall, based on the effects on body weight gain noted in, the doses used are considered sufficient.

Reduced ovary weights down to 0.3x control weight were not correlated with macro or microscopic effects. Given the large effect on ovary weight, this is odd. Reduced kidney weight correlated with electrolyte balance effects, and is together with the effects on water consumption likely an effect downstream of aldosterone inhibition. Further anti-aldosterone effects were seen in the adrenals and included slight to severe diffuse hypertrophy of zona glomerulosa, vacuolation of zona glomerulosa and increased incidence of cortico-medullary pigments at 20mg/kg/day.

The only neoplastic observation was fibroadenoma in the mammary gland. However, while there were increased incidences in the 1 and 10mg/kg/day dose-groups, the incidence was even higher in the saline control group compared to the vehicle control. Further, this is a very common tumour in the rat with low progression to malignancy. Collectively, the finding is not considered finerenone induced and clinically relevant. Therefore, the highest dose-levels tested in both sexes are considered to be without evidence of carcinogenicity.

2.5.4.5. Reproductive and developmental toxicity

A full programme of reproductive and developmental studies has been performed with finerenone, which also includes a 13-week juvenile toxicity study in rats to support paediatric development in patients from the age of 6 months. Further, a fertility study in juvenile female rats was performed over a period of 94 days. While the present application concerns adult patients, the juvenile toxicity studies have been evaluated in the assessment report.

FEED study in rats

In the fertility study, reductions in body weight gain was noted in both sexes and from the lowest dose tested. In males, dose-related reductions of up to 52% were noted in the premating period, which led to mean body weights 0.96-0.89x control weights. In females, weight gains were drastically reduced from 10mg/kg/day during premating, whereas similar weight changes were noted during gestation.

No differences were noted on time to insemination, and absolute testes weights were comparable across groups. Absolute and relative ovary weights were decreased from 10mg/kg/day. The number of corpora lutea and number of implantation sites were significantly lower at 30mg/kg/day suggesting effects on female fertility. Further, at the same dose, postimplantation loss was increased and the number of viable embryos was reduced suggesting effects on early embryonic development. According to the applicant, no systemic toxicity NOAEL was possible due to the body-weight effects noted at all dose-levels. This is agreed. Fertility NOAEL is set to 30mg/kg/day in males and 3mg/kg/day for female fertility and early embryonic development corresponding to MoE of 16x and 10x respectively.

Embryo-foetal development (EFD) studies

Rat

Based on maternal toxicity and malformations in a DRF-study in rats at 100mg/kg/day, 30mg/kg/day was chosen as the high-dose in the pivotal study. No deaths or early terminations were noted in the study, and clinical signs were mainly restricted to increased water consumption at 10mg/kg/day and increased urination at 30mg/kg/day. Body-weight development was clearly and significantly decreased in the dams from 10mg/kg/day. Between GD6 and GD17, body-weight increases were 0.75x and 0.46x control values at 10 and 30mg/kg/day respectively. Food consumption was decreased during the initial days of gestation.

Fertility rates, number of implantations, pre-implantation loss, post-implantation loss and foetal sex were overall similar between groups. However, placental weights and foetal weights were significantly reduced in dams administered 10 or 30 mg/kg/day which also correlated with significantly retarded skeletal ossifications at these dose-levels.

At 30mg/kg/day, one foetus displayed several malformations, including double aortic arch, septal defects and further heart and vessel malformations, reduced spleen size and malformed lung. It is noted that a similar malformation was evident in one foetus in the DRF-study. As no data has been made available from the DRF-study, it is however difficult to further evaluate similarities between the findings. The applicant was therefore asked to further discuss these malformations. Further, the full reports from the DRF-studies in both rat and rabbit should be submitted. The applicant gave a very limited discussion of the double aortic arch noted in two finerenone-treated foetuses. While it is curious that such a finding occurs twice in a development programme, it is agreed that the significance is unclear.

Skeletal malformations were also noted at 30mg/kg/day which were inside historical control data and thus with unclear treatment relation.

Among visceral and external deviations, the shorter umbilical cords at 30mg/kg/day seems clearly treatment related. It has been proposed, also in the rat, that restrictions in foetal movements may lead to short umbilical cord (doi: 10.1203/00006450-198202000-00006). Further, shorter cords have been associated with low birth-weight (doi: 10.1097/01.AOG.0000102706.84063.C7) and adverse foetal outcomes, why a causative correlation to the smaller foetuses seen at 10 and 30mg/kg/day is possible. According to the applicant, shorter umbilical cords were also noted in the DRF-study.

Oedema was noted in 4 foetuses at 30 and 1 each at 3 and 10mg/kg/day. The oedema finding at 30 mg/kg/day is considered to be likely treatment related as it was outside historical control data. The single occurrences at the lower doses are possibly chance findings.

Skeletal variations were increased from 10mg/kg/day, and were mainly related to ossification retardations. However, at 30mg/kg/day skeletal variations also included increased findings of slightly enlarged fontanelle.

Collectively, finerenone induced clear and significant effects on maternal body-weight development from 10mg/kg/day, which also correlated with reduced foetal weights and also shortened umbilical cords at 30mg/kg/day. Further, retarded skeletal ossifications from 10mg/kg/day with findings of enlarged fontanelle at 30mg/kg/day were evident. One foetus at the highest dose displayed several malformations, including double aortic arch, septal defects and further heart and vessel malformations, reduced spleen size and malformed lung. As this rare finding was previously found also in the pilot study, it is considered related to the finerenone treatment. Due to maternal toxicity (mainly body-weight reductions) at and above 10mg/kg/day, a NOAEL is set at 3mg/kg/day. Foetal malformations and variations were noted from 10mg/kg/day why foetal NOAEL is set at 3mg/kg/day. Given a margin to clinical exposure of only 10, there is concern for early pregnancy in the clinical situation.

Rabbit

In the pivotal study, finerenone was overall well-tolerated. However, one female (at the high-dose) was found dead on SD24 after having displayed general toxicity (including body-weight loss and decreased water consumption), why this mortality may be treatment related.

No effects on water consumption were documented, but food consumption was reduced (17%) at 2.5mg/kg/day during the first 6 treatment days. No effects were noted on female fertility or early and late embryonic development. While no effects were evident on placenta weights, hardened and discoloured parts of placenta were found with the highest incidence noted at 0.25mg/kg/day. The significance of this finding is unclear. Foetal weights were not affected by finerenone treatment.

Forelimbs were malrotated in 11 foetuses of finerenone treated dams but no control foetuses had this malformation. Even if the applicant declared that this finding may occur spontaneously in the rabbit strain used and that the incidences (3.8% affected foetuses, 23.5% affected litters) lay inside the normal range of scattering, the treatment-relation cannot be completed excluded. According to the study report, this finding may occur spontaneously in the rabbit strain used and malposition of the forelimb(s), which does not include skeletal changes, is the most common spontaneous malformation in the rabbit strain used and is caused most likely by restriction of foetal movement in the uterus. Further, the study report suggests that 3.8 % affected foetuses (23.5 % affected litters) lay inside the normal range of scattering (up to 5.9 % affected foetuses, up to 31.25 % affected litters with malposition of forelimb). While it seems to be a spontaneous finding in the rabbits used (based on the historical control data provided) the most recent historical control data (2010) suggests an incidence of 0.9%. Also, while not a clear dose-response effect, the effect is clearly finerenone treatment related given the lack of findings in the control group. It is to this end surprising that not a word is spent in the toxicological summary on this matter. It is merely stated that "no effects on external, visceral and skeletal variations and not indication of an increase in malformations was found". The applicant was

therefore asked to further elaborate on the significance of the malpositioned forelimb findings and reflect on why finerenone exposure leads to restricted movement in the uterus. The applicant elaborated on the significance of the malpositioned forelimb and also provided with plausible explanations for the restricted movement in the uterus. The malposition of the forelimb is by the applicant considered a relatively common deformation rather than a malformation, which is exacerbated by the finerenone treatment at 0.75 mg/kg/day. It is agreed that there is a finerenone-relation in the finding and that the Himalayan rabbit is prone to develop these malpositions. The applicant further suggests, based on Palmer (1978), that these effects can occur with drugs which reduced the amniotic fluid volume. While only indirect inference can be made, based on the PD of finerenone, an indirect effect on amniotic fluid volume is possible but has not been shown. Still, given that roughly one foetus per litter was affected (in the affected litters) and the variation in PD symptoms of the dams (e.g. dehydration) it would be expected that the females with the most severe symptoms would generate the foetuses with the malpositioned forelimbs. It is not clear if this is the case. Further, did the foetal position within the uterine horn affect the outcome of the foetal forelimb malposition? To what extent are these findings reversible postnatally? The applicant was therefore asked to further elaborate on the findings along these lines and include detailed descriptions of the findings. In the response, the applicant stated that the malpositioned forelimbs noted in the rabbit EFD-study with 1(1), 5(5) and 5(4) foetuses (litters) showing the deviation at 0.25, 0.75 and 2,5 mg/kg/day respectively, was a spontaneous background finding. This was not fully agreed. While the particular strain of rabbit (Himalayan rabbit) shows a relatively high (but very variable over time) background incidence of the finding in the performing site, the lack of such deviations in the control group suggests a treatment relation. The applicant further clarified that the finding was confined to the ventral flexure of the forelimb at the region of the wrist (i.e. carpal flexure) without any associated skeletal findings. Further, the applicant stated that the flexures resolve spontaneously in a short time and are therefore not adverse. This latter conclusion is in part derived from a publication from DeSesso and Scialli (2018) where the authors further suggest that more appropriate classification for carpal flexure with normal skeletal anatomy in rabbits is that of (reversible) deformation. While it can be agreed that the finding (as described) is not considered adverse as it likely resolves postnatally, the deformation was still considered treatment related but of minor clinical relevance. Based on a likely treatment-related mortality and effects on food consumption and correlated reduction in weight development at 2.5 mg/kg/day, a maternal NOAEL of 0.75mg/kg/day is supported.

PPND study

A pivotal PPND-study was performed in Wistar rat (Crl:WI(Han)). As this strain is different from the strain used in the EFD-study, the applicant performed a DRF study at 3, 10 and 30mg/kg/day to support dose-selection in the pivotal study. In the DRF-study, stillbirths were noted in all finerenone groups (2, 2 and 3 stillbirths at 3, 10 and 30mg/kg/day respectively). Further, complete litter losses were noted at 3 and 30mg/kg/day. At 30mg/kg/day, a higher incidence of missing/presumed cannibalised pups was noted including blue coloured pups. Thus, all doses in the DRF study were associated with pup mortalities suggestive of late developmental and/or parturition effects. As only macroscopic evaluations were made, no data are available on visceral and skeletal malformations or variations/deviations.

In the pivotal study, bodyweight gain was significantly decreased in all finerenone exposed groups but translated only to a significant body weight reduction in the 10mg/kg/day dose group. Body-weight reductions correlated with food intake reductions during gestation all dose-groups in a dose-dependent fashion. A reduced food consumption was also seen during lactation in all groups (up to 0.88x mean consumption in the control group), but without dose-relation.

3 pups were stillborn at 10mg/kg/day, and 1 stillborn pup with a deformed head was found in the 1mg/kg/day group. Further, the number of dead/missing/canibalised pups increased in finerenone

exposed groups. While one pup each was missing in the control and 1 mg/kg/day group, 2 pups were found dead at 3mg/kg/day (PND0 and PND9) and 2 were cannibalised. At 10 mg/kg/day, 1 pup was found dead on LD0 and 3 were canibalised before PND1. While the nature of pup cannibalisation in the early postnatal period is unclear, maternal stress and/or deformed or dead pups are often cited as possible underlying reasons. Given the deformed head noted in one dead pup in the 1mg/kg/day group (which may be incidental) and the pups found dead early after parturition in the 3 and 10mg/kg/day dose-groups, it is not excluded that the pups cannibalised were not fit for postnatal life.

In the surviving pups, mean weights were reduced in the finerenone treatment groups at birth and through lactation. As concentrations in the pups on PND 7 (see toxicokinetics section) were 17-24% of respective values in the dams it can be concluded that lactational exposure occurs. Pinna unfolding was significantly later in pups to mothers exposed at 10mg/kg/day, which is an indication of developmental toxicity. While bodyweights were decreased in all finerenone exposed groups (11-12% lower at PND22 in the 10mg/kg/day dose-group), no significant effects were noted were noted on sexual development. That said, mean day for vaginal opening in females developmentally exposed to finerenone at 3 or 10mg/kg/day was 33 days compared to 32 for controls, but without statistical significance.

Behaviour assessments in the F1-generation on PND 28 evidenced increased counts in all parameters of locomotor activity (total activity, mobile counts and rears) in rats to mothers exposed to finerenone at 3mg/kg/day or higher. No treatment-related effects were noted on learning and memory in the Morris water maze or in pre-pulse inhibition measurements.

The F1-generation mated without effects on mating, fecundity or fertility noted. However, the mean number of corpora lutea and implantation sites was reduced in the F1-dams related to finerenone exposure at 3 or 10mg/kg/day. According to the applicant, this was due to unusually high numbers of corpora lutea and implantation sites in controls, why the findings should be considered incidental. It is agreed that the control group has unusually high implantation numbers. However, while numerically small effects, it is curious that there is dose-relation in the reductions noted, suggesting a potential treatment effect. Further, given that other indices of toxicity were noted in the F1-generation of females (including effects on bodyweight through gestation) a treatment effect is considered likely.

The data described in the PPND-study makes clear that maternal exposure to finerenone at 3 and 10mg/kg day is associated with developmental toxicity where dam bodyweight and feed reductions in the F0-generation translated into increased incidences of foetal- and postnatal pup mortalities in F1. The surviving F1 pups had consistently lower body weights through weaning and into gestation of the second generation. Further, neurodevelopmental effects in the F1-generation were noted on locomotor activity, where increased activity (i.e. a hyperactive behaviour) was clear. While no effects were evident on mating, fertility or fecundity in this generation, an arguable reduction of the mean number of corpora lutea and implantation sites was noted.

Finerenone-related effects at 1mg/kg/day included slight bodyweight and bodyweight gain and feed reductions in the F0-generation. 1 stillborn pup (with deformed head) and one missing pup postnatally (likely cannibalised on PND 0) is of concern. Further, F1 males displayed macroscopic liver (large, mottled) and kidney (pale, mottled) effects which are considered treatment related. The significance of these macroscopic effects are not clear, as no histopathology evaluations are performed on F1 adults. The lack of kidney and liver findings in females is not considered assuring, but the overall conclusion is that the findings are not adverse. Collectively, a dam NOAEL is set to 3mg/kg/day, whereas a pup NOAEL of 1mg/kg/day is derived. The pup NOAEL corresponds to a margin to clinical exposure (AUC) of 1.8. Accordingly, the findings noted are considered of clear clinical concern, which should be reflected in recommendations for WOCBP, pregnancy and lactation in section 4.6.

Collectively, the DART programme has evidenced reproductive toxicity including malformations and still-births with low margins to clinical exposure. These findings are not compatible with a safe

finerenone use during pregnancy and lactation, and the substance should not be used by women of reproductive age not using appropriate contraception. This is reflected in the SmPC section 4.6. in accordance with the updates provided in the SmPC document, along with qualitative descriptions with margins to clinical exposure based on NOAEL in section 5.3.

Juvenile toxicity

A 3-month juvenile toxicity study with a 4-week recovery period has been performed in Wistar rats with start of exposure at PND 14. Body weights in males were differently affected with dose, as the weights were significantly decreased at 3mg/kg/day, but significantly increased at 10mg/kg/day. According to the applicant, body weights in high dose main group males were higher compared to control males already prior to first treatment, why the effect in this group is seen as a chance finding. Further, the applicant is of the opinion that the slight reduction in the mid dose is not relevant as no trend is seen. Indeed, it seems as if the weights were increased in the HD already from start, and it is very unfortunate. This makes the weight measurements difficult to evaluate. While it was anticipated that the weights would be reduced with treatment (based on general toxicity data in adults) it is not possible to conclude that. Further, no data has been made available on food consumption, which would have been another useful, possibly related, metric.

No effects were noted on sex development (balano-preputial separation and vaginal opening). Selected findings on haematology parameters observed after recovery but they were not seen during the dosing period. The only histopathological correlates were readings of zona glomerulosa hypertrophy, which were only partly resolved after recovery. Further, vacuoles were seen in both zona fasciculata and zona glomerulosa (also after recovery).

Curiously, according to the study report, 3 histiocytic sarcomas were encountered at terminal sacrifice in 3 animals in the study (2 males at 3mg/kg/day and one female at 10mg/kg/day). The tumours had already spread to several organs and caused the moribund condition of one animal A treatment-relation was not assumed by the applicant and these animals were excluded from all data tables. However, histiocytic sarcoma is the most frequent haematopoietic tumour in rats, but rarely occurs before 12 months of age (doi: 10.1293/tox.23.161). It is characterised by the proliferation of malignant cells that have the morphological and immunohistochemical characteristics of mature tissue histiocytes. The tumour cells have a typical histiocytic appearance. Based on literature, the cytoplasm is relatively broad and eosinophilic and may contain vacuoles or phagocytised erythrocytes (doi:10.1007/978-3-642-84110-1_7). The applicant was asked to further comment on the sarcoma findings in relation to the age of the rats, the exposure, and the possible association of the haematology findings in the study. According to literature, genetic traits may influence the frequency of histiocytic sarcoma. The applicant describes that two, and possibly all three cases in the study were siblings and therefore suggests that a genetic trait is the most likely cause of the sarcomas. While there may be a genetic (likely polygenic) factor involved, it is a neoplasm that may occur de novo or in the context of a previous haematologic malignancy (https://doi.org/10.3324/haematol.2019.230375). We do not know why the sarcomas developed in these animals, and although the cases were all in finerenone-treated groups it is not possible to label the findings as clearly treatment-related. No similar findings were evident in the repeated-dose toxicity studies or in the carcinogenicity studies, except for one case in the control group of the 104-week study in rat. It is unclear if any of his siblings were included in a finerenone-treated group. In any case, the histiocytic sarcomas identified in three animals in the juvenile toxicity study are likely spurious findings with unclear relation to finerenone treatment. While the indication applied for in this MAA concerns adults, it is stressed that this issue should be further discussed in the event a future application for finerenone in paediatric population.

The epididymis, seminal vesicles and prostate weights (among other organs) are reduced at 10mg/kg/day after recovery. General toxicology findings of reduced prostate weights and other

effects on male and female genitals have been seen in the programme, where "a mild hormonal imbalance" has been suggested as a possible explanation for the effects. With this in mind, the applicant was therefore asked to further discuss this finding. According to the applicant, the weights of the male reproductive organs never differed significantly when the comparisons relative to body weight were made (data not included in the response). Further, at the end of the recovery phase the control groups showed a higher body weight and the high dose males had a slightly lower body weight which according to the applicant is likely a chance finding. When bodyweights are considered unreliable, other relative comparisons are frequently seen, e.g. relative to brain weight. The applicant was thus asked to provide with additional relative comparisons of the reproductive organs to increase clarity. In the response, the applicant clarified the mean weights of male sex organs both in relation to body weight and also for brain weight. Regarding the prostate weights, a single control individual had an unusually high weight, which was likely the result of a technical mistake. The other relatively small differences in sex organ weights (including the epididymes weights) were not considered to be related to finerenone treatment.

Collectively, the toxicity profile in the juvenile population is similar to the profile in adult animals. However, histiocytic sarcomas were evident in the juvenile rat study with finerenone. Although according to literature, genetic traits may influence the frequency of histiocytic sarcoma and the applicant describes that two, and possibly all three cases in the study were siblings, histiocytic sarcoma may also occur de novo or in the context of a previous haematologic malignancy. It is not possible to label the findings as clearly treatment related. No similar findings were evident in the repeated-dose toxicity studies or in the carcinogenicity studies, except for one case in the control group of the 104-week study in rat. The histiocytic sarcomas identified in three animals in the juvenile toxicity study are likely spurious findings with unclear relation to finerenone treatment.

Juvenile fertility study in females

In the juvenile female fertility study, finerenone treatment was well-tolerated, and no deaths or clinical signs considered finerenone-related were seen. No effects were noted on fertility, fecundity or intrauterine development of the foetuses. Based on the lack effects, a NOAEL is set on the highest dose 10mg/kg/day.

2.5.4.6. Toxicokinetic data

Toxicokinetic investigation have been performed in mice, rats and dogs, both in terms of total AUC and Cmax as well as after correction for protein binding (AUCu and Cmax,u).

After single dose administration in mice, the exposure of finerenone (AUC(0-24) and Cmax) increased less than proportionally with increase of dose, indicating a plateau from 30 mg/kg onwards. Saturation of exposure at 30 mg/kg was confirmed during 3-weeks repeat-dose administration via gavage in mice: exposure at the dose of 50 mg/kg/day was comparable to the one reached at 150 mg/kg/day.

In the pivotal 13-week repeat-dose toxicity study with once daily administration by gavage, finerenone was tested at dose levels of 1 to 10 mg/kg/day in males and 0.75 to 7.5 mg/kg/day in females in order to achieve comparable exposure levels in both sexes. In this study, multiples of exposure of 15 to 21 were reached at the high dose.

In rats, finerenone was tested in pivotal repeat-dose toxicity studies with treatment duration of 4, 13 and 26 weeks. As already observed in mice, toxicokinetic investigation showed a dose-related and less than dose proportional increase of exposure in female rats over the whole dose range, and in male rats starting at 15 mg/kg/day. In rats, exposure was higher in females than in males, which was considered for dose selection in the long-term study, where female rats were treated at lower dose levels than

males, so that similar exposure ranges were reached in both sexes. The high dose of 30 mg/kg/day resulted in clear-cut signs of general toxicity including markedly reduced body weight gain, which was more pronounced in female animals (because of the difference in exposure between sexes).

In dogs, toxicokinetics revealed no differences in exposure between sexes. AUC(0-24) increased considerably more than proportionally with increase of dose from the mid to the high dose group after multiple dose administration. From the low to the mid dose group a tendency for a moderate more than dose proportional increase of AUC was observed. With regard to Cmax only from the low to the mid dose group a slightly over-proportional increase of exposure occurred.

2.5.4.7. Local Tolerance

No local tolerance studies are considered necessary as the oral route is intended for the product. However, to support a clinical bioavailability study, a local tolerance study using intravenous and paravenous administration was performed in the rabbit. No relevant findings of irritation were noted.

2.5.4.8. Other toxicity studies

Metabolites

While all human major metabolites have been covered in the performed toxicology study programme in rats, a SAR study further concluded that the major human metabolites have no alerts for mutagenicity and were assigned to impurity class 5.

Impurities

Based on information provided referencing data from the quality dossier, no further impurity studies should be necessary. However, see quality AR for further information on this issue.

Phototoxicity

A phototoxicity assessment of finerenone was performed, based on two GLP-compliant studies in the test facility. In the first 3T3-NRU phototoxicity assay, considerable variability was seen, and the mean was over 5 (suggestive of a phototoxic effect). In the second assay, a mean PIF of 1.8 resulted. The applicant was asked to explain why the results in the two studies were so different, considering that they were both GLP-compliant and run at the same test facility. Further, a conclusion regarding the phototoxic potential of finerenone should be provided. The applicant provided with an explanation for the variability in test results for the two performed GLP-compliant phototoxicity studies. Collectively the approach taken is agreed with and supports that finerenone has no phototoxic potential.

To conclude, the non-clinical toxicity of finerenone has been evaluated in a full programme of toxicity studies. Given the MR-antagonist pharmacology of the substance, expected effects have been noted on water and electrolyte balance, including compensatory hypertrophy of the zona glomerulosa (the site of aldosterone synthesis in the adrenal cortex) in all species from the lowest doses tested. Further, effects on kidney, liver, reproductive organs were evident, but they should overall be monitorable in the clinical setting.

Reproductive toxicities during pregnancy and early postnatal period should limit the use of the product in women of child-bearing potential not using contraception. Further, given the behavioural effects in offspring exposed during pregnancy and lactation, and the passage of the substance to breast-milk, breast-feeding should clearly be avoided. Treatment was well-tolerated in juvenile animals. However, 3 cases of histiocytic sarcomas were encountered in the treated groups of unclear significance.

In the mouse carcinogenicity study, an increased incidence of Leydig cell adenoma was noted in males administered 30 mg/kg/day when compared to both study control groups and the Covance historical control data in mice of this strain. In combination with the lack of genotoxic effects of finerenone, this supports that the finding is likely an indirect effect perhaps related to hormonal perturbation.

2.5.5. Ecotoxicity/environmental risk assessment

Distribution studies showed that finerenone is primarily distributed to the sediment compartment, and not degraded. The degradation half-life in sediment (equal to total systems half-life) was between 14.5 and 44.2d (temperature adjusted to 12C). There are some issues with the DT50 calculations (see Discussion). It should be noted that the applicant used sediments from the Teltowkanal located in the middle of Berlin, Germany for both test systems. The Teltowkanal is known for its high degree of pollution. Therefore, the outcome of the sediment study is likely to be influenced by a variety of chemicals including other pharmaceuticals. That being said, considering the results of the present study, it is unlikely that a new study would not lead to different conclusions. The dissipation half-life from water was determined with 78.9 and 147.9 days for sediment 1 and 2, respectively. The degradation half-life in sediment (= whole system degradation half-life) was 80.05 and 191.7 days for sediment 1 and 2, respectively. Based on the data, finerenone has to be classified as very persistent (vP).

Fish (fathead minnow) was the most sensitive species for finerenone aquatic effects, with a NOEC of 0.00001 mg/L (0.01µg/L). RQ-values (based on unrefined and refined PECsw values) show that finerenone poses a risk to the surface-water compartment but not the ground water.

Since the applicant used non-labelled test substance and open systems in the OECD 307 study, it is impossible to track the fate of the test substance over the course of the study. The dissipation rates in the test systems and in the sterile control were comparably high. Thus, the dissipation rates cannot be explained by degradation. No transformation products were detected, no mineralisation could be determined due to the open systems and the extraction method used by the applicant was weak. Consequently, according to the very high log K_{OC} value of 8.1 for finerenone the dissipation has to be considered as adsorption instead of degradation. Therefore, it is not suitable to calculate plausible DT50 values out of the data provided.

The presence of finerenone in the wastewater treatment plants following excretion will not impact the performance of the sludge microorganisms. Studies in sediment dwellers (*Chironomus riparius)* gave a NOEC of 46.7mg/kg, resulting in a RQ for sediment of 27, indicating an environmental risk to the sediment compartment.

Terrestrial toxicity tests suggested that Glycine max was the most sensitive species (phytotoxicity). The EC20 of 5.66 mg/kg (fresh weight reduction) was used as surrogate for the NOEC for determining risk for aquatic plants. Based on EUSES modelling (EUSES 2.1.1), a PEC_{SOIL} was calculated using the calculated PEC_{SW}, finerenone physico-chemical parameters and default parameters from EUSES (v2.2.0). The model estimations yielded a predicted environmental concentration (PEC_{SOIL}) of 0.00296-0.00421 µg/kg soil based on wet weight. Using the lowest NOEC-value in the terrestrial plant tests (EC20 of 5.66 mg/kg for Glycine max) and an assessment factor of 10, a $PNEC_{SOIL}$ of 0.566 mg/kg or 566 µg/kg is derived. The corresponding RQ is therefore 0.7×10^{-5}, suggesting that no risk for the soil compartment is anticipated.

Thus, collectively finerenone persistence and exposure at the proposed dosing may pose a risk to the aquatic and sediment organisms. Therefore, finerenone should be used according to the precautions

stated in the SmPC and in order to minimize any potential risks to the environment, appropriate labelling should be included in the SmPC and product label documents.

Substance (INN/Invented Name): Finerenone					
CAS-number (if available): 1050477-31-0					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	Log Kow (pH7) =2.61 at pH7			Potential PBT (Y/N)
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}	2.61			not B
	BCF	?			B/not B
Persistence	DT50	80.5-191.7d in sediment and likely in soil.			vP
Toxicity	NOEC	0.01ug/L (fish) <5ug/L (daphnids)			T
PBT-statement:	Log Kow for finerenone is below trigger value for PBT assessment.				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC surfacewater (default)	0.1	µg/L			> 0.01 threshold (Y/)
Other concerns (e.g. chemical class)	N/A	N/A			
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 121	*log* K_{oc} >5.52 *log* $K_{oc\ (estimated)}$ 8.1			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	<u>*25C*</u> DT50water (SFO) = 31d-78.9d DT50whole/sed1 (SFO) = 31.6d DT50whole/sed2 (DPOP) = 75.3d <u>12C</u> DT50water = 78.9d-147.9d DT50while/sed1 = 80.5d DT50while/sed2 = 191.7d % shifting to sediment at 15d >10% (78.1-79.3%)			One main transformation product ("M1)" represented 81% at 100d while finerenone represented ~3% at 100d.
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**Value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC LOEC (growth rate)	3.46 11.04	mg/L	Desmodesmus Subspicatus 72h
Daphnia sp. Reproduction Test	OECD 211	NOEC LOEC (offspring) EC_{10}	<0.005 0.005 0.005 (0.0002-0.016)	mg/L	21d
Fish, Early Life Stage Toxicity (fathead minnow)	OECD 210	NOEC LOEC (survival)	0.00001 0.00007	mg/L	Pimephales promelas 28d
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	>100	mg/L	3h
Phase IIb Studies					
Aerobic and anaerobic transformation in soil	OECD 307	DT50 LUFA 6S DT50 LUFA 2.1 DT50 LUFA 2.3 %Corg LUFA 6S	0.6 0.4 0.7 1.78	d d d	There are issues with the DT50 calculations and,

		% Corg LUFA 2.1 % Corg LUFA 2.3	0.67 0.66		considering the high log Koc (8.1), it is very likely that the test substance is strongly bound to soil particles/persistent in soil.
Soil Micro-organisms: Nitrogen Transformation Test	OECD 216	%effect		mg/kg	
Terrestrial Plants, Growth Test/*Species*	OECD 208	NOEC LOEC NOEC LOEC NOEC LOEC	12.3 37.0 <12.3 12.3 12.3 37.0	mg/kg	Brassica napus Glycine max Avena sativa
Earthworm, Acute Toxicity Tests	OECD 207	NOEC LOEC	500 1000	mg/kg	
Collembola, Reproduction Test	ISO 11267	NOEC	>1000	mg/kg	
Sediment dwelling organism	2007	NOEC	7 (46.7 in standard sediment)	mg/kg	Chironomus riparius

2.5.6. Discussion on non-clinical aspects

Pharmacology

The mineralocorticoid receptor (MR) is not expressed only in the kidney and the heart, but in various tissues. In response to the questions in the first round of the procedure the applicant provided a presentation on what is known regarding the distribution of the MR in various tissues. Expression of the MR has been well described in heart, vasculature, kidneys and also in colon, brain, skin, lung, liver, skeletal muscle, salivary and sweat glands. The MR is expressed in various cell types; renal epithelial cells, epithelium of salivary and sweat glands and urinary bladder, glomerular cells, vascular smooth muscle cells, endothelial cells, fibroblasts, white and brown adipocytes, keratinocytes, airway epithelia, macrophages and T-cells. MR expression has also been reported in ocular tissues, placenta, uterus, ovaries and testes.

The applicant has also discussed the possible consequences of an on-target antagonistic action by finerenone in relation to what is observed in the toxicity studies presented in this file. The identified target organs in the repeat-dose toxicity studies in rats were adrenal, pituitary, lacrimal glands, liver, kidney, urinary bladder, and female genital tract. In the studies in dogs, adrenals and prostate were identified as target organs. Most findings were considered to be related to direct pharmacological effects or secondary adaptational effects.

No information was presented on the binding of finerenone to the MR in mouse or rabbit. Since both mouse and rabbits are used in toxicological studies, and the relevance of the species is primarily based on the availability of the target, and action on the target in humans vs the specific animal, data on binding in these species are also of importance. It is acknowledged that the mouse has been used in several of the presented pharmacodynamic *in vivo* studies and the results indicate that finerenone do have an activity at MR in mouse. Furthermore, the results from the toxicity study, further supports the mouse as a pharmacologically relevant species. The applicant was asked to provide data or a thorough

justification on the lack thereof on the binding of finerenone to the MR in mouse and rabbit. No data was presented however a thorough justification was presented including affinity to MR with aldosterone in rabbit and mouse preparations and presentations on sequence homologies of the receptors. The ligand binding pocket of the ligand binding domain of mouse and rabbit MR are 100% homologous to rat and human MR the receptor, the respective larger LBDs show a homology of >95%. Although only indirect evidence of the binding of finerenone to MR, it is considered that rabbit and mouse are pharmacologically relevant as suitable species in the assessment of finerenone.

In the initial submission no data or discussion on the binding capacity of finerenone towards other steroid hormone receptors in the common experimental animals was presented. Since finerenone is claimed to be selective, it is for the interpretation of the findings of interest to know if this is true also in the animal species in which the pharmacological and toxicological studies are conducted. The applicant was therefore asked to discuss, and present data if available, the selectivity of finerenone in the investigated species. The applicant discussed and presented data on the sequences of the steroid hormone receptors which are well conserved amongst species. The conclusion that the high selectivity of finerenone towards the MR in comparison with all human steroid hormone receptors should be applicable at least for all mammalian steroid hormone receptors, is agreed upon.

The applicant was also asked to discuss if the relatively high doses administered in the *in vivo* pharmacological studies could have had an impact on the selectivity and pharmacological results. It is agreed that pharmacologically expected results were seen at systemic exposures in the same range as in patients treated with 20 mg finerenone once daily.

Several of the studies included eplerenone as a comparative agent. While this might be of interest from a clinical perspective it should be noted that as the compounds have different affinity to the MR a dose-to-dose comparison would not be relevant. This has been accounted for in some of the experiments. However, from these experiments it is not possible to draw any conclusions regarding the possible effectiveness of finerenone vs eplerenone (or spironolactone) in the clinical setting.

It should be noted that in many of the *in vivo* studies a relatively high dose of finerenone is administered. The 10 mg/kg dose used in many of the experiments for example, is also administered in the toxicological studies. In the 4-week toxicity study in rats, the 10 mg/kg gives a multiple of exposure vs the clinical exposure of 1505 and 3122 times in male and female animals respectively based on the total exposure. When comparing the unbound exposures, the multiples are significantly lower, 8 for males and 17 for females. It is acknowledged that to achieve statistically significant results in this kind of animal models, of which some are induced by surgical interventions, with the relatively small number of animals, higher doses might be needed. Nevertheless, the used clinically non-relevant doses should be taken into consideration when interpreting the details of the results and when comparing with other compounds already in clinical use. Furthermore, with the high doses, finerenone might bind to the other steroid receptors and the action on the mineralocorticoid receptor could thus be less specific than what is claimed.

Finerenone displays a different binding to mineralocorticoid receptors when compared to spironolactone and eplerenone. Finerenone acts an inverse agonist, whereas spironoloactone acts as a partial agonist. The applicant was in the first round of the procedure asked to give an explanation why the different binding sites and functional effects of finerenone on the mineralocorticoid receptor when compared to steroidal mineralocorticoid receptor antagonists (spironolactone, eplerenone) lead to lower hyperkalaemia when given on top of ACE inhibitors or AT1 receptor antagonists. In response, the applicant has provided a discussion on the difference between finerenone as an inverse agonist and spironolactone as a partial agonist and the effects on hyperkalaemia. A plausible explanation is the difference in recruitment of transcriptional co-factors due to different chemical structures and binding modes (‘bulky’ vs ‘planar’). The modulation of MR by cofactors is identified as a factor of differential gene

expressions, were finerenone vs spironolactone or eplerenone has been shown to more overall pronounced antifibrotic efficacy. The exact molecular mechanism describing how finerenone could differently modulate urinary potassium levels is not known. However, the different effects on renal pro-fibrotic gene expression is likely part of the difference observed with the compounds in different models. See further discussion in section on Clinical Pharmacology.

Overall, administration of finerenone in the different studies resulted in MR-antagonising effects with a beneficial/ protective effect on heart and kidneys in rodents. According to the applicant, finerenone has properties which include less risk for hyperkalaemia in comparison to spironolactone and eplerenone. In the clinical section, the applicant is asked to further explain the mechanistic basis for this beneficial mode of action.

Pharmacokinetics

Pharmacokinetics of finerenone has primarily been investigated *in vivo* in rat and dog with some additional studies in mouse and monkey. Rabbit was also included in studies on plasma protein binding, blood cell/plasma partitioning and drug metabolism and compared to human data. Possible drug-drug interactions were also analysed and is evaluated as part of the clinical assessment.

Nonclinical pharmacokinetics is considered sufficiently characterised and show that the toxicological species used are acceptable and relevant to use. No human specific metabolite was detected. Large species difference in the free fraction in plasma, with higher levels in humans, suggests that this should be considered when exposure margins are calculated.

Toxicology

A full programme of toxicity studies has been performed to evaluate the toxicity profile of the substance. The programme was comprised of general toxicology studies and studies of genotoxicity, carcinogenicity, reproductive toxicity and phototoxicity. The study programme also included three studies in juvenile animals (one single dose TK study, one systemic toxicity study and one juvenile toxicity study focused on female fertility). While these studies have been included and assessed in this assessment report, they are outside the scope of the present application.

Because of the mineralocorticoid receptor blockade MoA of finerenone, a compensatory hypertrophy of the zona glomerulosa (the site of aldosterone synthesis in the adrenal cortex) was seen in all species (graded minimal-extensive) from the lowest doses. In the 4-week study in rats, vacuoles in the zona fasciculata are reported only in the recovery animals. It was unclear what these vacuoles are composed of, and the applicant was asked to clarify the intracellular accumulation and deposition that resulted in the vacuoles. Based on the described morphology of the discussed findings in the report, the vacuoles are considered by the applicant composed of lipids. Further, the applicant suggests that a possible mechanism for the increase of vacuoles in the zona fasciculata could be extensive activation of the zona glomerulosa resulting in an increased production of corticosterone and aldosterone.

In male dogs, chronic administration (up to 39-weeks) of finerenone resulted in reduced prostate size and weight starting at 1.5 mg/kg/day which correlated with reduced size of prostate at necropsy in one male at 1.5mg/kg/day and 2 males at 5mg/kg/day. The prostate had not been a target organ of toxicity in the 4- and 13-week studies, suggesting that longer-term exposures are required for the development. While no supporting histopathology findings were noted this is still considered treatment related and possibly clinically relevant as the MoE is only 10. Accordingly, the applicant was asked to include the findings in section 5.3 of the SmPC. In the response, the applicant agreed that the low margin of exposure for the prostate finding in the dog to human clinical exposure may suggest a clinical relevance. However, it was the applicant's view that the limited effect size (in terms of absolute prostate weight change), the lack of clear progression with increased dose and the identification of the prostate finding in only a subset of the animals suggests limited clinical relevance. While it was agreed

that the effect size was not great, the lack of dose-response was not considered a valid argument in this case. The finding was only identified in the 39-week study, was considered adverse by the study pathologist and had limited margins to clinical exposure at NOAEL and LOAEL. Further, as no recovery group was used in the study, the potential for recovery is not known. As finerenone treatment is a chronic treatment it was also not clear if the effects would progress with longer treatment. The applicant agreed to include the finding in section 5.3 of the SmPC and proposed an update of the repeated dose toxicity paragraph. This text was edited by the Assessor to reflect that the relevance of the finding is unclear. Further clinical development of the product may clarify to what extent the prostate is a target of toxicity also in human. According to the applicant, the MR antagonist eplerenone also caused prostate weight reduction in dogs, but in addition caused atrophy. For eplerenone, a mild hormonal imbalance was identified as the most likely cause for the changes, why it is possible that a similar explanation holds true also for finerenone.

In the mouse carcinogenicity study, macroscopic examinations revealed enlargement and/or a pale area of the testes in several male mice from 3mg/kg/day. This correlated microscopically with increased incidence of Leydig cell adenoma in males administered 30 mg/kg/day when compared to both study control groups and the Covance historical control data in mice of this strain. The adenomas were present unilaterally in all animals, and (except in one case) only in animals surviving to terminal sacrifice suggesting a late occurrence. In combination with the lack of genotoxic effects of finerenone, this supports that the finding is likely an indirect effect perhaps related to hormonal perturbation. However, the applicant was asked to further support this issue. As MR are expressed in rat testes (selectively localised to Leydig cells) and aldosterone increases testosterone production in Leydig cells, the applicant suggests that blocking of the MR by finerenone may reduce testosterone production in Leydig cells. This blocking may then increase LH secretion (from the pituitary) to increase testosterone production. While this sequence of events is possible, available data do not support reduced hormone levels in the carcinogenicity studies. Therefore, the applicant suggests that the findings were only an enhancement of spontaneous age-related changes. While the findings in the control group may represent background findings, the clear increase in pale area and/or macroscopic enlargement of the testis in males administered 3, 10, or 30 mg/kg/day, and a statistically significant increased incidence of Leydig cell adenoma in the testis of males administered 30 mg/kg/day are considered finerenone-induced effects. However, given the known susceptibility of rodents to develop adenomas, differences in the number of LH and LH-related aging changes and the fact that the increase in adenoma findings were only noted with a MoE of 22x to human clinical exposure the clinical relevance is uncertain. Still, the findings are reflected in section 5.3 of the SmPC.

Thus, collectively chronic toxicity and carcinogenicity studies in rats and mice have shown that the administration of finerenone had effects on genital organs and reproductive tissue. Due to the pronounced species difference in the extent of plasma protein binding (about 92 % in humans, >> 99 % in mice and rats), the determination of the free plasma concentration of finerenone in the rodent toxicity studies is difficult, why the determination of safety margins based on unbound plasma concentrations is uncertain. Nevertheless, the gonadal effects observed in rodents seem to occur at free plasma concentrations only slightly above therapeutically effective free plasma concentrations in humans. The applicant was asked to give an explanation for the mechanism of the gonadal effects observed after administration of finerenone in rodents and its therapeutic relevance to humans, taking into account that, in contrast to spironolactone, finerenone up to 10 µM has no effects on androgen and progesterone receptors. In the response, the applicant agreed that the free fraction in rodents was much lower than in humans with 0.047% in rats, and 0.077% in mice compared to roughly 8% in humans. Thus, in combination with the inherent difficulty in accurately measuring the free concentrations at such high protein binding, it is possible that the MoE is underestimated. However, when comparing the given protein binding data with pharmacology data from the 2- and 4-week studies in rat, it is the applicant's view that this is not the case. While the approach taken by the

applicant may have its merits, the reliability of the safety margins are still considered unclear. However, this is an inherent problem with high protein-binding drugs as such. Regarding the potential mechanisms underlying the effects on gonads, the applicant has provided with discussions all focusing on the antagonism of finerenone on the MR. Considering the selective binding properties towards this receptor, mechanisms along these lines are considered likely. Still, to further delineate a molecular sequence of events additional studies would be of interest. However, at this point, such studies are not considered needed.

For both rat and rabbit, DRF-studies were performed prior to the conduct of the pivotal EFD studies. In the rat EFD study, at 30mg/kg/day, one foetus displayed several malformations, including double aortic arch, septal defects and further heart and vessel malformations, reduced spleen size and malformed lung. It is noted that a similar malformation was evident in one foetus in the DRF-study. As no data had been made available from the DRF-study, it was however difficult to further evaluate similarities between the findings. The applicant was therefore asked to further discuss these malformations. The applicant gave a very limited discussion of the double aortic arch noted in two finerenone-treated foetuses. While it is curious that such a finding occurs twice in a development programme, it is agreed with the applicant that the significance is unclear. In the rabbit EFD study, forelimbs were malrotated in 11 foetuses of finerenone treated dams but no control foetuses had this malformation. Even if the applicant declared that this finding may occur spontaneously in the rabbit strain used and that the incidences (3.8 % affected foetuses, 23.5 % affected litters) lay inside the normal range of scattering, the treatment-relation cannot be completed excluded. According to the study report, this finding may occur spontaneously in the rabbit strain used and malposition of the forelimb(s), which does not include skeletal changes, is the most common spontaneous malformation in the rabbit strain used and is caused most likely by restriction of foetal movement in the uterus. Further, the study report suggests that 3.8 % affected foetuses (23.5 % affected litters) lay inside the normal range of scattering (up to 5.9 % affected foetuses, up to 31.25 % affected litters with malposition of forelimb). While it seems to be a spontaneous finding in the rabbits used (based on the historical control data provided) the most recent historical control data (2010) suggests an incidence of 0.9%. Also, while not a clear dose-response effect, the effect is clearly finerenone treatment related given the lack of findings in the control group. The applicant was therefore asked to further elaborate on the significance of the malpositioned forelimb findings and reflect on why finerenone exposure leads to restricted movement in the uterus. The applicant elaborated on the significance of the malpositioned forelimb and also provided with plausible explanations for the restricted movement in the uterus. The malposition of the forelimb is by the applicant considered a relatively common deformation rather than a malformation, which is exacerbated by the finerenone treatment at 0.75 mg/kg/day. It is agreed that there is a finerenone-relation in the finding and that the Himalayan rabbit is prone to develop these malpositions. The applicant further suggested, based on Palmer (1978), that these effects can occur with drugs which reduced the amniotic fluid volume. While only indirect inference can be made, based on the PD of finerenone, an indirect effect on amniotic fluid volume is possible but has not been shown. Still, given that roughly one foetus per litter was affected (in the affected litters) and the variation in PD symptoms of the dams (e.g. dehydration) it would be expected that the females with the most severe symptoms would generate the foetuses with the malpositioned forelimbs. It is not clear if this is the case. The questions were posed if the foetal position within the uterine horn affect the outcome of the foetal forelimb malposition and also to what extent are these findings reversible postnatally. The applicant was therefore asked to further elaborate on the findings and include detailed descriptions of the findings. In the response, the applicant stated that the malpositioned forelimbs noted in the rabbit EFD-study with 1(1), 5(5) and 5(4) feetuses (litters) showing the deviation at 0.25, 0.75 and 2,5 mg/kg/day respectively, was a spontaneous background finding. This was not fully agreed. While the particular strain of rabbit (Himalayan rabbit) shows a relatively high (but very variable over time) background incidence of the finding in the performing site, the lack of such deviations in the control

group suggests a treatment relation. The applicant further clarified that the finding was confined to the ventral flexure of the forelimb at the region of the wrist (i.e. carpal flexure) without any associated skeletal findings. Further, the applicant stated that the flexures resolve spontaneously in a short time and are therefore not adverse. This latter conclusion is in part derived from a publication from DeSesso and Scialli (2018) where the authors further suggest that more appropriate classification for carpal flexure with normal skeletal anatomy in rabbits is that of (reversible) deformation. While it can be agreed that the finding (as described) is not considered adverse as it likely resolves postnatally, the deformation was still considered treatment related but of minor clinical relevance.

In the PPND-study, 3 pups were stillborn at 10mg/kg/day, and 1 stillborn pup with a deformed head was found in the 1mg/kg/day group. Further, pinna unfolding was significantly later in pups to mothers exposed at 10mg/kg/day, which is an indication of developmental toxicity. Also, behaviour assessments in the F1-generation on PND 28 evidenced increased counts in all parameters of locomotor activity (total activity, mobile counts and rears) in rats to mothers exposed to finerenone at 3mg/kg/day or higher. Collectively, the DART programme evidenced reproductive toxicity including malformations and still-births with low margins to clinical exposure. These findings are not compatible with a safe finerenone use during pregnancy and lactation, and the substance should not be used by women of reproductive age not using appropriate contraception. This is reflected in the updated version of the SmPC section 4.6. along with qualitative descriptions with margins to clinical exposure based on NOAEL in section 5.3.

In the juvenile toxicity study, the epididymis, seminal vesicles and prostate weights (among other organs) are reduced at 10mg/kg/day after recovery. General toxicology findings of reduced prostate weights and other effects on male and female genitals have been seen in the programme, where "a mild hormonal imbalance" has been suggested as a possible explanation for the effects. With this in mind, the applicant was therefore asked to further discuss this finding. According to the applicant, the weights of the male reproductive organs never differed significantly when the comparisons relative to bodyweight were made (data not included in the response). Further, at the end of the recovery phase the control groups showed a higher body weight and the high dose males had a slightly lower body weight which according to the applicant is likely a chance finding. When bodyweights are considered unreliable, other relative comparisons are frequently seen, e.g. relative to brain weight. The applicant was thus asked to provide additional relative comparisons of the reproductive organs to increase clarity**.** In the response, the applicant clarified the mean weights of male sex organs both in relation to body weight and also for brain weight. Regarding the prostate weights, a single control individual had an unusually high weight, which was likely the result of a technical mistake. The other relatively small differences in sex organ weights (including the epididymes weights) were not considered to be related to finerenone treatment. Further, 3 histiocytic sarcomas were encountered at terminal sacrifice in 3 animals in the study (2 males at 3mg/kg/day and one female at 10mg/kg/day). The tumours had already spread to several organs and caused the moribund condition of one animal. A treatment-relation was not assumed by the applicant and these animals were excluded from all data tables. However, histiocytic sarcoma is the most frequent haematopoietic tumour in rats, but rarely occurs before 12 months of age (doi: 10.1293/tox.23.161). It is characterised by the proliferation of malignant cells that have the morphological and immunohistochemical characteristics of mature tissue histiocytes. The tumour cells have a typical histiocytic appearance. Based on literature, the cytoplasm is relatively broad and eosinophilic and may contain vacuoles or phagocytised erythrocytes (doi:10.1007/978-3-642-84110-1_7). The applicant was thus asked to further comment on the sarcoma findings in relation to the age of the rats, the exposure, and the possible association of the haematology findings in the study According to literature, genetic traits may influence the frequency of histiocytic sarcoma. The applicant describes that two, and possibly all three cases in the study were siblings and therefore suggests that a genetic trait is the most likely cause of the sarcomas. While there may be a genetic (likely polygenic) factor

involved, it is a neoplasm that may occur de novo or in the context of a previous haematologic malignancy (https://doi.org/10.3324/haematol.2019.230375). We do not know why the sarcomas developed in these animals, and although the cases were all in finerenone-treated groups it is not possible to label the findings as clearly treatment-related. No similar findings were evident in the repeated-dose toxicity studies or in the carcinogenicity studies, except for one case in the control group of the 104-week study in rat. It is unclear if any of his siblings were included in a finerenone-treated group. In any case, the histiocytic sarcomas identified in three animals in the juvenile toxicity study are likely spurious findings with unclear relation to finerenone treatment. While the indication applied for in this MAA concerns adults, it is stressed that this issue should be further addressed in the event of a future application for finerenone in a paediatric population.

A phototoxicity assessment of finerenone was performed, based on two GLP-compliant studies in the test facility. In the first 3T3-NRU phototoxicity assay, considerable variability was seen, and the mean was over 5 (suggestive of a phototoxic effect). In the second assay, a mean PIF of 1.8 resulted. The applicant was asked to explain why the results in the two studies were so different, considering that they were both GLP-compliant and run at the same test facility. Further, a conclusion regarding the phototoxic potential of finerenone was asked for. The applicant provided with an explanation for the variability in test results for the two performed GLP-compliant phototoxicity studies. Collectively the approach taken is agreed with and supports that finerenone has no phototoxic potential.

ERA

Distribution studies showed that finerenone is primarily distributed to the sediment compartment, and not degraded. Based on the data, finerenone has to be classified as very persistent (vP) in sediment. One major transformation product (M-1) was detected which increased over time and accounted for more than 90 %AR at the end of the study. This indicates that M-1 is also persistent.

Based on toxicity criteria for PBT assessments, finerenone is considered toxic for both fish and daphnia (NOEC<10ug/L). Fish (fathead minnow) was the most sensitive species for finerenone aquatic effects, with a NOEC of 0.00001 mg/L (0.01µg/L) but based on refined (SimpleTreat) PEC values, the RQ is <1. Based on sediment-dweller toxicity (OC10% NOEC ~46.1mg/kg dw) and refined sediment PEC (0.12mg/kg dw), there was also no indication of environmental risk to sediment-dwellers (RQ<1).

Due to strong adsorption to sludge, finerenone is likely to be distributed to soils. Due to methodological challenges (in OECD TG307), no DT50 could be determined for soils. Based on the data, it is very likely that finerenone is strongly adsorbed to the soil matrix and likely persistent to very persistent in soils. This speculation is supported by the very high Koc of 125.892.541L/kg. In the terrestrial toxicity test battery, the most sensitive species was soybean (NOEC/LOEC boundary around 10-12.3mg/kg with a calculated EC_{20} of 5.66 mg/kg). Based on FOCUS guidance for assessing degradation/dissipation in various compartments, a default DT50 of 1000d was used to calculate a soil PEC of (1 year and accumulated over 10 years), giving a RQ of 0.0061 (RQ<1). Based on this, there is no environmental risk for soil organisms.

2.5.7. Conclusion on the non-clinical aspects

In conclusion, the applicant has provided with a comprehensive evaluation of the non-clinical pharmacology, pharmacokinetics and toxicology of finerenone. The issues identified in the non-clinical programme have been properly addressed. Studies in animals have shown reproductive toxicity which has been reflected in the recommendations for finerenone use during pregnancy and lactation. Women of childbearing potential should use effective contraception during finerenone treatment, and the

substance should not be used during pregnancy unless the clinical condition of the woman requires treatment with finerenone. Collectively, Kerendia is considered approvable from a non-clinical perspective.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant 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.

- **Tabular overview of clinical studies**

An overview of studies included in the clinical pharmacology package are given in Table 1 and Table 2, while an overview of phase II and II studies are provided in Table 3.

Table 1. Completed clinical pharmacology studies.

Study Number	Report Number	Type of Study	Finerenone Dose [mg][a]	Subjects Exposed to Finerenone (N)	Subjects Exposed to Placebo (N)
Basic Phase 1					
13782	PH-36501	Single dose escalation	1, 2.5, 5, 10, 20, 40 (PEG solution)	34	11[b]
13785	PH-36896	Multiple dose escalation (Part A); effect on midazolam (exploratory interaction, Part B)	Part A: 10 BID, 20 (2 × 10) BID, 40 (4 × 10) OD, 10 days Part B: 20 BID, 10 days	37	10[b]
14502	PH-37548	Mass-balance in two parts A and B	Part A: 10 (aqueous solution vs tablet) Part B: 10 ([^{14}C]finerenone aqueous solution)	8 4	0 0
Biopharmaceutic studies described in Module 2.7.1					
13784	PH-36582	Relative bioavailability and food effect 10 mg tablet	10 (PEG solution), 10, 80 (8 × 10) (tablet)	15	0
15526	PH-36700	Relative bioavailability study	1.25, 5 (4 × 1.25), 10	12	0
15481	PH-37391	Dose-proportionality	1.25, 2.5, 5, 7.5, 10	25	0
16536	PH-39623	Dose-proportionality, food effect 20 mg	10, 20	18	0
16535	PH-38789	Absolute bioavailability in two parts 1 and 2	Part 1: 0.25, 0.5, 1 (iv) Part 2: 1 (iv), 5 (tablet)	12 16	0 0
16538	PH-39783	Relative bioavailability of crushed tablet and suspension, food effect suspension	20	16	0
18290	PH-39812	Relative bioavailability and food effect of mini-tablet	1.25, 5 × 0.25 (mini-tablet), 10 (tablet)	16	0

Study Number	Report Number	Type of Study	Finerenone Dose [mg][a]	Subjects Exposed to Finerenone (N)	Subjects Exposed to Placebo (N)
19092	PH-40303	Relative bioavailability of continuously manufactured tablet	20	16	0

Table 2. Completed clinical pharmacology studies (continued).

Report Number	Type of Study	Finerenone Dose [mg][a]	Subjects Exposed to Finerenone (N)	Subjects Exposed to Placebo (N)
Studies with specific topic				
13786	PH-36781	Proof-of-concept study; effect on natriuresis after administration of fludrocortisone	2.5, 5, 10, and 20 (PEG solution), 20 (2 × 10) (tablet)	66	67
15113	PH-38555	Thorough QT study	20, 80 (4 × 20)	59	60
Special populations (Effect of intrinsic factors)				
14508	PH-36801	Age and gender	10	36	12[b]
14509	PH-36810	Renal impairment	10	33	0
14510	PH-38432	Hepatic impairment	5	27	0
15528	A62502	Single dose escalation in Singapore Chinese subjects	1.25, 10, 40 (4 × 10)	27	9[b]
15171	PH-36979	Multiple dose escalation in Japanese subjects	10 BID, 20 (2 × 10) BID, 40 (4 × 10) OD, 10 days	27	9[b]
16537	PH-40466	Multiple dose escalation study in mainland Chinese subjects	10 OD, 20 OD, 10 days	18	6[b]
Drug-drug interaction studies (Effect of extrinsic factors)				
14504	PH-37055	Effect of erythromycin on finerenone	1.25	15	0
16910	PH-38891	Effect of verapamil on finerenone	5	13	0
15112	PH-38930	Effect of gemfibrozil on finerenone	10	16	0
14506	PH-36593	Effect of omeprazole or antacid on finerenone	10	12	0
15111	PH-39782	Effect of finerenone on CYP3A4 substrate midazolam	20 OD (10 days)	31	0
16541	PH-38625	Effect of finerenone on CYP2C8 substrate repaglinide	20	29	0
14503	PH-38718	Effect of finerenone on warfarin	20 OD (6 days)	26	25
14505	PH-39189	Effect of finerenone on digoxin	20 OD (10 days)	24	0

Table 3. Overview of Phase II and Phase III studies with finerenone supporting the application.

Study ID	Design Interventions	Number of subjects	Study population Number of subjects	Primary endpoint
Phase II studies				
ARTS-DN Study 16243 (completed) 148 sites (23 countries)	Randomised, adaptive, double-blind, placebo-controlled, parallel-group, multicentre 8 arms with placebo or finerenone 1.25, 2.5, 5, 7.5, 10, 15 or 20 mg once daily	823 randomised 821 treated 812 in FAS	Subjects with T2D and the clinical diagnosis of diabetic nephropathy 639 men, 182 women Median age: 65 years (30–90 years)	Change in UACR after treatment with different oral doses of finerenone given once daily from baseline to Visit 5 (Day 90±2)
ARTS-DN Japan Study 16816 (completed) 16 sites (1 country)		96 randomised 96 treated 95 in FAS	Japanese subjects with T2D and the clinical diagnosis of diabetic nephropathy 77 men, 19 women Median age: 64 years (41–83 years)	
ARTS-HF Study 14564 (completed) 173 sites (25 countries)	Randomised, adaptive, double-blind, double-dummy, comparator-controlled, parallel-group, multicentre 6 arms with eplerenone 25 mg every other day, with possible up-titrations to 25 mg once daily at visit 5 (Day 30±2) or at Visit 7 (Day 60±2) (if not up-titrated or finerenone 2.5-5, 5–10, 7.5-15, 10-20 or 15-20 mg once daily	1066 randomised 1055 treated 1002 in FAS	Subjects with worsening CHF and reduced ejection fraction, and either T2D with/without CKD or moderate CKD alone 815 men, 240 women Median age: 73 years (33–92 years)	Percentage of subjects with a relative decrease in NTproBNP by more than 30% from baseline to Day 90±2.
ARTS-HF Japan Study 16815 (completed) 31 sites (1 country)		72 randomised 72 treated 72 in FAS	Japanese subjects with worsening CHF and reduced ejection fraction, and either T2D with/without CKD or moderate CKD alone	

			53 men, 19 women Median age: 74.5 years (46–93 years)	
ARTS Study 14563 (completed) 51 sites (10 countries)	Multi-centre, randomised, adaptive, double-blind, placebo-controlled, parallel group Part A: 4 arms with placebo or finerenone at 2.5, 5 or 10 mg once daily Part B: 6 arms with placebo or finerenone at 2.5, 5 or 10 mg once daily or 5 mg twice daily, or spironolactone (open label) at 25 mg or 50 mg once daily	Part A: 65 randomised 65 treated 65 for PK Part B: 393 randomised 392 treated 389 in FAS	Subjects with stable CHF with reduced ejection fraction and CKD Stage 2 (Part A) and stable CHF with reduced ejection fraction and CKD Stage 3 (Part B). Part A: 52 men, 13 women Part B: 312 men, 80 women Median age Part A: 66 years (42–85 years) Part B: 73 years (40–89 years)	Part A: Safety and tolerability of finerenone Part B: Mean change from baseline in serum potassium at Visits 6 and 7
Phase III study				
FIDELIO-DKD Study 16244 (completed) 1024 sites (48 countries)	Randomised, double-blind, placebo-controlled, parallel group, multicentre, event-driven	Finerenone 10 or 20 mg OD: 2866 randomised 2833 FAS 2827 treated 2824 completed Placebo 2868 randomised 2841 FAS 2831 treated 2832 completed	3983 men, 1691 women Median age: 66 years (28–97 years)	Time to the first occurrence of the composite endpoint of onset of kidney failure, a sustained decrease of eGFR ≥40% from baseline over at least 4 weeks, or renal death
FIGARO-DKD Study 17530 (ongoing)	Randomised, double-blind, placebo-controlled, parallel-group, multicentre, event-driven	Study is ongoing		Time to the first occurrence of CV death, non-fatal MI, non-fatal stroke, or hospitalisation for heart failure

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Finerenone clinical development programme consisted of 28 Phase I clinical studies to obtain the necessary clinical pharmacology data including the elucidation of required pharmacokinetic (PK)

properties of finerenone. The overview of all completed Clinical Pharmacology studies is presented in Table 1 and Table 2 above.

Clinical Pharmacology studies were categorised into "basic Phase 1 studies" including a single dose escalation first-in-man study, multiple dose escalation study and mass-balance study, "biopharmaceutical studies", "studies in special populations" to evaluate the effects of intrinsic factors on PK properties, drug-drug interaction (DDI) studies in which finerenone was investigated as potential DDI victim (extrinsic factors) or perpetrator, and studies designed for specific purposes.

In these Phase 1 clinical pharmacology studies, finerenone was mainly administered as a tablet, except for the single dose escalation study (Study 13782), the [^{14}C] finerenone mass balance study (Study 14502), and the absolute bioavailability study (Study 16535), in which either oral solutions or an intravenous (i.v.) solution were administered instead of, or in addition to the tablet.

Analytical methods

The analytical methods for the quantification of finerenone and its metabolites in plasma utilised the protein precipitation followed by high performance liquid chromatography coupled with tandem mass spectrometric detection (HPLC-MS/MS). In urine, finerenone and its metabolites were determined after 10-fold dilution with human plasma and then applying the assays for plasma.

For the sole determination of finerenone in human plasma, methods were initially developed for a concentration range from 0.1 to 200 µg/L (MW1398 and SBQ-13062). For the determination of finerenone and its metabolites in plasma in one assay format, methods for a concentration range from 0.1 to 500 µg/L for finerenone and 0.5 to 500 µg/L for the metabolites were validated (MW1452 and SBQ-14068), very similar to the methods for sole quantitation of finerenone. At a later stage of development some methods were transferred to a new generation of mass spectrometers and new method descriptions were filed accordingly (MW1921 based on MW1398, MW1882 based on MW1452). Furthermore, a method for the determination of finerenone in the concentration range from 0.1 to 200 µg/L for a low plasma volume (e.g. from capillary blood) was validated (MW2007 based on MW1398).

Like for plasma, urine assays were adapted over the course of development from a concentration range of 1.00 to 2000 µg/L for finerenone (MW1398) towards 1.00 to 5000 µg/L and 5.00 to 5000 µg/L for finerenone and its metabolites, respectively (MW1452, SBQ-14069).

Absorption

Finerenone is almost completely absorbed after its oral administration. Apparent permeability *in vitro* in Caco-2 cells was comparable to values obtained for highly permeable markers (metoprolol and propranolol), thus implying that finerenone is a highly permeable compound. Furthermore, *in vitro* studies have also revealed that finerenone acts as a P-glycoprotein (P-gp) substrate. However, due to its high permeability, the impact of efflux transporters on the *in vivo* absorption of finerenone is considered negligible.

Mass-balance study conducted with radiolabelled finerenone [^{14}C] finerenone has implied a complete absorption of finerenone (Study 14502). Of note, considering its high permeability and a low solubility, finerenone could be regarded as a BCS (Biopharmaceutical Classification System) Class 2 compound.

Despite its almost complete absorption, in a dedicated clinical study (Study 16535) the absolute bioavailability (BA) of finerenone was measured to be around 43.5%. This is attributed to the first-pass metabolism of finerenone that takes place in both gut-wall and liver.

Overall, the absorption of finerenone was rapid with T_{max} appearing between 0.5 and 1.25 h after tablet intake in fasting conditions. The food (i.e. high-fat high calorie meal) led to an increase in AUC

(+ 21%) and reduction in C_{max} (-19%) of finerenone compared to fasting conditions. However, the resulting changes in the finerenone exposure are not considered as clinically relevant and therefore finerenone tablets can be taken regardless of mealtime.

Distribution

Study 16535 which investigated the absolute BA of finerenone included the administration of i.v. infusion of aqueous solution (containing either 0.25, 0.5 and 1 mg finerenone) over 1h. Based on the PK data from this study, the calculated Vss of finerenone was between 52.6 and 66.9 L (geometric mean values). Thus, the calculated Vss of finerenone of 52.6 L is similar to the volume of total body water (0.6 * mean body weight of study subjects = 48.4 L).

The plasma protein binding of finerenone was determined by the ultrafiltration. The unbound fraction (%), fu in human was 8.3%. Most of the drug in human plasma was bound to the albumin fraction. Moreover, finerenone was similarly distributed between the red blood cells and plasma with the blood-to-plasma ratio of about 0.94 in human.

Elimination

Finerenone is rapidly eliminated from plasma with a terminal elimination half-life between 2 to 3 h, a value observed in the dose range of finerenone up to 20 mg.

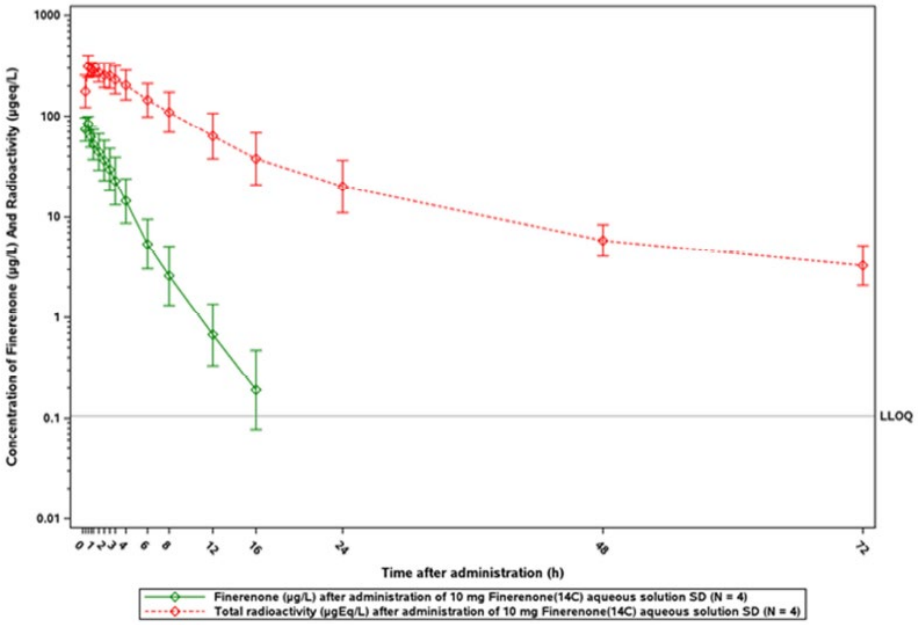
CYP3A4 is a major enzyme responsible for about 90% metabolism of finerenone, while CYP2C8 has a minor role contributing to about 10% of finerenone metabolism. Drug undergoes extensive first-pass metabolism in the gut-wall and liver.

Plasma clearance of finerenone determined after its i.v. administration (study 16535) was in a range between 22.3 to 31.4 L/h. Plasma CL of 22.3 L/h is equivalent to a blood CL of 24.8 L/h (i.e. based on a Cb/Cp ratio of 0.9) and this systemic blood CL value is reported in the SmPC.

Mass-balance study

Mass-balance study was conducted to measure the cumulative amount as well as the time course of drug-related, radiolabelled material excreted in the urine and faeces following a single dose of 10 mg [^{14}C] finerenone (oral solution), and to characterize the metabolite pattern in plasma, urine, and faeces.

Figure 2. Concentrations of finerenone (µg/L) and total radioactivity (µg-eq/L) in plasma after administration of [^{14}C] finerenone 10 mg aqueous solution; (geometric means and SD – semilogarithmic scale; N=4).



The mean recovery of total radioactivity in the excreta urine and faeces was 101% (range: 88.0%-106%). About 79.6% (range: 76.2%-83.3%) of the radioactivity was excreted via urine, while 21.2% (range: 9.6%-26.9%) of the radioactivity was excreted via faeces. Unchanged finerenone represented about ~1% of the administered dose in faeces and urine.

The AUC of finerenone (determined by LC-MS/MS) accounted for only about 7% of the AUC of total radioactivity in plasma after administration of [^{14}C] finerenone. Furthermore, based on the total radioactivity AUC in plasma, metabolite M-1 represented 48.9%, metabolite M-2 represented 21.5%, metabolite M-3 represented 9.0%, metabolite M-4 represented 2.4%, and metabolite M-5 represented 1.4% of total radioactivity. In summary, based on total plasma radioactivity AUC >90% of the radioactivity could be assigned to known chemical structures.

Table 4. Total radioactivity in plasma (%) for finerenone and its metabolites from a mass-balance study.

		Total rad.	Finerenone	M-1a	M-1b	M-2a	M-2b	M-3a	M-3b	M-4	M-5
AUC	[µg-eq·h/L]	2805	200	1088	284	571	32.6	249	2.26	67.3	39.4[b]
	[%]		**7.1**	**38.8**	**10.1**	**20.3**	**1.2**	**8.9**	**0.1**	**2.4**	**1.4**[b]

Furthermore, detailed investigations revealed that the predominant human plasma metabolites M-1, M-2, and M-3 exhibited an axial chirality as pairs of atropisomers, each consisting of an "a"- and "b"-series (see figure below). Further analysis of plasma showed the predominant appearance of the atropisomers of the a-series, with the following "a" to "b" ratios M-1a : M-1b = 79 : 21; M-2a : M-2b = 95 : 5; M-3a : M-3b = 99 : 1. Based on these percentages, metabolites M-1a (38.8%), M-1b (10.1%) and M-2a (20.3%) were regarded as the major human plasma metabolites. In addition, metabolite M-3a was also regarded as a major plasma metabolite by the applicant, based on the study conducted in patients with impaired renal function (Study 14509), in which M3 metabolite represented about 30% of total drug-related plasma exposure.

Figure 3. Atropisomers of finerenone metabolites M-1, M-2, M-3.

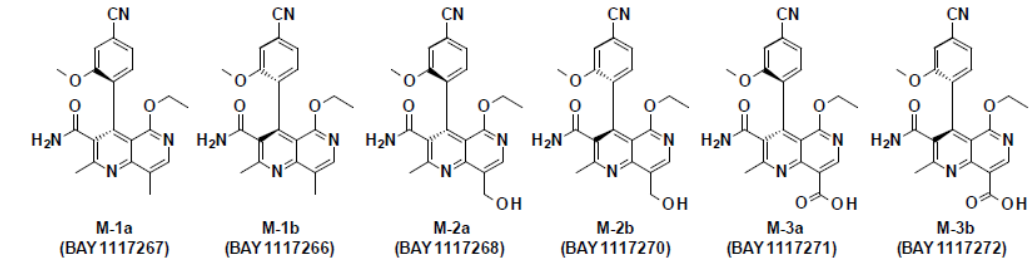


Figure 4. Proposed biotransformation pathways of finerenone *in vivo*.

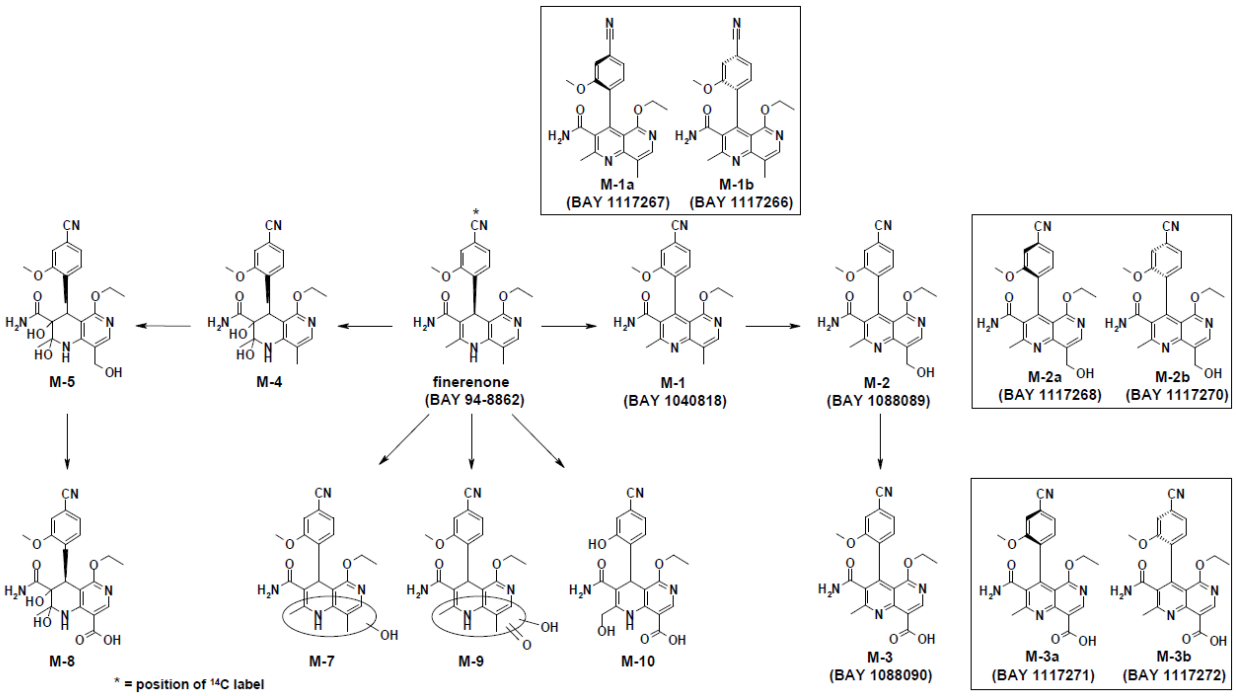
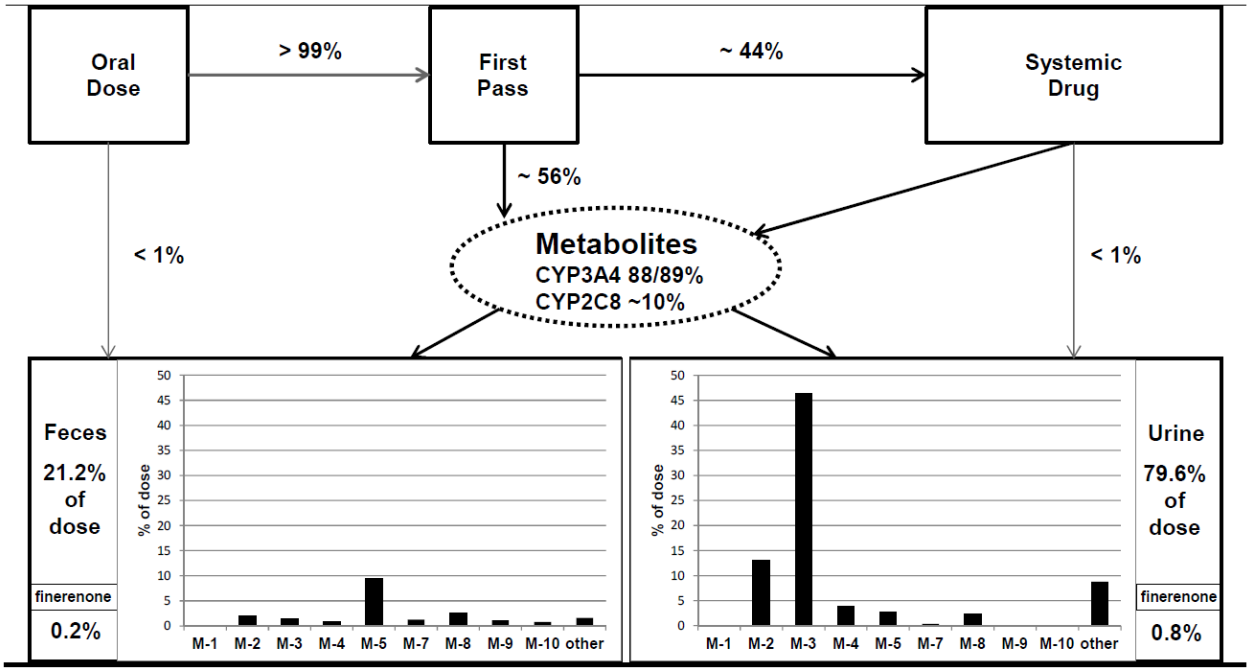


Figure 5. Schematic representation of excreted metabolites, and corresponding CYP enzymes involved in the biotransformation of finerenone.



Additionally, the applicant has conducted two *in vitro* studies addressing different aspects of the finerenone metabolism by implementing incubations in liver microsomes and hepatocytes of different species. *In vitro* data indicated no significant species differences, and no human-specific pathways in the *in vitro* metabolism of finerenone. Turnover of [^{14}C] finerenone in human microsomal incubations was about 93%, while in human hepatocytes (2 h incubation period) it was between 44-52%.

Furthermore, *in vitro* CYP phenotyping data indicated that CYP3A4 is the most relevant enzyme in the biotransformation of finerenone, followed by CYP2C8. The hepatic fraction metabolised by CYP3A4 is estimated to be ≥ 80%. According to the applicant, glucuronides were not observed neither of the parent nor of the metabolites, i.e. no UGT enzyme contribution.

Finally, the major contribution of CYP3A4 enzyme in the metabolism of finerenone as well as the minor role of CYP2C8 enzyme are confirmed in the respective *in vivo* DDI "victim" studies.

Dose proportionality and time dependencies

Dose-proportionality

The applicant has conducted several clinical Phase I studies implementing different doses of finerenone which allowed for the estimation of its dose-proportionality. Study **13782** was the first-in-man study which investigated finerenone PK with increasing single oral doses of 1, 2.5, 5, 10, 20 and 40 mg administered as a PEG solution. This study overall indicated a dose-proportional increase in finerenone AUC and a slightly less than dose-proportional increase in its C_{max}.

Furthermore, there were several Phase I studies using different doses of finerenone tablets with additional treatment arms addressing different aspects of bioavailability. Study **15481** investigated the PK of finerenone administered as single oral doses as tablets of 1.25, 2.5, 5, 7.5 and 10 mg, while the study **16536** included finerenone tablets of 10 and 20 mg. Both studies have implied a dose-proportional increase in finerenone AUC and C_{max} within its proposed therapeutic range (i.e. doses up to 20 mg). Moreover, studies **13784** and **15113** have also included investigation of finerenone PK

given as tablets at its supratherapeutic dose of 80 mg (i.e. 4-fold higher than the highest proposed therapeutic dose of 20 mg) which also implied a dose-proportional PK. Overall, the applicant has sufficiently demonstrated the dose-proportional PK properties of finerenone given as single dose tablets in the dose range from 1.25 up to 80 mg.

Time-dependency

Clinical study **13785** involved multiple oral doses of 10 mg twice daily (BID), 20 mg BID and 40 mg OD of finerenone given over a period of ten days. However, none of the dosing regimens which were implemented in this study was reflecting the actually proposed finerenone posology (i.e. 10 or 20 mg OD). The corresponding ratios of drug exposure observed at day 10 ($AUC_{tau, ss}$) and after its first dose ($AUC_{0\text{-infinity}}$) denoted as R_{LIN} implied a time-dependent PK of finerenone. R_{LIN} ratios have implied a slight increase in finerenone exposure after its repeated dosing with R_{LIN} of 110% (i.e. +10%) after OD dosing, and even higher increase of 120-132% (i.e. + 20-32%) after BID dosing regimens. Moreover, similar tendencies towards the time-dependent PK were also observed in studies conducted in Chinese (study **16537**) and Japanese (study **15171**) population.

When considering the relatively short half-life of finerenone of 2-3 h as well as the OD dosing regimen, the observed increase in AUC after multiple dosing of finerenone would not be expected. However, the applicant believes that the reason for the observed time-dependencies in finerenone PK might be the time-dependent inhibition (TDI) of CYP3A4 for which finerenone is a substrate.

Overall, the auto-inhibition appears a plausible explanation based on the observed *in vitro* signals for TDI of CYP3A4, as well as based on the obtained *in vivo* DDI data with midazolam (study 15111) in which a slight inhibitory effect was observed (about +10% increase in midazolam AUC).

Special populations

Renal Impairment (RI)

Study **14509** (Report **PH-36810**) investigated the impact of renal impairment (RI) on the PK of finerenone (given once as 10 mg tablet) and its major metabolites M-1, M-2 and M-3. Results have indicated that the mild RI had no impact on the PK of finerenone. However, moderate and severe RI led to an (similar) increase in total finerenone AUC by 34% and 36%, respectively. No RI impact on the C_{max} of finerenone was observed. Considering that finerenone is primarily eliminated via metabolism (i.e. <1% of dose eliminated as unchanged finerenone via urine) the observed increase in the finerenone exposure in moderate and severe RI is likely due to the RI impact on other non-renal routes of drug elimination.

Table 5. Study 14509 – PK parameters of total finerenone in plasma and urine following a single dose of one 10 mg finerenone tablet (geometric mean/%CV [range]; N=33; and excluding outlier, N=32).

Parameter	Unit	Normal renal function CL_{CR}: ≥90 mL/min (n=7)	Mild renal impairment CL_{CR}: 60 to <90 mL/min (n=6)	Moderate renal impairment CL_{CR}: 30 to <60 mL/min (n=11)	Moderate renal impairment CL_{CR}: 30 to <60 mL/min (n=10)[a]	Severe renal impairment CL_{CR}: 15 to <30 mL/min (n=9)
AUC	µg*h/L	233/19.2 (191-296)	198/60.6 (88.1-437)	352/74.8 (114-1230)	311/59.6 (114-567)	317/83.3 (60.0-773)
AUC_{norm}	kg*h/L	1.86/25.3 (1.44-2.66)	1.55/55.5 (0.670-2.89)	2.72/79.9 (0.889-9.81)	2.39/64.4 (0.889-4.71)	2.54/97.5 (0.408-5.87)
AUC/D	h/L*10^{-3}	23.3/19.2 (19.1-29.6)	19.8/60.6 (8.81-43.7)	35.2/74.8 (11.4-123)	31.1/59.6 (11.4-56.7)	31.7/83.3 (6.00-77.3)
AUC(0-t_{last})	µg*h/L	232/19.3 (190-295)	197/60.4 (87.5-433)	351/75.0 (113-1230)	309/59.6 (113-565)	315/83.9 (59.0-771)
C_{max}	µg/L	96.2/35.0 (67.4-146)	118/48.8 (59.6-235)	109/50.9 (51.8-256)	99.9/42.5 (51.8-170)	88.4/58.1 (24.7-166)
$C_{max,norm}$	kg/L	0.770/35.1 (0.512-1.20)	0.921/49.2 (0.453-1.55)	0.840/52.4 (0.355-2.05)	0.769/43.3 (0.355-1.41)	0.710/66.8 (0.168-1.40)
C_{max}/D	1/L*10^{-3}	9.62/35.0 (6.74-14.6)	11.8/48.8 (5.96-23.5)	10.9/50.9 (5.18-25.6)	9.99/42.5 (5.18-17.0)	8.84/58.1 (2.47-16.6)
t_{max}[b]	h	0.750 (0.500-2.00)	0.500 (0.500-1.00)	0.750 (0.500-3.00)	0.750 (0.500-3.00)	0.750 (0.500-4.00)
$t_{1/2}$	h	2.25/14.7 (1.89-2.76)	2.23/15.9 (1.93-2.79)	2.75/37.6 (1.32-4.83)	2.60/33.8 (1.32-3.53)	2.78/45.8 (1.28-4.56)
MRT	h	2.92/19.0 (2.29-4.15)	2.58/14.0 (2.24-3.03)	3.74/39.7 (2.29-6.81)	3.52/35.5 (2.29-6.65)	3.87/37.5 (2.48-6.63)
CL/F	L/h	43.0/19.2 (33.8-52.5)	50.4/60.6 (22.9-114)	28.4/74.8 (8.15-87.4)	32.2/59.6 (17.6-87.4)	31.6/83.3 (12.9-167)
V_z/F	L	140/23.1 (94.3-182)	162/46.5 (92.0-322)	113/42.6 (56.8-265)	121/36.9 (80.0-265)	127/44.8 (79.0-308)
$A_{E,ur}$[c]	µg	87.0/27.8 (55.7-128)	50.7/24.0 (23.4-85.1)	66.7/54.8 (6.06-212)	52.1/27.3 (6.06-95.2)	37.5/22.0 (7.94-65.9)
%$A_{E,ur}$[c]	%	0.870/0.278 (0.557-1.28)	0.507/0.240 (0.234-0.851)	0.667/0.548 (0.0606-2.12)	0.521/0.273 (0.0606-0.952)	0.375/0.220 (0.0794-0.659)
CL_R	L/h	0.357/21.4 (0.289-0.484)	0.231/32.8 (0.133-0.326)	0.140/56.8 (0.0530-0.308)	0.137/59.8 (0.0530-0.308)	0.0931/121 (0.0156-0.190)

a PK parameters summarized for subjects valid for PK without the outlying subject
b Median (range)
c Arithmetic mean / SD (range)

Hepatic Impairment (HI)

Study **14510** (Report **PH-38432**) investigated the impact of hepatic impairment (HI) on the PK of finerenone (given once as 5 mg tablet) and its inactive major metabolites M-1, M-2 and M-3. There was no significant increase in the finerenone exposure (neither as total AUC_{tot} nor unbound $AUC_{,u}$) in the subjects with mild HI (Child Pugh A). On the other hand, in subjects with moderate HI (Child Pugh B) there was an increase in AUC_{tot} by 38% compared to healthy volunteers, and even a higher increase in AUC_u by 55% compared to healthy volunteers. This higher increase in unbound AUC is likely a consequence of lower albumin levels which led to slightly higher unbound fractions (fu) compared to healthy volunteers. A trend towards prolonged $t_{1/2}$ was also observed with HI. C_{max} was not affected by HI and was similar in all studied groups.

There are no clinical PK data available in subjects with severe HI (Child Pugh C). However, it is anticipated that the finerenone exposure for these patients will exceed the therapeutic exposure range and as such the applicant's proposal to avoid treatment in severe HI patients is supported in general.

Age and gender

Study **14508** (Report **PH-36801**) investigated the influence of both, age and gender on the PK of finerenone (and its metabolites) given as 10 mg tablet single dose in the fasted state. According to the ANOVA analysis performed in study **14508**, the gender did not appear to influence the PK of finerenone. On the other hand, age appeared to have statistically significant influence on PK with an increase in both AUC and C_{max} (34% and 51%, respectively) in elderly subjects (≥65 years) compared to younger study subjects (≤ 45 years). However, this increase was not considered as clinically relevant, and dose adjustments are not required in elderly patients according to the proposed recommendations in 4.2 section of the SmPC.

Table 6. Number of study subjects with PK data from age 65 and above.

Study number	Study phase	65 – 74 years	75 – 84 years	≥85 years
14502	I	1	0	0
14508	I	16	2	0
14509	I	14	3	0
14510	I	8	1	0
14563	IIa	127	110	11
14564	IIb	259	279	46
16243	IIb	297	75	4
16815	IIb	19	22	3
16816	IIb	32	7	0
16244	III	1071	368	14
Total		**1844**	**867**	**78**

Race

The applicant has conducted three Phase I studies in subjects with Asian ethnicity: Study **15528** Single dose escalation in Singapore Chinese subjects; Study **15171** (Report PH-36979) Multiple dose escalation in Japanese subjects; Study **16537** (Report PH-40466) Multiple dose escalation study in mainland Chinese subjects. Based on the integrated analysis of Phase I available data, the Asian subjects exhibited a tendency towards the higher finerenone exposures compared to Caucasian subjects. However, this difference was greatly reduced by normalisation to body weight, thus indicating the large contribution of the lower body weight in Asian subjects.

Pharmacokinetic interaction studies

Investigations of DDIs with finerenone involved several *in vitro*, *in silico* and *in vivo* studies.

- Finerenone as "perpetrator" drug

For the purpose of *in vitro* DDI evaluations, the applicant has reported the maximum plasma concentration (C_{max}) of finerenone with the proposed therapeutic dose (i.e. 20 mg given once daily) to be 161 µg/L which corresponds to 0.43 µM (MW=378.42 g/mol). Furthermore, reported fraction unbound for finerenone in human plasma was about 8.33%. Therefore, the systemic concentration cut-off for the *in vitro* investigation of DDI potential is 0.0833 * 0.43 µM = 0.035 µM. Finally, when taking into account the EMA safety factor of 50, the calculated systemic concentration cut-off is 50 x $C_{max,u}$ = 50 * 0.035 µM = **1.75 µM**. Furthermore, the corresponding concentration EMA cut-off for the intestinal exposure is estimated to be **21.1 µM**, while the hepatic-inlet exposure was **7.29 µM**.

All *in vitro* studies have included sufficiently high finerenone concentrations (as "perpetrator" drug) covering EMA's concentration cut-off values as calculated above, and therefore *in vitro* perpetrator studies appear adequate in this regard.

Overall, *in vitro* results have implied that finerenone acts as an inhibitor of CYP3A4 enzyme, both as a direct and as time-dependent inhibitor (TDI). Furthermore, finerenone inhibited *in vitro* CYP2C8, CYP2C9 and CYP2C19 enzymes. Finally, finerenone also demonstrated an induction of CYP3A4 *in vitro*.

The potential clinical relevance of these *in vitro* signals was further investigated in corresponding clinical DDI studies. The perpetrator impact on CYP3A4 enzymes in terms of both induction and inhibition was excluded in studies 15111 and 13785 with midazolam as a CYP3A4 probe substrate, in which no relevant change in midazolam exposure was observed. Furthermore, clinical studies with repaglinide as CYP2C8 substrate (study 16541), and warfarin as CYP2C9 substrate (study 14503) have ruled out an inhibitory impact of finerenone on these CYP enzymes *in vivo*.

When it comes to transporters, finerenone has exhibited an inhibitory potential *in vitro* towards P-gp (IC_{50}=47 µM), BCRP (IC_{50}=17.4 µM) and OATP1B1 (IC_{50}=3.2 µM) transporters. The clinical relevance of P-gp inhibition was excluded by a clinical study with digoxin (study 14505) which showed no difference in digoxin exposure with and without the concomitant administration of finerenone. Inhibition of OATP1B1 transporters was also ruled out by the clinical data from repaglinide study (i.e. study 16541 which was also used for CYP2C8 inhibition purposes). Furthermore, the applicant has conducted additional clinical DDI study (Study 21429; completed and presented after the initial marketing authorisation application submission) with rosuvastatin as a "victim" drug representing a substrate of both BCRP and OATPs, which confirmed no DDI risk with finerenone as a potential transporter inhibitor.

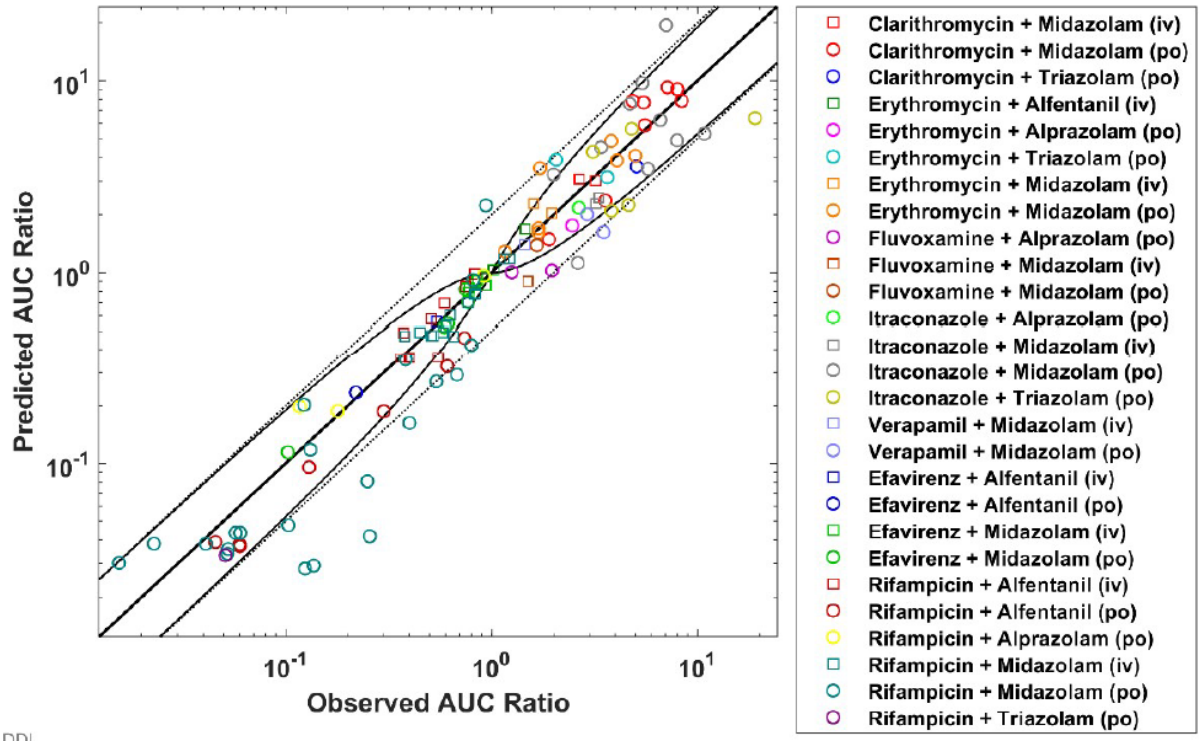
- Finerenone as "victim" drug

The key role of CYP3A4 enzyme in the elimination of finerenone was confirmed in two clinical DDI studies with moderate CYP3A4 inhibitors erythromycin (study 14504) and verapamil (study 16910). Erythromycin led to a 3.5-fold increase in AUC of finerenone, and 1.9-fold increase in C_{max}. Verapamil led to a 2.7-fold increase in AUC of finerenone, and 2.2-fold increase in C_{max}. In addition, clinical study with gemfibrozil (CYP2C8 inhibitor) showed no relevant increase in finerenone AUC nor C_{max} (i.e. 1.10- and 1.16-fold, respectively), which confirmed the minor role of CYP2C8 enzyme in the metabolism of finerenone.

The applicant has developed a PBPK DDI model for finerenone as a "victim" drug via CYP3A4, to investigate non-studied DDI scenarios, i.e. concomitant use of finerenone with weak and strong CYP3A4 inhibitors as well as the concomitant use with moderate and strong CYP3A4 inducers.

The PBPK analysis was conducted using the software PK-Sim® and MoBi® as part of the Open Systems Pharmacology Suite (OSPS version 9.) and Matlab (version R2017b). The predictive performance of the PBPK platform for the intended purpose (i.e. prediction of CYP3A4 "victim" studies) was assessed via a network of PBPK models of selected index CYP3A4 DDI perpetrators and respective sensitive index CYP3A4 victim drugs (midazolam, triazolam, alprazolam, alfentanil) and a comprehensive dataset from published clinical DDI studies (see figure below).

Figure 6. Qualification of the PBPK platform: Predicted vs. observed mean AUCR for all combinations of DDI in the established CYP3A4 network (dotted lines representing a 2-fold difference).



After the qualification of the PBPK platform step, the verification step of DDI model was performed by comparing the predicted data for finerenone with concomitant erythromycin and verapamil versus the clinically observed data from erythromycin (study 14504) and verapamil (study 16910) DDI study. The predictive performance of finerenone "victim" DDI inhibition model appeared adequate in terms of both AUCR and $C_{max}R$ for both perpetrator drugs erythromycin and verapamil (see table below).

After the model verification step, the applicant has proceeded with PBPK model application step, to predict other non-studied DDI scenarios with finerenone as a "victim" drug via CYP3A4 enzyme. According to the prediction of the applied PBPK model, fluvoxamine as a weak CYP3A4 inhibitor led to an AUCR of 1.57 and $C_{max}R$ of 1.38. These predicted numerical values are supported and are included in the finerenone SmPC.

Furthermore, the PBPK model has predicted a significant increase in finerenone exposure when given together with strong CYP3A4 inhibitors itraconazole and clarithromycin (see table below). However, it is worth emphasizing that the highest finerenone dose (supratherapeutic dose) studied in a clinical setting was 80 mg (i.e. 4-fold higher than its highest proposed therapeutic dose of 20 mg), while the PBPK model predicts an increase of 6-fold which falls outside of the clinically studied range of finerenone exposure. Therefore, due to uncertainties in the PBPK model prediction which goes beyond the clinically studied exposure for finerenone, the predicted numerical values for strong CYP3A4 inhibitors are removed from the initially proposed SmPC text. Importantly, the SmPC contraindication text regarding the concomitant use of strong CYP3A4 inhibitors is generally supported, because a high DDI impact can be expected based on the fact that finerenone acts as a sensitive CYP3A4 substrate.

Finally, the applicant has also applied the same PBPK model to predict the magnitude of finerenone interaction with CYP3A4 inducers rifampicin (strong CYP3A4 inducer) and efavirenz (moderate CYP3A4 inducer). However, the number of selected compounds was considered insufficient to qualify the PBPK platform for the intended purpose, i.e. CYP3A4 induction prediction. Furthermore, there were no clinically observed data available with finerenone as a "victim" of CYP3A4 induction in order to verify

the model predictive performance. Therefore, PBPK predicted numerical values for CYP3A4 inducers were considered unreliable and removed from the initially proposed SmPC text. Importantly, it is agreed that the expected magnitude of interaction between finerenone and strong and moderate CYP3A4 inducers is high when considering the elimination pathway of finerenone and the key role of CYP3A4 enzyme in this process. Thus, the proposed SmPC text which restricts the concomitant use of strong and moderate CYP3A4 inducers with finerenone is supported.

Table 7. Comparison of simulated and observed finerenone AUCR and $C_{max}R$ and its variabilities.

Perpetrator in combination with finerenone	AUCR geo. mean	AUCR geo. CV	$C_{max}R$ geo. mean	$C_{max}R$ geo. CV
Itraconazole 200 mg BID simulated	6.31	0.39	2.37	0.20
Clarithromycin 500 mg BID simulated	5.28	0.40	2.25	0.17
Erythromycin observed in study 14504	**3.48**	**0.22**	**1.88**	**0.22**
Erythromycin 500 mg TID simulated	3.46	0.25	2.00	0.16
Verapamil 120/240 mg* simulated	2.91	0.29	1.86	0.15
Verapamil obs. in study 16910 (120/240 mg*)	**2.70**	**0.15**	**2.22**	**0.24**
Fluvoxamine 100 mg BID simulated	1.57	0.16	1.38	0.10
Efavirenz 400 mg SD simulated	0.58	0.13	0.69	0.10
Efavirenz 400 mg OD simulated	0.20	0.21	0.34	0.18
Efavirenz 600 mg OD simulated	0.19	0.21	0.32	0.18
Rifampicin 600 mg OD simulated	0.07	0.25	0.14	0.20

PK parameters that are calculated from observed data are bold.
*: Verapamil dosing was 120 mg on day 1 followed by 240 mg on day 2, 3 and 4
Abbreviations: AUCR = AUC ratio; geo. = geometric; $C_{max}R$ = C_{max} ratio; CV = Coefficient of variation; SD = single dose, OD = once daily, BID = twice daily, TID = thrice daily.

Population pharmacokinetic analysis

Population pharmacokientic (popPK) analyses were used throughout the clinical drug development in a sequential manner. The popPK analysis of phase2b data (ARTS-DN and ARTS-DN Japan studies) was used to provide exposure predictions for an exposure-response analysis, and to evaluate potential PK differences between Japanese and non-Japanese patients. The final popPK analysis was based on data from the FIDELIO-DKD study.

Phase 2b analysis

The final combined PK dataset, based on studies ARTS-DN and ARTS-DN Japan, contained 705 and 82 subjects, and 4109 and 488 PK observations, respectively. The distribution of race in the global population from study 16243 was: 84.6% Caucasian, 10.1% Asian, 3.3% Black/African American and 2.0% other/not reported.

A two-compartment model with first-order absorption (and 3 transit compartments) and elimination adequately described the PK of finerenone over the 1.25 to 20 mg dose range in both populations. Covariate effects eGFR-MDRD on CL/F and F, and body weight on V/F were included in the model. Low to moderate shrinkage values for empirical Bayes estimates indicate that the exposure predictions were adequate for exposure-response analysis.

Following differences between the Japanese and the global population were observed. BW was 20% lower in the Japanese population, resulting in a 10% lower V_c/F. eGFR-MDRD was 3.5% lower in the Japanese population, resulting in a 0.4% difference (not significant) of $AUC_{\tau,md}$ between both populations. Neither dose normalised $C_{max,md}$ ($C_{max,md}/D$), nor dose normalised $AUC_{\tau,md}$ ($AUC_{\tau,md}/D$), nor the model parameters CL/F, F, V_c/F or the absorption rate (K_a) were significantly different between both populations.

Phase 3 analysis

The final PK dataset contained 5057 valid finerenone concentrations from 2284 subjects (FIDELIO-DKD study). The number of subjects receiving a starting dose of 10 mg or 20 mg dose was 2112 (92.5%) and 172 (7.53%), respectively.

The PK of finerenone in the phase 3 population was best described by a linear two-compartment model in which Vc/F was assumed to be equal to Vp/F, with first-order elimination from the central compartment. The delay in absorption was described as first order absorption via three transit compartments with a lag time. Inter-individual variability of CL/F and V/F was estimated at 32.1% and 33.5%, respectively. Shrinkage in empirical Bayes estimates for CL/F and V/F was 26.4% and 47.4%, respectively.

In the covariate analysis, in addition to BW, race/ethnicity (Korean subjects only) was found to have a statistically significant influence on V/F, while in addition to time varying eGFR, body heights, creatinine, smoking status, CYP3A4 inhibitor and SGLT2i use showed a statistically significant effect when applied on both CL/F and F. Furthermore, gamma glutamyl transferase (GGT) was found to have a statistically significant influence on CL/F.

Steady-state $C_{max,md}$ and $AUC_{\tau,md}$ values from FIDELIO-DKD study were 163 µg/L and 668 µg*h/L, respectively.

2.6.2.2. Pharmacodynamics

Three studies in healthy individuals were conducted to characterise the pharmacodynamics of finerenone. In addition, a thorough QT-study was conducted. Finerenone is a mineralocorticoid receptor (MR) antagonist. The desirable properties for the intended population of patients with T2D and CKD are cardiorenal protection and not the potassium-sparing diuretic effect. The following pharmacodynamic studies investigated single- and multiple dose response of finerenone, as well as the response after fludrocortisone challenge.

Mechanism of action

Finerenone (BAY 94-8862) is a novel, non-steroidal and selective mineralocorticoid receptor (MR) antagonist. The steroidal hormones, aldosterone and cortisol, are natural ligands of the MR, which is expressed extensively in the heart, kidneys and blood vessels. 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 combines high *in vitro* potency (IC50 of 17.8 nM) and selectivity (at least 500-fold compared to other steroid hormone receptors) toward the MR. Finerenone blocks the relevant MR agonists aldosterone and cortisol more potently than the steroidal MRAs spironolactone and eplerenone. Importantly, finerenone does not exhibit any activity up to 10 µM at the androgen receptor.

The non-steroidal structure of finerenone, its 'bulky' binding mode to the MR and its differential effects on downstream myocardial hypertrophy gene expression compared to eplerenone, suggest a different pharmacological profile[31,32]. Furthermore, unlike spironolactone and eplerenone, which reach higher concentrations in kidney tissue in comparison to cardiac tissue, finerenone is distributed equally

[31] Grune J, Beyhoff N, Smeir E, Chudek R, Blumrich A, Ban Z, et al. Selective Mineralocorticoid Receptor Cofactor Modulation as Molecular Basis for Finerenone's Antifibrotic Activity. Hypertension. 2018 Apr;71(4):599-608.
[32] Kolkhof P, Delbeck M, Kretschmer A, Steinke W, Hartmann E, Barfacker L, et al. Finerenone, a novel selective nonsteroidal mineralocorticoid receptor antagonist protects from rat cardiorenal injury. J Cardiovasc Pharmacol. 2014 Jul;64(1):69-78.

between the heart and the kidney in rodents[33]. Finerenone has a short plasma half-life of 2 to 3 hours and has no pharmacologically active metabolites.

Primary and Secondary pharmacology

Study 13782: Single dose escalation study

This First-in-Man study was a single-centre, randomised, single-blinded, parallel-group, placebo-controlled study conducted in healthy male subjects. It investigated safety and tolerability after increasing single oral doses of 1, 2.5, 5, 10, 20 and 40 mg finerenone or placebo administered as PEG solution.

Forty-five (45) healthy male subjects received a single dose of study drug, 34 subjects received finerenone and 11 subjects received placebo. Dose groups consisted of 5 subjects each in the groups exposed to 1 and 2.5 mg finerenone, and 6 subjects each in the groups exposed to 5, 10, 20, and 40 mg finerenone. The subjects had a mean age of 33.6 years (range: 20 to 45 years) and a mean body mass index (BMI) of 24.2 kg/m² (range: 20.1 to 29.6 kg/m²).

Pharmacodynamic results

Single doses of 1 to 40 mg of finerenone did not influence BP, HR, or RAAS components in plasma. With regard to urine electrolytes, no general effect of finerenone on urinary excretion of electrolytes was found.

Study 13785: Multiple dose escalation study

This was a single centre, randomised, single-blind, placebo-controlled, group-comparison study. In Part A, the study investigated safety and tolerability of finerenone after multiple oral doses of 10 mg twice daily (BID), 20 mg BID and 40 mg OD given as 10 mg tablets over a period of 10 days (subjects in the 10 and 20 mg BID arms only received one dose of finerenone on the last study day to allow for PK assessments of the terminal elimination phase) in healthy male white subjects, 18 to 45 years of age, BMI ≥ 18.0 and ≤ 29.9 kg/m².

Pharmacodynamic results

After 10 days of repeated treatment with finerenone, the RAAS hormone levels (renin and aldosterone) were increased compared to placebo, without a clear dose dependency of the effect: a pronounced increase was seen for plasma-renin-activity for the 10 mg BID and 20 mg BID treatments and for serum aldosterone at the 20 mg BID and the 40 mg OD dose levels compared to placebo (*Table 8*). The observed effects on hormone levels reversed within 48 h after last study drug intake.

[33] Kolkhof P, Delbeck M, Kretschmer A, Steinke W, Hartmann E, Barfacker L, et al. Finerenone, a novel selective nonsteroidal mineralocorticoid receptor antagonist protects from rat cardiorenal injury. J Cardiovasc Pharmacol. 2014 Jul;64(1):69-78.

Table 8. Baseline adjusted LS-means with 95%-confidence intervals for the placebo-corrected effect of finerenone (BAY 94-8862) on neurohormones: change from baseline on Day 10 (all subjects valid for PD, N=37).

Parameter	P-value of F-statistic	BAY 94-8862 treatment	Difference "active-placebo"	95% Confidence limits Lower	Upper	P-value of T-statistic
Plasma-renin activity (ng/mL/h)	0.0491	10 mg bid	0.72	0.07	1.38	0.0319
		20 mg bid	0.81	0.19	1.43	0.0117
		40 mg od	0.30	-0.31	0.91	0.3264
Aldosterone (ng/L)	0.0007	10 mg bid	50.13	-7.46	107.73	0.0855
		20 mg bid	126.86	71.45	182.27	<.0001
		40 mg od	63.67	8.30	119.04	0.0257

Note: values below LLOQ were set to 0.5*LLOQ for aldosterone (LOQ = 30 ng/l)
changes from baseline were only calculated if at least one value was >=LOQ; p-value of f-statistic: test of equal treatment means; p-value of t-statistic: test of difference active-placebo equals zero
Source: Table 16.1.9.1/1.5

There was no consistent evidence of clinically relevant increase of natriuresis or reduction of urine potassium after multiple oral administration of 10 mg and 20 mg bid or 40 mg od of finerenone tablets in this study.

Study 13786: Mechanistic proof of concept study after fludrocortisone challenge

This was a single-centre, randomised, single-blinded, placebo-controlled, active-controlled, combined 3-fold crossover and parallel-group study to investigate the effectiveness (PD) of different single doses of finerenone with regards to natriuresis after administration of 0.5 mg fludrocortisone in white healthy male subjects. Eplerenone (50 mg) was used as an active control.

This study investigated the natriuretic effects of finerenone in comparison to the MRA eplerenone after administration of a single oral dose of 0.5 mg fludrocortisone as MR activator 2 h prior to the administration. Urine was collected in aliquots up to 26 hours after administration of finerenone.

For each subject the study consisted of 3 periods, each including a 3-day in-house adaptation phase (start of defined food and beverage intake), 1 profile day, an in-house observation until 60 h after administration of study drug, and a wash-out period of approximately 1 week after administration of the test substance

Each subject received the following treatment sequence (crossover):

- Treatment A: finerenone (2.5, 5, 10, 20 mg in PEG or 2x10 mg tablets)
- Treatment B: corresponding placebo of finerenone dose.
- Treatment C: 50 mg eplerenone

The wash-out phase between each treatment period consisted of at least 1 week.

Results

Finerenone showed dose-dependent natriuretic effects starting from the dose of 2.5 mg PEG solution. In the 2 to 10 h urine collection interval after treatment, finerenone 20 mg PEG solution increased urinary Na^+ excretion significantly more than 50 mg eplerenone. In contrast, 50 mg eplerenone led to a significantly higher Na^+ excretion compared to finerenone at doses of 2.5 and 5 mg PEG solution

during most time intervals, whereas no relevant differences were observed between 50 mg eplerenone and finerenone 10 mg PEG solution and 20 mg (2 × 10 mg) tablets.

Both finerenone and 50 mg eplerenone significantly decreased urinary K^+ excretion as compared to placebo. K^+ excretion in urine was higher with eplerenone than with any dose of finerenone; however, these differences reached statistical significance in only few instances.

In the placebo group 0.5 mg fludrocortisone decreased urinary Na^+/K^+-ratio as expected. In the 2 to 10 h urine collection interval after treatment, both finerenone and 50 mg eplerenone as MRAs blocked the fludrocortisone effect and significantly increased the specific parameter log10 ($10*Na^+/K^+$ ratio) compared to placebo (*Table 9*). This increase was significantly higher after administration of 20 mg finerenone (given either as PEG solution or tablets) than with 50 mg eplerenone in the 2 to 10 h interval after dosing and similar between eplerenone and 10 mg PEG solution. In contrast, the parameter was significantly higher after administration of 50 mg eplerenone compared to finerenone at doses of 2.5 and 5 mg PEG solution during most time intervals.

Table 9. Study 13786 – LS-means and 90% CI for the ratios 'finerenone/placebo' and eplerenone/placebo' of each 3-fold crossover treatment for the parameter log10(10*Na+/K+) in urine samples.

Treatment (Dose step)	02h-10h	02h-06h	06h-10h	10h-14h	14h-18h	18h-22h	22h-26h
Finerenone/placebo							
2.5 mg PEG solution (DS 5)	1.71* (1.48 - ∞)	1.78* (1.50 - ∞)	1.38* (1.12 - ∞)	1.00 (0.82 - ∞)	1.03 (0.84 - ∞)	0.96 (0.81 - ∞)	0.83 (0.68 - ∞)
5 mg PEG solution (DS 3)	1.57* (1.26 - ∞)	1.60* (1.28 - ∞)	1.34 (1.03 - ∞)	0.90 (0.76 - ∞)	0.87 (0.76 - ∞)	0.92 (0.76 - ∞)	1.17 (0.98 - ∞)
10 mg PEG solution (DS 2)	2.88* (2.38 - ∞)	3.15* (2.68 - ∞)	3.23* (2.62 - ∞)	1.53* (1.26 - ∞)	1.32* (1.11 - ∞)	1.10 (0.96 - ∞)	0.93 (0.81 - ∞)
20 mg PEG solution (DS 1)	3.09* (2.71 - ∞)	2.99* (2.61 - ∞)	3.61* (2.99 - ∞)	1.38* (1.18 - ∞)	1.01 (0.92 - ∞)	1.06 (0.91 - ∞)	0.97 (0.82 - ∞)
2x10 mg tablet (DS 4)	4.57* (3.87 - ∞)	3.82* (3.34 - ∞)	7.79* (5.78 - ∞)	2.33* (1.99 - ∞)	1.35* (1.19 - ∞)	0.88 (0.76 - ∞)	1.09 (0.97 - ∞)
Eplerenone/placebo							
50 mg Eplerenone (DS 5)	2.94* (2.53 - ∞)	2.49* (2.09 - ∞)	3.53* (2.84 - ∞)	1.49* (1.22 - ∞)	1.06 (0.87 - ∞)	0.81 (0.69 - ∞)	0.81 (0.66 - ∞)
50 mg Eplerenone (DS 3)	2.86* (2.31 - ∞)	2.29* (1.83 - ∞)	3.55* (2.75 - ∞)	1.59* (1.35 - ∞)	1.25* (1.09 - ∞)	1.25* (1.04 - ∞)	1.32 (1.10 - ∞)
50 mg Eplerenone (DS 2)	3.13* (2.58 - ∞)	2.74* (2.34 - ∞)	5.01* (4.07 - ∞)	2.76* (2.29 - ∞)	1.68* (1.41 - ∞)	1.39* (1.22 - ∞)	0.90 (0.79 - ∞)
50 mg Eplerenone (DS 1)	2.29* (2.00 - ∞)	1.83* (1.59 - ∞)	4.17* (3.43 - ∞)	1.91* (1.63 - ∞)	1.55* (1.42 - ∞)	1.38* (1.20 - ∞)	0.95 (0.80 - ∞)
50 mg Eplerenone (DS 4)	2.99* (2.53 - ∞)	2.21* (1.93 - ∞)	4.63* (3.44 - ∞)	2.25* (1.93 - ∞)	1.59* (1.40 - ∞)	1.03 (0.90 - ∞)	1.22* (1.09 - ∞)

*:significant treatment differences at a significance level of 0.05
Source: Module 5.3.4.1, Report PH-36781, Table 14.2 / 14

Secondary pharmacology

MR is expressed extensively in the heart, kidneys and blood vessels, thus the pharmacological effects are mainly expected to be related to these organs. The PD parameters measured to assess potential MR antagonism-related effects in the early studies previously discussed in the report were BP and heart rate as standard parameters. In all studies, no clinically relevant influence was found up to the highest single dose of 80 mg and the highest multiple dose treatment of 40 mg for 10 days.

Apart from a thorough QT study, no specific studies have been performed on the secondary pharmacology.

Effect on QT

Thorough QT study (Study 15113)

The study was conducted according to CPMP 986/96 and ICH E14 in a single-centre, randomised, double-blinded, double-dummy, 4-way crossover design with placebo- and active- (400 mg moxifloxacin) control arms to investigate the influence of single doses (20 mg, intended maximum

therapeutic dose and 80 mg, to establish safety range for supratherapeutic dose) of finerenone on the QTc interval in 60 white healthy male and female subjects. Additionally, other PD parameters (HR, BP), PK of finerenone and its metabolites, safety and tolerability were assessed.

The primary analysis showed that for all time points, the upper limits of the one-sided 95% CIs of the mean differences to placebo of QTcF values remained below the threshold of Δ=10 msec, i.e. there was no relevant treatment effect after administration of 20 mg or 80 mg finerenone on QTcF.

For the secondary variables QTcB, QTcI (corrected using individual correction formula) and QT, the upper limits of the one-sided 95% CIs of the mean differences to placebo remained completely below the threshold of Δ=10 msec, i.e. no relevant prolongation was seen at any time after administration of 20 mg finerenone and 80 mg finerenone.

From 1 h to 6 h following administration of moxifloxacin, the LS-mean differences moxifloxacin – placebo in QTcF ranged from 8.53 msec to a peak of 11.87 msec (one-sided 95% CI: [9.95 msec, inf]) found at 4 h after drug administration.

Minimum and maximum LS-means differences as well as corresponding 95% CIs are summarised in *Table 10*.

Table 10. Study 15113 – Minimum and maximum LS-Means differences and one-sided 95% CIs for ECG over time (results of ANCOVA; PDS, N=57)

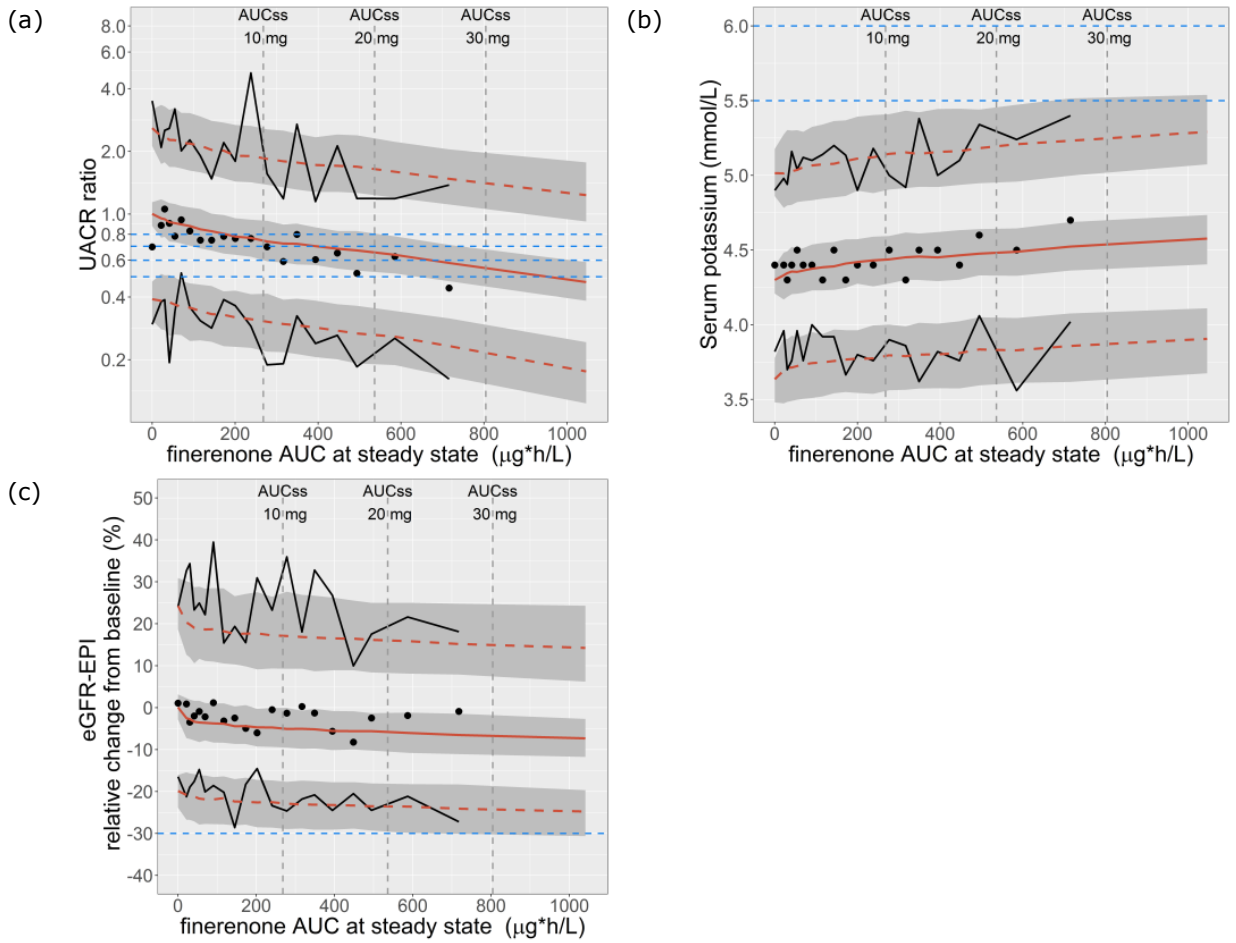
		Minimum LS-Means Difference (Verum – Placebo) [one-sided 95% CI] (time point)	Maximum LS-Means Difference (Verum – Placebo) [one-sided 95% CI] (time point)
QTcF	20 mg finerenone	-1.37 [-Inf, 0.22] (12 h p.d.)	1.17 [-Inf, 3.00] (6 h p.d.)
	80 mg finerenone	-3.40 [-Inf, -1.81] (12 h p.d.)	1.58 [-Inf, 3.48] (0.75 h p.d.)
	400 mg moxifloxacin	8.53 [6.32, Inf] (1 h p.d.)	11.87 [9.95, Inf] (4 h p.d.)
QTcB	20 mg finerenone	-1.37 [-Inf, 1.04] (0.5 h p.d.)	2.13 [-Inf, 4.67] (24 h p.d.)
	80 mg finerenone	-2.00 [-Inf, 0.82] (2 h p.d.)	3.38 [-Inf, 6.00] (0.75 h p.d.)
	400 mg moxifloxacin	10.71 [8.09, Inf] (6 h p.d.)	14.01 [11.39, Inf] (4 h p.d.)
QTcI	20 mg finerenone	-2.22 [-Inf, -0.44] (12 h p.d.)	0.45 [-Inf, 2.22] (6 h p.d.)
	80 mg finerenone	-3.56 [-Inf, -1.78] (12 h p.d.)	1.61 [-Inf, 3.45] (0.75 h p.d.)
	400 mg moxifloxacin	8.57 [6.75, Inf] (6 h p.d.)	12.24 [10.30, Inf] (4 h p.d.)
QT	20 mg finerenone	-4.79 [-Inf, -1.77] (3 h p.d.)	1.72 [-Inf, 4.33] (6 h p.d.)
	80 mg finerenone	-6.72 [-Inf, -3.88] (12 h p.d.)	1.85 [-Inf, 4.37] (2 h p.d.)
	400 mg moxifloxacin	3.98 [1.26, Inf] (1 h p.d.)	9.07 [6.29, Inf] (4 h p.d.)
VR	20 mg finerenone	-0.59 [-Inf, 0.78] (1 h p.d.)	2.00 [-Inf, 3.41] (3 h p.d.)
	80 mg finerenone	-0.96 [-Inf, 0.29] (2 h p.d.)	2.47 [-Inf, 3.99] (36 h p.d.)
	400 mg moxifloxacin	0.94 [-0.42, Inf] (6 h p.d.)	2.07 [0.67, Inf] (1 h p.d.)

Exposure – response relationship for UACR, eGFR, and serum potassium in ARTS-DN

ER relationships were investigated based on ARTS-DN data and ARTS-DN Japan employing indirect response models for UACR, eGFR, and serum potassium. The ARTS-DN studies included a range of fixed finerenone doses (0-20 mg).

The concentration–effect relationship over time for the efficacy marker UACR was characterised by a maximum effect model indicating saturation of effect at high exposures. For the safety markers, a log-linear model and a power model were identified for serum potassium concentration and eGFR, respectively. The model-predicted times to reach the full (99%) steady-state drug effect on UACR, serum potassium, and eGFR were 138, 20, and 85 days, respectively. The PK half-life was 2–3 h and PK steady-state was achieved after 2 days, indicating timescale separation. A visualisation of the ER relationships is presented in *Figure 6*. Neither the concentration-effect relationship for the efficacy marker nor that for the safety markers is considered steep. There was no apparent ethnic effect on the investigated PK/PD relationships when comparing data from ARTS-DN and ARTS-DN Japan.

Figure 7: Predicted and observed (a) UACR ratio, (b) absolute serum potassium concentration, and (c) relative change from baseline in eGFR-EPI vs finerenone AUCT,md (=AUCss).



The model was fitted to individual data. For plotting purposes, the data were binned in 20 categories based on equal numbers of records.

Blue dashed lines: reference/threshold lines; dark gray dashed lines: simulated AUC_{SS} for a typical subject for doses of 10, 20, and 30 mg; black solid lines: 5th and 95th percentiles of the observations; black dots: medians of the observations; red solid line and dashed lines: median predictions and 5th and 95th percentiles of the predictions; gray areas: 90% CIs of the median and 5th and 95th percentiles.

AUC_{SS} = area under the curve at steady-state (=$AUC_{\tau,md}$), CI = confidence interval, eGFR = estimated glomerular filtration rate, eGFR-EPI = eGFR calculated using the 'CKD epidemiology collaboration' formula, UACR = urinary albumin-to-creatinine ratio

Source: (Snelder et al. 2020) based on Module 5.3.3.5, Report R-9603, Figure 8.2:15, Figure 8.3:16, and Figure 8.4:17

ARTS-DN demonstrated a dose-dependent reduction in UACR with finerenone as an adjunct to RAS inhibitor therapy over 90 days of treatment. Statistically significant reductions compared to placebo of 21%, 25%, 33% and 38% were observed with the 4 highest doses investigated: 7.5 mg, 10 mg, 15 mg, and 20 mg OD, respectively. UACR did not return back to baseline after treatment discontinuation. Subgroup analyses by eGFR at baseline revealed no relevant differences. There was a small reduction in mean eGFR from baseline to Visit 5 (Day 90±2), especially at the finerenone 10 mg OD to 20 mg OD dose range. Mean eGFR then showed a tendency to return towards baseline values at the follow-up visit (30±5 days after the last intake of study drug) in these finerenone dose groups.

Exposure – response in FIDELIO-DKD

Exposure – time-to-event analyses for the primary renal and key secondary cardiovascular composite endpoints of FIDELIO-DKD were performed. Using parametric time-to-event models with E_{max} models for the exposure-driven drug effect, these analyses indicate that patients with higher finerenone show a slightly stronger reduction of the risk for a primary and secondary endpoint event than patients with lower finerenone exposure. The E-R relationships based on the FIDELIO-DKD data indicate that several

patient factors influence the renal and cardiovascular hazard independently of finerenone treatment. Among them are known risk factors like high UACR and low eGFR, but also co-medications such as SGLT2is that decrease the hazard for the primary endpoint by 28.2% (95%CI: 11.8-44.5%).

2.6.3. Discussion on clinical pharmacology

Pharmacokinetics

Finerenone clinical development programme consisted of 34 clinical studies in total. The applicant has conducted 28 Phase I clinical studies to obtain necessary clinical pharmacology data for finerenone. In addition to clinical data, *in vitro* and *in silico* analyses were done to address relevant Clinical Pharmacology aspects. Overall, the Pharmacokinetic (PK) properties are well described by the applicant and sufficient data are generated to describe its disposition, PK in special patient populations, drug-drug interaction (DDI) potential.

In the phase 3 study (FIDELIO-DKD) the dose was titrated based on serum potassium levels and eGFR was employed. The predicted exposure range in FIDELIO-DKD at steady-state was Cmax 57-238 µg/L (5^{th} and 95^{th} quantiles for 10 mg and 20 mg, respectively) and AUC 229-1123 µg.h/L (5^{th} and 95^{th} quantiles for 10 mg and 20 mg, respectively), which is considered the therapeutic exposure range where efficacy and safety have been studied. No exposure data is available in patients with severe hepatic impairment or in patients with concomitant strong CYP3A4 inhibitors. However, it is anticipated that the exposure in these patients will exceed the therapeutic exposure range and as such the applicant's proposal to avoid treatment in severe HI patients and in patients with concomitant use of strong CYP3A4 inhibitors is supported.

Pharmacokinetic properties

PK properties of finerenone were adequately and well-investigated within several phase I studies and many popPK models have been developed to further investigate PK profile of the drug in phase I, II and III studies. In addition, a PBPK models has been developed.

During clinical development, two IR tablet formulations have been used, namely the "Phase I-IIa" tablets and the "Phase IIb-III" tablets. Such clinical formulations present only minimal quantitative differences within the tablet's core composition, while minor differences can be found in the film-coating, which excipients are not expected to influence the dissolution rate. Both core composition and total amount of pigment in the film-coat are identical between the clinical "Phase IIb/III" tablet formulation and the proposed commercial product, whereas minimal differences exist both in the ratio of pigments in the film-coat and one pigment itself.

Interactions

Several issues were noted within the *in vitro* DDI experiments which needed to be further addressed in order to be able to exclude risk for a clinically relevant DDIs.

In the *in vitro* CYP induction experiment (PH-39130) no stability data were found for finerenone during the incubations with hepatocytes (i.e., only nominal finerenone concentrations were provided). Stability data were provided upon request and were sufficient to make conclusions about the CYP induction effects.

In vitro experiment (R-9574) investigated finerenone as a potential substrate of OATP1B1 and OATP1B3 transporters at two concentrations of 0.5 and 5 µM (i.e. all concentrations were above the clinical concentration range) and was therefore considered inadequate and inconclusive as too high concentration of the investigational drug might saturate transporters in question. Therefore, new substrate experiments with the hepatic OATP1B1 and OTP1B3 transporters were performed including

lower finerenone concentrations, which were in line with the Appendix III of the EMA DDI guideline. New experimental data have confirmed that finerenone is not a substrate of OATP transporters.

Of further note, new clinical DDI study denoted as Study 21429 was completed and presented after the initial marketing authorisation application was submitted. This clinical study which included rosuvastatin as the "victim drug" (OATPs and BCRP substrate) has provided additional DDI data which excluded an interaction risk with finerenone as a potential inhibitor of OATPs and BCRP transporters.

Population pharmacokinetic analyses

PopPK analyses were used to throughout the clinical drug development to propagate PK knowledge across the development stages, which is an approach that is highly supported. The popPK analyses considered relevant for this submission are the analyses of phase 2b and phase 3 data.

The phase 2b analysis (ARTS-DN global and Japan studies) contained a range of finerenone fixed doses (1.25 mg – 20 mg), and as such the exposure range could provide valuable information in the subsequent E-R analysis. The final model could describe the PK sufficiently well and the shrinkage values (<30%) indicate that the predicted exposure were adequate for the E-R analysis. The only formally tested covariate was ethnicity (Japanese/non-Japanese), and no statistically significant difference was detected in clearance or volume of distribution which can be translated to no difference in AUC or C_{max}, respectively.

A popPK analysis was also performed on the (sparse) PK data collected in the confirmatory FIDELIO-DKD study, with the main objectives to evaluate covariate factors for PK and derive exposure predictions to be used in exposure-response analyses. The model diagnostics and evaluations indicate that the model can describe the data reasonably well (some under-prediction is noted), and as such the exposure predictions could be used in the exposure-response analyses. There is some uncertainty in the accuracy of the dosing history in the popPK dataset since individual administrations only seem to be available at visit 3, 5, 8, 11 and 14, and the fact that treatment interruptions and dose titration were allowed throughout the study.

Correlated covariates have been tested in the development and further included in the final model, i.e. eGFR, height and creatinine on V/F. When correlated covariates are included in the model, the magnitude covariate effects are not independent and the effect of a single covariate (e.g. height) should be interpreted with caution. This was considered in simulations considering multivariate covariate distributions. In addition, Korean ethnicity was identified as a significant covariate although only 54 Korean subjects (2.4%) were included in the analysis so it is highly questionable whether reliable information regarding ethnicity can be derived from such a small sample. In future analyses, the applicant is strongly recommended to make pre-specified decisions to include only one of several correlated covariates as well as a restriction on the minimum number of subjects (or proportion of data) for a covariate to be tested to avoid selection-bias and correlated covariate effects. Nonetheless, the effect of body weight on V/F and eGFR on CL/F were similar across analyses (phase 1-3) which gives some reassurance that these effects are reliable. Nevertheless, due to the titration-based dosing based on potassium levels and kidney function, the covariate effects are considered of less importance and thus the covariate model deficiencies are not further pursued.

In conclusion, the population PK analysis of FIDELIO-DKD data is considered to have low impact of the finerenone label, hence improvements of the analysis are not perceived to influence the dosing recommendation of finerenone.

Pharmacodynamics

Finerenone is a novel, non-steroidal mineralocorticoid receptor (MR) antagonist. Several pathological conditions, including hyperglycaemia, are associated with MR receptor over-activation which promotes

cardiovascular and renal inflammatory and fibrotic processes. The previously approved MR-antagonists (MRA) spironolactone and eplerenone are associated with hyperkalaemia. In addition, spironolactone has anti-androgenic effects.

According to the applicant, finerenone has properties that may provide renal protection with a lower risk for hyperkalaemia compared to spironolactone and eplerenone. The applicant claims that unlike eplerenone and spironolactone, a differential modulation can be exerted by finerenone across the spectrum of MR activities depending upon its tissue distribution, as well as potency and selectivity toward MR, all of them determined by its molecular structure. Specifically, the non-steroidal nature of the compound is believed to make treatment with finerenone more advantageous than therapy with the mentioned steroidal MRA by promoting a higher degree of protection against pro-fibrotic mechanisms while reducing the risk of the hyperkaliaemic effect. The applicant's argument is not sustained by experimental data, since preclinical mass balance studies did not characterise the organ distribution of finerenone relative to commercially available MR antagonists, and human ADME investigations only provided information on excretory pathways. Moreover, clinical PD investigations in Phase 2 trials comparing finerenone with either spironolactone or eplerenone revealed similarity in terms of both efficacy and safety parameters. Therefore, the advantage of finerenone over spironolactone or eplerenone is not considered proven.

The first-in-man single dose escalation study (Study 13782) investigated oral doses of 1, 2.5, 5, 10, 20 and 40 mg finerenone. No effects on blood pressure, heart rate and the RAAS system or related electrolyte changes was observed, which may be expected given the short exposure time of finerenone. The effects of aldosterone are those on renal electrolyte handling where the hormone acts to secrete potassium while increasing sodium reabsorption. The effect on sodium reabsorption acts to increase blood pressure via an increased extracellular volume. This is a relatively slow process that is involved in the long-term regulation of blood pressure and electrolyte homeostasis. Acute MR inhibition as in the present study with finerenone is therefore not expected to have a great impact on these parameters. In line with this, no effects on the RAAS system or related electrolyte changes were observed. This study is therefore mainly important from a safety perspective, where it showed that the finerenone was safe and tolerable in the dose range tested. The absence of PD effects also indicates that finerenone does not have any acute secondary pharmacological effects on the cardiovascular system.

The multiple dose escalation study (Study 13785) investigated doses of 10-20 mg twice daily and 40 mg film-coated tablet once daily for 10 days increased plasma renin and aldosterone hormone levels which are expected findings during MR-antagonism. There was no clear dose dependency of the effect. No consistent effects on electrolyte excretion were observed. In this model in healthy volunteers, the effects on electrolytes are complex due to the concomitant increase in plasma renin. The study showed that finerenone is safe and tolerable after repeated administration. Furthermore, the observed changes are in line with the mode of action of finerenone as a MR antagonist.

Study 13786 was a mechanistic proof of concept study. A dose of fludrocortisone was administered in order to increase basal sodium reabsorption whereupon different doses of finerenone or eplerenone 50 mg was administered. Both agents caused an increased Na^+/K^+ ratio and reduced urine potassium concentration. Although these effects are undesirable in the context of treatment of CKD, the findings provide clinical evidence for the mode of action of finerenone as an MR-antagonist. The desirable effects of finerenone, i.e. protection of the kidneys and the CV system cannot be assessed in this short timeframe. The study provides clinical evidence for the mode of action of finerenone. Furthermore, the study indicates that finerenone has potential to cause hyperkalaemia.

Any QT-prolongating effect of finerenone is unlikely based on absence of prolonged interval in preclinical studies and the thorough QT-study.

Exposure-response

The ER relationships based on the phase 2b studies are considered most useful for this submission. The ARTS-DN studies included a wide range of fixed (no titration) doses which enable an adequate analysis of the E-R relationships.

A range of fixed doses (0 – 20 mg QD) were included in the ARTS-DN studies, thus the data are considered adequate for assessing E-R relationships. No covariates were detected on the concentration-response relationships, although a difference in inter-individual variability between Japanese and non-Japanese patients was identified for all endpoints. A decrease in UACR with increasing plasma exposure was identified. Descriptive results indicate an effect of finerenone on UACR independently on renal filtration in a short-term evaluation setting. No meaningful clinical differences can be observed to explain the inter-ethnic differences in response. However, an increased use of beta-blockers (46.7% vs 7.3%) and diuretics (66.9% vs 20.8%). Among anti-hypertensive medications, their marked effect on aldosterone level is well described; in line with this, a higher level of aldosterone at baseline is observable in the ARTS-DN study versus the Japanese study (mean values: 55.45±45.51 vs 20.48±18.5, with median values: 44.35 pg/ml vs 13.18). However, literature data from studies on eplerenone and spironolactone have not shown a significant correlation between baseline aldosterone levels and treatment response. Whether the same applies to finerenone is uncertain. However, the low sample sizes (12 subjects per treatment arm) limit further interpretation. Furthermore, E-R relationships were described for potassium and eGFR, where an increase in potassium levels with increasing plasma concentrations, and a decrease in eGFR with increasing plasma exposure were identified, respectively. No covariates were detected for either relationship.

In the ARTS-HF study, the MDRD formula was used for eGFR calculation. Currently, the eGFR-EPI-based calculation is preferred due to high accuracy in estimating preserved renal function (eGFR≥60 mL/min/1.73m^2). In the response to questions the applicant has provided reassurance on the correspondence between the concentration-effect relationships of the effect of finerenone with eGFR as measured by either MDRD or EPI formula.

Due to the potassium and eGFR-based dose-titration in the FIDELIO-DKD study, the E-R relationships may be influenced by the titration-scheme of the study, thus it should be interpreted with caution. Also, and it should be noted that the E-R relationships are only valid within this study design, dose range, and corresponding titration scheme. In conclusion, the E-R analyses based on FIDELIO-DKD data are not considered meaningful.

Overall, the identified E-R relationships for eGFR and serum potassium, based on ARTS-DN studies, are shallow over the therapeutic exposure range indicating that a change in exposure lead to a small change in eGFR and serum potassium. The justification for the dosing regimen is further discussed in the Clinical efficacy section.

2.6.4. Conclusions on clinical pharmacology

Pharmacokinetic aspects of finerenone are generally well described. The applicant has presented clinical data on electrolyte handling and RAAS hormones that support the intended mode of action of finerenone as a MR-antagonist. Data on electrolyte handling indicate that finerenone has potential to cause hyperkalaemia. A QT-prolongating effect of finerenone is unlikely based on the thorough QT-study. There is a shallow exposure-response relationship for finerenone in the different tested clinical settings.

2.6.5. Clinical efficacy

This application is based on efficacy data obtained from the following studies:

- Two Phase II dose finding studies: ARTS-DN & ARTS-DN Japan (Study 16243 & 16816),
- The pivotal Phase III study: FIDELIO-DKD (Study 16244)
- Supportive data from the ARTS-HF (Study 14564), ARTS-HF Japan (Study 16815) and ARTS (Study 14563) conducted in patients with chronic heart failure

An overview of the clinical development programme is given in Table 3, above.

2.6.5.1. Dose response studies

The clinical development programme comprised two phase II dose-finding studies in the target population for the sought indication.

ARTS-DN (Study 16243)

Design

The ARTS-DN study was a Phase 2b, randomised, adaptive, double-blind, placebo-controlled, parallel-group, multi-centre study with a planned treatment duration of 90 days.

Methods

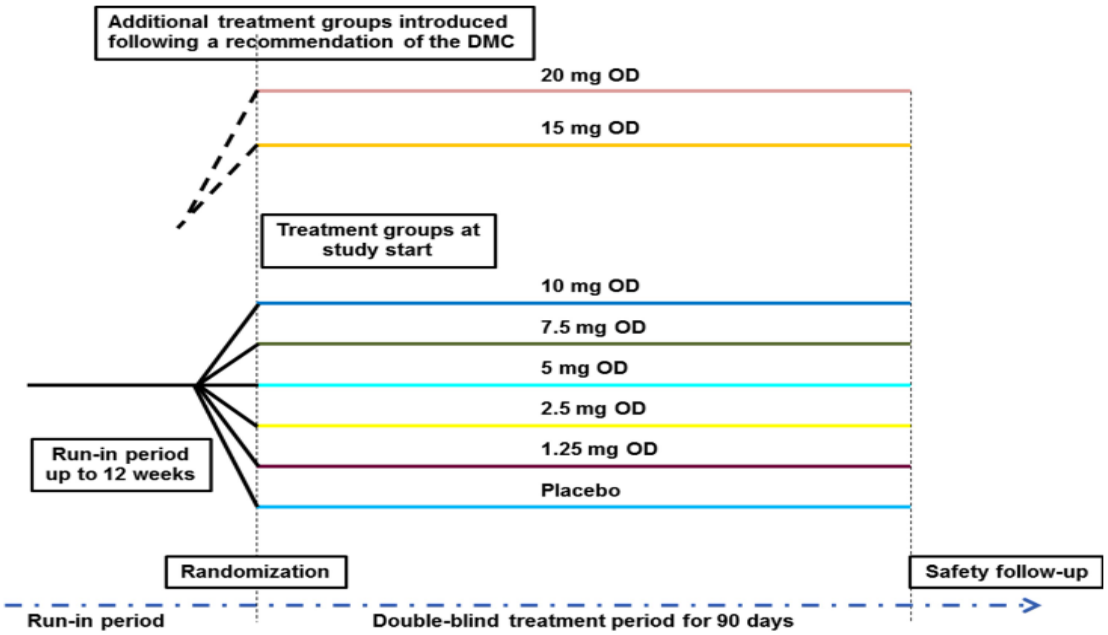
Participants were male and female subjects (≥18 years of age) with type 2 diabetes mellitus and a clinical diagnosis of DN treated with an ACEI and/ or ARB for at least 3 months; subjects with an eGFR of 30-45 mL/min/1.73m^2 according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation must also be treated with a non-potassium sparing diuretic at screening. Serum potassium should be ≤4.8 mmol/L at screening. The clinical diagnosis of DN must be based on at least one of the following criteria:

- Persistent very high albuminuria defined as UACR of ≥300 mg/g (≥34 mg/mmol) in 2 out of 3 first morning void samples and estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m^2 but < 90mL/min/1.73 m^2 (CKD-EPI) or
- Persistent high albuminuria defined as UACR of ≥30 mg/g but <300 mg/g (≥3.4 mg/mmol but <34 mg/mmol) in 2 out of 3 first morning void samples and eGFR ≥30 mL/min/1.73 m^2 but < 90mL/min/1.73 m^2 (CKD-EPI)

The primary objective of this study was to investigate the change in UACR from baseline to day 90 after treatment with different oral doses of finerenone given once daily.

Following an open-label run-in and screening period of up to 12 weeks, eligible subjects were randomised to one of 7 doses of finerenone or placebo on top of standard of care to receive a 90-day study drug treatment. Initially, the following 5 doses of finerenone and placebo were administered in a double-blind manner: 1.25 mg, 2.5 mg, 5mg, 7.5 mg, and 10 mg OD. After the safety and tolerability of these doses had been assessed by an independent DMC, 2 further doses of finerenone - 15 mg and 20 mg OD - were introduced (*Figure 7*).

Figure 8. Study design of ARTS-DN.



Results

In total 1501 subjects were randomised at 128study centres in 23 countries worldwide. Of the 823 subjects randomised, 2 (0.2%) subjects did not receive any study drug; the remaining 821 randomised and treated subjects made up the safety analysis set (SAF). Of the 821 subjects in the SAF, 812 subjects (98.7%) had at least one post-baseline UACR value and were thus valid for the FAS. Of the 812 subjects in the FAS, 687 subjects (83.5%) had no major protocol deviations and were thus valid for the PPS.

764 (92.8%) of the 821 subjects in the SAF completed the treatment phase. The remaining 59 subjects discontinued study drug, 35 of these due to AEs.

Baseline characteristics

In the SAF and FAS, the treatment groups were comparable with respect to demographic characteristics. In the SAF, male subjects accounted for 71 to 85% of each treatment group; most subjects were white (from 82 to 88%) and median age ranged from 63 to 66 years across treatment groups. Over half of the subjects (58%) in the SAF had a BMI of >30 kg/m^2; 61% of subjects were former or current cigarette smokers, and most subjects (>85% in each treatment group) reported abstinence from alcohol or light alcohol use.

Baseline UACR and numbers of subjects with high (<300 mg/g) and very high (≥300 mg/g) albuminuria at screening were consistent across the treatment groups; 503 subjects (61.3%) had high albuminuria and 318 subjects (38.7%) had very high albuminuria at screening. Overall, medical history findings were similar across treatment groups. In accordance with inclusion criteria, the study population was subjects with type 2 diabetes mellitus and clinical diagnosis of DN based on high or very high albuminuria; in addition, 774 subjects (94.3%) had hypertension. Other medical history findings reported in ≥20% of subjects in the SAF were obesity, dyslipidaemia, hyperlipidaemia, hypercholesterolaemia, diabetic retinopathy, and diabetic neuropathy. Reports of prior use (i.e. that started and ended before administration of study drug) of medications of interest (i.e. ACEIs, ARBs, beta-blockers, diuretics, potassium supplements, alpha blocking agents, calcium channel blockers, centrally-acting antihypertensives and strong, moderate, and weak CYP3A4 inhibitors, CYP3A4 inducers, and CYP2C8 inhibitors) were balanced across treatment groups. The most frequently

reported prior medication of interest was diuretics, taken by 42 subjects (5.1%). Diuretics were also the most commonly reported concomitant medication of interest (reported by 68.8% of subjects), followed by calcium channel blockers, ARBs, beta-blockers, ACEIs, CYP3A4 inducers, and weak CYP3A4 inhibitors. Use of concomitant and new (i.e. started after start of study drug) concomitant medications of interest was generally balanced across treatment groups.

Efficacy

The primary efficacy variable demonstrated a dose-dependent reduction in the ratio of UACR at Day 90 to UACR at baseline with finerenone compared to placebo. An ANCOVA demonstrated statistically significant reductions in UACR compared with placebo with the 4 highest finerenone treatment groups (i.e. 7.5 mg, 10 mg, 15 mg, and 20 mg OD groups), with larger effects seen with increasing dose in those 4 treatment groups (*Table 12*). The placebo-corrected reduction in UACR was 21%, 25%, 33%, and 38% in the finerenone groups respectively. The treatment effect in these higher dose groups appeared to increase over time, with an effect already being observed at Visit 3 (Day 30±2) and Visit 4 (Day 60±2), but with the greatest treatment effect (i.e. the smallest ratio to baseline) being observed at Visit 5 (Day 90±2) (except for the finerenone 10 mg OD group, for which the greatest change was observed at Visit 4 [Day 60±2]). The geometric mean UACR levels had not returned to baseline values for these dose groups 30 days after completion of treatment, with an approximately 16% reduction in UACR relative to baseline observed at Day 120 in the finerenone 20 mg OD arm compared to placebo.

A slightly lower treatment effect was seen in the very high albuminuria group (UACR ≥300 mg/g) than in the high albuminuria group (UACR ≥30 mg/g but <300mg/g)(*Table 13*). A summary of LS-mean change from baseline in serum potassium is given in *Table 11*. Compared to placebo, serum potassium was significantly increased in all dose group 90 days after start of treatment without a clear dose-dependency.

Potassium ≥5.6 mmol/L that was confirmed on re-test within 48 h leading to subsequent discontinuation of study drug was defined as AE of special interest in this study. 12 subjects (1.5%) reported such an AE, all in the finerenone group without a clear dose-dependency.

Table 11. Summary of ANCOVA for change from baseline to Visit 5 (Day 90±2) of serum potassium (mmol/L)(safety analysis set).

Analysis visit	p-value for main factors[a]	Actual Treatment	N	LS-mean change from baseline	95% CI of change from baseline	LS mean Difference Finerenone - Placebo	95% CI of Difference Finerenone - Placebo	p-value for treatment difference[b]
Visit 5 (Day 90±2)	0.0003; 0.8093; 0.1999							
		Placebo	90	0.002	[-0.077; 0.081]			
		1.25 mg OD	90	0.109	[0.030; 0.187]	0.107	[0.003; 0.210]	0.0428
		2.5 mg OD	87	0.123	[0.043; 0.203]	0.121	[0.017; 0.225]	0.0223
		5 mg OD	85	0.202	[0.122; 0.282]	0.200	[0.096; 0.305]	0.0002
		7.5 mg OD	88	0.127	[0.047; 0.207]	0.125	[0.021; 0.229]	0.0181
		10 mg OD	87	0.167	[0.087; 0.248]	0.166	[0.061; 0.270]	0.0019
		15 mg OD	109	0.238	[0.165; 0.310]	0.236	[0.137; 0.334]	<.0001
		20 mg OD	112	0.188	[0.116; 0.259]	0.186	[0.088; 0.284]	0.0002

ANCOVA with factors treatment group, type of albuminuria at screening, and region, and baseline value as covariate.
[a] F-test of equal means between the factor levels: treatment; type of albuminuria at screening; region (in that order).
[b] Two-sided t-test of difference finerenone - placebo equals zero.
In cases where a sample was repeated within 7 days after the scheduled sample: If the potassium value from the repeated sample was ≥5.6 mmol/L, the higher of the two values (values from the original and the repeated samples) was used.
If the value from the repeated sample was <5.6 mmol/L, this value was used for analysis. In cases where the repeated sample was more than 7 days after the scheduled sample, the initial sample was used for analysis.
Centrally analyzed samples >6.0 mmol/L not confirmed by the locally analyzed sample (<5.6 mmol/L) were not considered for analysis.
Source: Table 14.3.4 / 79

Table 12. UACR - Summary of ANCOVA for ratio to baseline on Day 90 - FAS, ARTS-DN.

Treatment	N	LS mean ratio to baseline	90% CI of ratio to baseline	LS mean ratio finerenone / placebo	90% CI of ratio finerenone / placebo	p-value for treatment ratio[a]
Placebo	94	0.938	[0.829; 1.061]			
1.25 mg OD	96	0.869	[0.772; 0.979]	0.926	[0.799; 1.074]	0.1973
2.5 mg OD	92	0.890	[0.786; 1.009]	0.949	[0.818; 1.101]	0.2808
5 mg OD	98	0.824	[0.730; 0.929]	0.878	[0.758; 1.017]	0.0723
7.5 mg OD	96	0.739	[0.653; 0.835]	0.787	[0.680; 0.912]	0.0039*
10 mg OD	96	0.708	[0.627; 0.800]	0.755	[0.651; 0.875]	0.0009*
15 mg OD	123	0.630	[0.563; 0.705]	0.671	[0.584; 0.772]	<0.0001*
20 mg OD	117	0.585	[0.523; 0.654]	0.624	[0.542; 0.718]	<0.0001*
p-value for linear contrast[b]		*<.0001 **				
p-value for main factors[c]		*<.0001; 0.2167; 0.8235*				

a One-sided t-test of ratio finerenone/placebo equals 1.
b One-sided F-test for linear contrast equals zero.
Linear contrast: (6.125, 5.125, 4.125, 2.125, 0.125, -1.875, -5.875, -9.875).
c F-test of equal means between the factor levels: treatment; type of albuminuria at screening; region (in that order).
* Significant at a one-sided significance level of 5%.
ANCOVA with factors treatment group, type of albuminuria at screening and region and log-transformed baseline value as covariate nested within type of albuminuria at screening.
The UACR was determined 3 times at each visit from first morning void urine samples collected on 3 consecutive days; if only one UACR measurement at a visit was available, then this measurement was not used for analysis.
ANCOVA = analysis of covariance, ARTS = minerAlocorticoid-Receptor antagonist Tolerability Study, DN = diabetic nephropathy, CI = confidence interval, LS mean = least squares mean, FAS = full analysis set, OD = once daily, UACR = urinary albumin-to-creatinine ratio
Source: Module 5.3.5.1, Report PH-37857, Table 14.2/22

Table 13. Summary statistics for UACR (g/kg) ratios to baseline at Visit 5 (Day 90±2) by type of albuminuria at screening (full analysis set).

	n	Geom. mean	Geom. SD	Geom. CV(%)	Min	Median	Max
High albuminuria (UACR ≥30 mg/g but <300 mg/g)	463	0.76	1.92	72.81	0.1	0.76	12.6
Placebo	58	1.00	1.91	72.39	0.2	0.93	12.6
1.25 mg OD	53	0.88	1.79	63.27	0.3	0.81	3.2
2.5 mg OD	53	0.91	1.70	57.34	0.2	0.84	3.7
5 mg OD	55	0.84	2.02	80.19	0.1	0.83	7.4
7.5 mg OD	58	0.76	1.90	71.25	0.2	0.77	3.4
10 mg OD	48	0.68	1.92	73.03	0.1	0.65	3.7
15 mg OD	71	0.61	1.82	65.85	0.2	0.66	3.3
20 mg OD	67	0.58	1.92	73.03	0.1	0.63	3.1
Very high albuminuria (UACR ≥300 mg/g)	288	0.76	1.89	70.52	0.0	0.79	6.2
Placebo	30	0.83	2.22	94.50	0.0	0.90	3.8
1.25 mg OD	37	0.88	1.71	57.97	0.2	0.90	2.3
2.5 mg OD	33	0.88	2.33	102.30	0.0	0.89	6.2
5 mg OD	33	0.90	1.89	71.00	0.2	0.97	2.6
7.5 mg OD	29	0.73	1.74	59.80	0.1	0.73	2.3
10 mg OD	39	0.76	1.49	41.44	0.2	0.77	2.3
15 mg OD	42	0.68	1.74	59.79	0.2	0.70	1.9
20 mg OD	45	0.60	1.90	71.33	0.1	0.61	3.2

UACR = Urinary albumin-to-creatinine ratio. The UACR was determined 3 times at each visit from first morning void urine samples collected on 3 consecutive days and summarized according to the SAP.
For Visit 1 (Day 1; baseline), only measurements taken prior to the first intake of study drug were used. If only one UACR measurement at a visit was available, then this measurement was not used for analysis.
Source: Table 14.2 / 2

ARTS-DN Japan (Study 16816)

Design

The ARTS-DN Japan study was a Phase 2b, randomised, adaptive, double-blind, placebo-controlled, parallel-group, multi-centre study with a planned treatment duration of 90 days with a similar design as ARTS-DN but in a Japanese population.

Methods

Participants were male and female subjects (≥18 years of age) with type 2 diabetes mellitus and a clinical diagnosis of DN. This study used the same inclusion criteria as described above for the ARTS-DN study.

The primary objective was to investigate the change of urinary albumin-to-creatinine ratio (UACR) after treatment with different oral doses of finerenone given once daily from baseline to Day 90.

Following a run-in and screening period of up to 12 weeks in total, eligible subjects were randomised to 1 of up to 7 doses of finerenone or placebo on top of standard of care to receive a 90-day study drug treatment.

No stratification for randomisation was considered. However, a ratio of approximately 50:50 for high and very high albuminuria was planned to be reached.

Initially, the following 5 doses of finerenone were to be compared to placebo in a double-blind manner: 1.25 mg, 2.5mg, 5mg, 7.5 mg, and 10mg once daily. After safety and tolerability of these doses had been assessed by an independent Data Monitoring Committee, none or 1 higher dose arm of finerenone 15 mg once daily could be introduced (the first dose recommendation meeting).

If the higher dose arm (15 mg finerenone once daily) was introduced, the second dose recommendation meeting was to assess safety and tolerability of all dose arms including the newly introduced 15mg finerenone dose arm and decide if the highest dose arm (20mg finerenone once daily) was allowed to be introduced to the study or not.

Results

A total of 120 subjects were enrolled and screened for their eligibilities for the study; 24 subjects failed screening and were not randomised, and 96 subjects were assigned to the study treatment. All the 96 subjects who were randomised took at least one study medication and were valid for safety analysis. Of the 96 subjects in the SAF, 95 subjects (99.0%) were valid for the FAS and 90 subjects (93.8%) were valid for the PPS.

A total of 93 (96.9%) of the 96 subjects in the SAF completed the treatment phase. The remaining 3 randomised subjects discontinued study drug prematurely, 1 of these due to AEs.

<u>Baseline characteristics</u>

The distribution of demographic and baseline characteristics was generally similar across treatment groups. Overall, 80.2% of subjects were men. The mean age as a whole was 62.95 years with a range of 41 to 83 years. Most subjects (76 subjects [79.2%]) had a BMI of ≤30 kg/m2.

Overall, 51 subjects (53.1%) had high albuminuria and 45 subjects (46.9%) had very high albuminuria at screening. Their distribution was imbalanced in some treatment groups (2.5 mg, 7.5mg and 20mg once daily [OD] groups) because of the limited number of subjects.

Overall, medical history findings were similar across treatment groups. In accordance with inclusion criteria, the study population was subjects with type 2 diabetes mellitus and albuminuria. In addition, 92 subjects (95.8%) had hypertension.

Reports of prior use of medications of interest were balanced across treatment groups. An ARB was the most commonly reported concomitant medication of interest (reported by 90.6% of subjects), followed by (in descending order of frequency) calcium channel blockers, weak CYP3A4 inhibitors, and diuretics. Other baseline characteristics (i.e. levels of potassium, creatinine, eGFR, BNP, aldosterone, NT-proBNP, galectin-3, cystatin C, troponin T, and vital signs findings) were similarly distributed across the treatment groups and among the populations analysed.

Efficacy

The primary efficacy analysis indicated a nominally significant effect of finerenone on the ratio of UACR at Visit 8 (Day 90±3) to UACR at baseline (primary efficacy endpoint) when adjusting for type of albuminuria at screening, and including the log-transformed baseline UACR as a covariate nested within type of albuminuria at screening (nominal p-value for the linear contrast = 0.0314). Pairwise comparisons of each of the finerenone dose groups with placebo resulted in nominally statistically significant differences from placebo for the highest treatment group (i.e. 20mg OD). (*Table 14*)

Table 14. UACR - Summary of ANCOVA for ratio to baseline on Day 90 - FAS, ARTS-DN Japan Study 16816 (Phase 2b).

Treatment	N	LS mean ratio to baseline	90% CI of ratio to baseline	LS mean ratio finerenone / placebo	90% CI of ratio finerenone / placebo	p-value for treatment ratio[a]
Placebo	12	1.062	[0.824; 1.369]			
1.25 mg OD	12	0.937	[0.730; 1.203]	0.882	[0.639; 1.219]	0.2610
2.5 mg OD	12	0.938	[0.730; 1.206]	0.884	[0.639; 1.221]	0.2633
5 mg OD	12	0.918	[0.707; 1.192]	0.865	[0.627; 1.192]	0.2266
7.5 mg OD	11	0.745	[0.574; 0.967]	0.702	[0.505; 0.975]	0.0383
10 mg OD	12	0.825	[0.618; 1.102]	0.777	[0.560; 1.078]	0.1019
15 mg OD	12	0.893	[0.704; 1.132]	0.841	[0.607; 1.165]	0.1898
20 mg OD	12	0.712	[0.556; 0.912]	0.670	[0.481; 0.934]	0.0240*
p-value for linear contrast[b]			*0.0314 **			
p-value for main factors[c]			*0.5023; 0.8068*			

a One-sided t-test of ratio finerenone/placebo equals 1.
b One-sided F-test for linear contrast equals zero.
Linear contrast: (6.125, 5.125, 4.125, 2.125, 0.125, -1.875, -5.875, -9.875).
c F-test of equal means between the factor levels: treatment; type of albuminuria at screening (in that order).
* Significant at a one-sided significance level of 5% according to the defined testing strategy.
ANCOVA with factors treatment group, type of albuminuria at screening and log-transformed baseline value as covariate nested within type of albuminuria at screening.
The UACR was determined 3 times at each visit from first morning void urine samples collected on 3 consecutive days; if only one UACR measurement at a visit was available, then this measurement was not used for analysis.
ANCOVA = analysis of covariance, ARTS = minerAlocorticoid-Receptor antagonist Tolerability Study, DN = diabetic nephropathy, CI = confidence interval, LS mean = least squares mean, FAS = full analysis set, OD = once daily, UACR = urinary albumin-to-creatinine ratio
Source: Module 5.3.5.1, Report PH-38022, Table 14.2/23

2.6.5.2. Main study

The application is based on a single pivotal phase III study, FIDELIO-DKD where 5658 patients were treated with either finerenone or placebo.

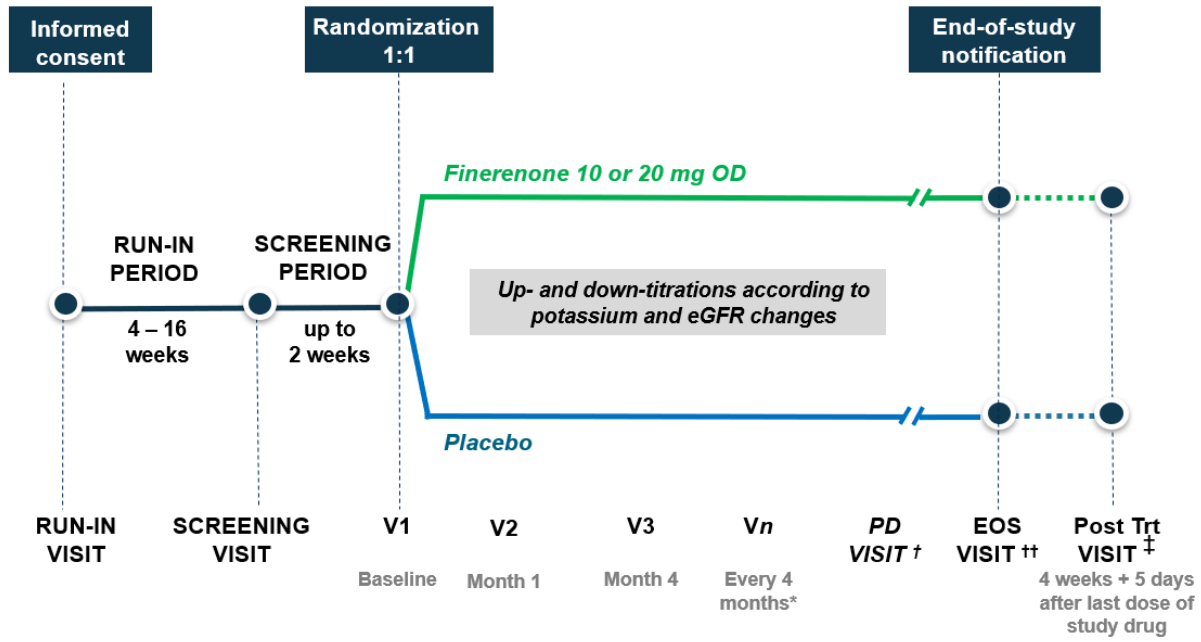
In addition to FIDELIO-DKD, the clinical development programme also includes the FIGARO-DKD phase III study. Compared to FIDELIO-DKD, the primary and main secondary endpoints of FIGARO-DKD have shifted places. Consequently, FIGARO-DKD has a primary CV endpoint whereas the kidney endpoint is the main secondary. The study was recently completed and a high level summary has been submitted with the D120 response. The applicant plans to submit the full results as a future type II variation.

FIDELIO-DKD (Study 16244)

Methods

The FIDELIO-DKD was a randomised, double-blind, placebo-controlled, parallel-group, multicentre, event-driven Phase 3 study to study the efficacy and safety of finerenone in patients with T2D and CKD. A schematic description of the overall study design is given in *Figure 8*.

Figure 9. Overall study design of FIDELIO-DKD.



** 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

- **Study Participants**

Key inclusion criteria

FIDELIO-DKD enrolled subjects with CKD and T2D who were treated with the individual maximum tolerated labelled dose of either an ACEI or an ARB (but not both) and who were eligible for enrolment in this study.

The main criteria for inclusion in FIDELIO-DKD were:

- Men or women ≥18 years of age

- T2D as defined by the American Diabetes Association 2013
- Diagnosis of CKD with at least one of the following criteria at run-in and screening visits:
    - persistent high albuminuria (UACR ≥30 to <300 mg/g in 2 out of 3 first morning void samples) and eGFR ≥25 but <60 mL/min/1.73 m^2 (CKD-EPI) and presence of diabetic retinopathy

      OR

    - persistent very high albuminuria (UACR ≥300 mg/g in 2 out of 3 first morning void samples) and eGFR ≥25 to <75 mL/min/1.73 m^2 (CKD-EPI).
- Prior treatment with ACEIs and ARBs as follows:
    - For at least 4 weeks prior to the Run-in Visit, subjects should be treated with either an ACEI or ARB, or both
    - Starting with the Run-in Visit, subjects should be treated with only an ACEI or ARB
    - For at least 4 weeks prior to the Screening Visit, subjects should be 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
- Serum potassium ≤4.8 mmol/L at both the Run-in and the Screening Visit.

Key exclusion criteria

- Known significant non-diabetic renal disease, including clinically relevant renal artery stenosis
- Uncontrolled arterial hypertension (i.e. mean sitting SBP ≥170 mmHg, sitting DBP ≥110 mmHg at run-in visit, or mean sitting SBP ≥160 mmHg, sitting DBP ≥100 mmHg at screening)
- HbA1c >12%
- Clinical diagnosis of CHF with reduced ejection fraction and persistent symptoms (NYHA class II – IV) at run-in visit (class 1A recommendation for MRAs)
- Stroke, transient ischemic cerebral attack, acute coronary syndrome, or hospitalisation for worsening heart failure, in the last 30 days prior to the Screening Visit
- Dialysis for acute renal failure within 12 weeks of run-in visit
- Renal allograft in place or scheduled within 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.

- **Treatments**

The design of FIDELIO-DKD (*Figure 8*) included a run-in period of 4 to 16 weeks duration to optimize guideline-directed standard of care therapy with RAS inhibitors prior to screening and subsequent randomisation to 2 treatment arms, finerenone and placebo with a dose-titration regimen (*Table 15*). The study used a dosing scheme based on eGFR at screening and the consequent blood potassium concentration throughout the study in order to reach maximum dose without comprising safety. Details for adjustments in relation to blood potassium are given in *Table 16*.

Table 15 Dosage of study drug for administration.

eGFR value at the screening visit, based on central laboratory results:	**25 to <60 mL/min/1.73 m²**		**≥60 mL/min/1.73 m²**	
Subject randomized to group: Receives	**Finerenone** 10 mg OD + standard of care	**Placebo** OD + standard of care	**Finerenone** 20 mg OD + standard of care	**Placebo** OD + standard of care
Study drug intake	One tablet of study drug 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 study drug as soon as possible. • If ≤8 hours of the next scheduled dose, the subject should wait and take the next tablet of study drug at the usual time.			
Up-titration of dose Allowed from visit 2 (month 1) onwards provided that: • potassium was ≤4.8 mmol/L [a] • eGFR decrease was less than 30% below the value measured at the last scheduled visit [a] Had to be documented in eCRF	20 mg finerenone OD, maintain standard of care	Sham-titrate, maintain standard of care	Not applicable	Not applicable
Down-titration of dose Only for safety reasons (see Section 7.4.4.3 for details) Allowed any time during the study (e.g. between scheduled visits) Had to be documented in eCRF An unscheduled safety visit was performed within an adequate timeframe proposed by the investigator	• If at higher dose of study drug, down-titrate to lower dose of study drug, maintain standard of care • If at lower dose of study drug, interrupt study drug, maintain standard of care			

a Potassium and eGFR according to local laboratory values
eGFR = estimated glomerular filtration rate, OD = once daily

Table 16. Dose adjustments in relation to blood potassium.

Blood potassium (mmol/L)	**Action**
First sample:	
≤4.8	If on lower dose of study drug, up-titrate to higher dose. If on higher dose of study drug, continue on the same dose.
4.9 to 5.5	Continue on the same dose.
>5.5	Withhold study drug and re-check potassium within 72 hours.
Second and subsequent samples:	
≤5.0	Re-start study drug at lower dose.
>5.0	Continue to withhold study drug; continue to monitor potassium and restart study drug at the lower dose only if potassium is ≤5.0

Lower dose = 10 mg once daily; higher dose = 20 mg once daily.

- **Objectives and endpoints**

The objectives and endpoints of the study are given in *Table 17*.

Table 17. Objectives and endpoints of FIDELIO-DKD.

Primary objective	**Primary endpoint**
To demonstrate whether, in addition to standard of care, finerenone is superior to placebo in delaying the progression of kidney disease, as measured by 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 time to the first occurrence of the composite endpoint of onset of kidney failure, a sustained decrease of eGFR ≥40% from baseline over at least 4 weeks, or renal death
Secondary objective To determine whether, in addition to standard of care, finerenone compared to placebo:	**Secondary endpoint**
Delayed the time to first occurrence of the following composite endpoint: CV death or non-fatal CV events (i.e. non-fatal MI, non-fatal stroke, hospitalisation for heart failure)	Time to first occurrence of the following composite endpoint: CV death, non-fatal MI, non-fatal stroke, or hospitalisation for heart failure
Delayed the time to all-cause mortality	Time to all-cause mortality
Delayed the time to all-cause hospitalisation	Time to all-cause hospitalisation
The change in 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: onset of kidney failure, a sustained decrease of eGFR ≥57% from baseline over at least 4 weeks, or renal death.	Time to the first occurrence of the following composite endpoint: onset of kidney failure, a sustained decrease in eGFR of ≥57% from baseline over at least 4 weeks, or renal death.

Efficacy endpoints were evaluated by a Clinical Event Committee. Pre-defined disease-related outcome events that were categorised as efficacy variables were kidney failure, renal death, chronic sustained decrease in eGFR, CV death, non-fatal stroke, non-fatal myocardial infarction, heart failure hospitalisation, new onset of atrial fibrillation or atrial flutter and other CV hospitalisation.

Kidney failure was defined as either the occurrence of ESRD or an eGFR of less than 15 mL/min/1.73 m^2, confirmed by a second measurement at the earliest 4 weeks after the initial measurement.

ESRD was defined as the initiation of chronic dialysis (haemodialysis or peritoneal dialysis) for at least 90 days or renal transplantation. In addition, the eGFR threshold of 15 mL/min/1.73 m^2 was consistent with the definition of kidney failure from Kidney Disease Improving Global Outcomes (KDIGO) 2013 and was chosen to include an objective component to the endpoint because the decision to initiate dialysis therapy or kidney transplantation might be affected by factors other than the eGFR.

- **Sample size**

A total of 1068 primary efficacy endpoint events were to imply a minimum 90% power to demonstrate superiority of finerenone to placebo using a log rank test at a two-sided significance level of 3.3333% and assuming a 20% relative risk reduction, i.e. a true hazard ratio of 0.80. For the calculations, a 12% annual event rate for the primary endpoint in the placebo group was assumed based on data from previous clinical studies. The two-sided significance level of 3.3333% (i.e. 2/3 of 0.05) was in alignment with the planned multiple testing procedure. Due to lower than expected recruitment rate, study duration as well as the number of sites were increased within a protocol amendment. Further, due to lower event rates than had been expected, the sample size was in addition increased by 1000 subjects: from initially 4800 to approximately 5800 randomised subjects.

- **Randomisation and Blinding (masking)**

In order to be eligible for randomisation, patients must have completed the run-in period, the purpose of which was to ensure that the subject's SoC therapy including treatment with ACEIs or ARBs was optimised and that all inclusion and exclusion criteria are met at the subsequent screening visit.

Eligible subjects were randomised 1:1 within ≤2 weeks after the screening visit. Randomisation was stratified according to the following:

- 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/1.73 m²)

The number of subjects with eGFR ≥60 to <75 mL/min/1.73 m^2 and very high albuminuria was capped at approximately 10% of the total study population with very high albuminuria at screening.

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.

Finerenone immediate release 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 authorisation 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.

- **Statistical methods**

The approved SAP version 1.0 was dated 03 AUG 2016, version 2.0 was dated 07 JUN 2019, and version 3.0 was dated 12 SEP 2019. The final version of the SAP (version 4.0) was dated 14 FEB 2020. In addition, there exists a supplemental SAP describing post-hoc efficacy and safety analyses. The changes from version 1 to version 2 concerned e.g. the sample size update and the exclusion of subjects from analysis sets due to critical GCP violations. In addition, the significance level which would remain for the final analysis after conducting the interim analysis was specified. The changes made leading to version 3 and version 4 respectively concerned mostly clarifications, corrections, specifications, additions, and deletions whereof none should have had any major impact on the primary analysis of the primary or key secondary endpoints.

Following the original database release on 19 JUN 2020 and before finalisation of the CSR, the database was updated to include, by the applicant, notated as necessary corrections that affected certain analyses of the study. With the re-release (29 JUL 2020) one missing non-fatal ischemic stroke event had been added, which impacted the results for the key secondary CV composite endpoint. Adjudication information on a death case was added with impact on the results for the secondary endpoint all-cause mortality as well as other time-to-event endpoints where the death date was used

as the new censoring date. Further, several missing hospitalisations were added. Of those 5 in the finerenone arm and 8 in the placebo arm became the new first hospitalisation event, which impacted the results for the secondary endpoint all-cause hospitalisation.

The primary analysis was performed on the FAS including all randomised subjects but for subjects with GCP issues. This concerned overall approximately 1% (60/5737) of randomised subjects and a similar number of subjects in each arm.

All the important endpoints but for one, change in UACR at month 4, were time-to event endpoints.

The primary efficacy variable was the time to first occurrence of the composite endpoint of onset of kidney failure, a sustained decrease of eGFR ≥40% from baseline over at least 4 weeks, or renal death. The primary analysis was based on the endpoint events (i.e. first occurrences) from randomisation up until the end-of-study visit that were positively adjudicated by an independent adjudication committee.

For the comparison of finerenone versus placebo, a log rank test stratified by the stratification factors region, type of albuminuria and eGFR category was used. The hazard ratio (HR) and corresponding two-sided 95% CI was estimated using a stratified Cox proportional hazard regression model. Censoring rules were pre-defined. The censoring mechanism of subjects without an event of the primary composite endpoint at the time of analysis was assumed to be non-informative.

Supportive and/or sensitivity analyses were planned and have been presented, among them a Tipping Point analysis for the primary and key secondary endpoint.

The primary analysis of the secondary time-to-event endpoints were conducted analogously to the primary analysis of the primary composite endpoint, with modifications to the censoring rules as the events differed. Consistent with the methods for the primary and secondary efficacy variables, components or composites of the components of the primary and secondary time-to-event endpoints were analysed as exploratory time-to-event variables using a stratified log rank test and a stratified Cox proportional hazard regression model.

For the analysis of change in UACR month 4, an ANCOVA model was fitted to logarithmised ratios of UACR at Month 4 to UACR at baseline including the factors treatment group, the stratification factors region, type of albuminuria and eGFR category and the logarithmised baseline UACR as covariate. Here, subjects without a measurement within the pre-defined time window were excluded. In the end, a high and similar proportion of subjects in each treatment arm had data available and hence was included in the primary analysis (>95% in both the finerenone and the placebo arm).

One formal interim analysis was planned when 2/3 of the required total number of primary efficacy endpoint events had been observed. In case of clear and consistent finerenone benefit, the DMC could recommend early study termination. Details of the interim analysis were covered in the DMC charter, the analysis was described in a separate DMC SAP and the statistical analysis were performed by an independent statistical analysis centre.

On 25 SEP 2019, the DMC communicated the decision to continue the study as planned without changes to the CSP.

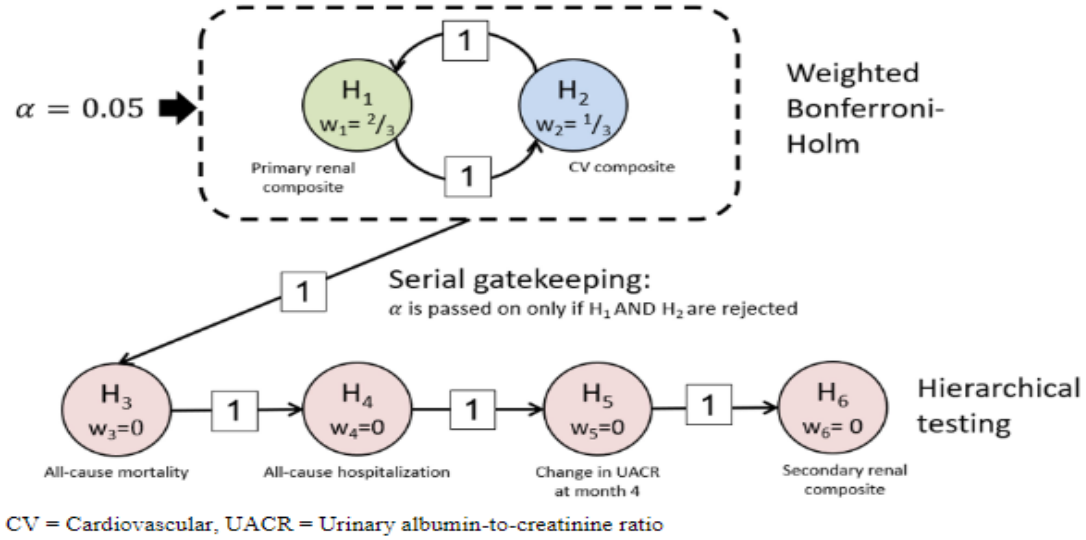
Since the study could not be stopped early for success, the final primary analyses were pre-planned as follows: The weighted Bonferroni-Holm procedure was to be used for the hierarchical testing of the primary and secondary efficacy endpoints with the following adjusted alpha levels:

• If the primary renal composite endpoint achieved statistical significance at a two-sided p value ≤0.03282695, the secondary CV endpoint was to be tested at the two-sided 0.04967388 level.

• Alternatively, if the secondary CV endpoint achieved statistical significance at a two-sided p value ≤0.01576184, the primary renal composite endpoint was to be tested at the two-sided 0.04967388 level.

• Only if both the renal and CV endpoints achieved formal statistical significance, were the remaining secondary endpoints to be tested at a two-sided level of 0.04967388 according to the pre-defined hierarchy, as described below.

Figure 7–4: Simplified scheme of the testing strategy



CV = Cardiovascular, UACR = Urinary albumin-to-creatinine ratio

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

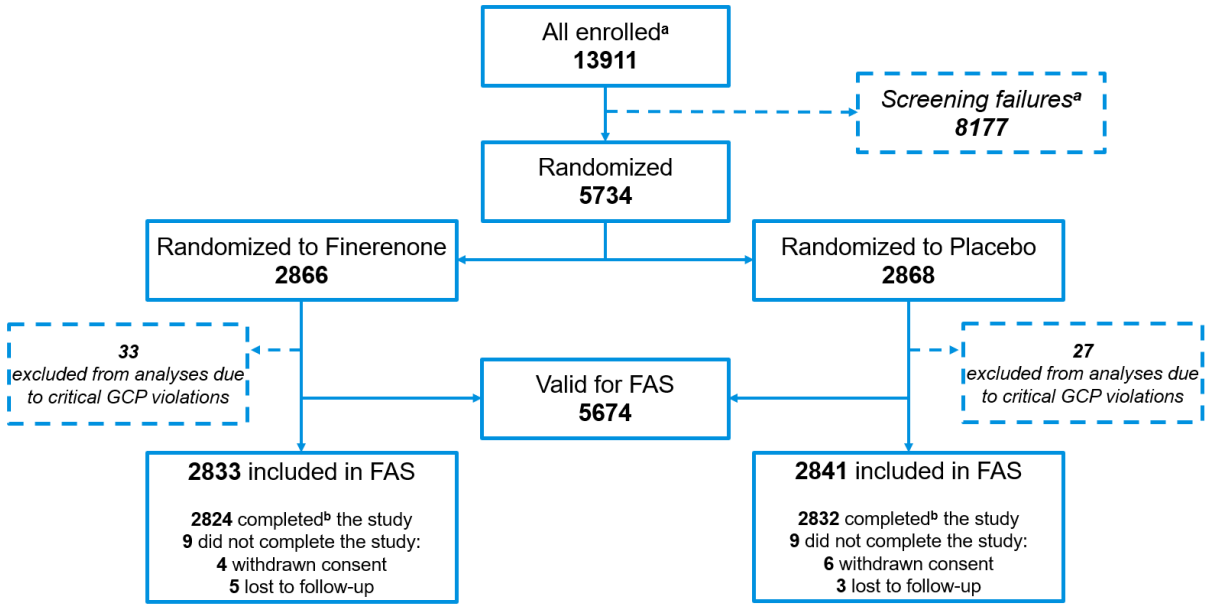
Results

- **Participant flow**

This study was conducted in 1024 sites across 48 countries and enrolled 13911 patients. 5734 subjects were randomly assigned 1:1 to receive oral finerenone or placebo. After randomisation and during study conduct, 60 subject identifiers were prospectively excluded from all analyses due to critical Good Clinical Practice violations, resulting in a FAS population of 5674 subjects. As 16 subjects did not take any study drug, 5658 subjects were valid for the SAF (2827 subjects on finerenone, 2831 subjects on placebo). *Figure 9* shows a flow chart over the study participants.

Figure 9 shows a flow chart over the study participants.

Figure 10. Subject disposition flow for FIDELIO-DKD.



[a]Number of subjects enrolled is the number of subjects who signed informed consent, including subjects who switched from study 17530 to study 16244.

[b]A subject is considered as having completed the study if there was a contact with the subject after the end-of-study notification or if the subject died. Contact with the subject could be actual visits, phone contacts, or information available from public records, etc.

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 26.882 and 27.039 months in the finerenone arm and 27.162 and 27.203 months in the placebo arm, respectively.

A total of 86.3% of subjects in the finerenone arm and 87.0% of subjects in the placebo arm took the study medication for at least 12 months. Over half of the subjects took the study medication for at least 24 months (57.6% in finerenone, 58.5% in placebo) and approximately a quarter of subjects took the study drug for at least 36 months (25.6% in finerenone, 25.3% in placebo).

- **Recruitment**

The total exposure of subjects to study drug was 12777 patient-years, with 6346 patient-years in the finerenone arm and 6431 patient-years in the placebo arm. The mean average daily dose was 15.138 mg (SD 4.472 mg) in the finerenone arm and 16.480 mg (SD 4.014 mg) in the placebo arm.

- **Conduct of the study**

The first patient was enrolled on September 17, 2015 and the last patient completed the study on April 14, 2020.

- **Baseline data**

Baseline characteristics were similar in the two treatment arms and reflects a population representative for the condition. Demographic data and baseline characteristics are given in *Table 18* and *Table 19*, respectively.

Medical history findings of interest are given in *Table 20*.

Information on new concomitant medication by ATC class and subclass, i.e. medication that began after the subject started study drug, showed comparable results for the 2 treatment arms (90.6% in

finerenone, 90.8% in placebo (*Table 21*).

Table 18. Demographic data (FAS) for FIDELIO-DKD (abbreviated).

	Finerenone N = 2833 (100%)	Placebo N = 2841 (100%)
Sex: Male	1953 (68.9%)	2030 (71.5%)
Female	880 (31.1%)	811 (28.5%)
Region		
Europe	1182 (41.7%)	1176 (41.4%)
North America	467 (16.5%)	477 (16.8%)
Asia	790 (27.9%)	789 (27.8%)
Latin America	295 (10.4%)	298 (10.5%)
Others	99 (3.5%)	101 (3.6%)
Age (years)		
n	2833	2841
Mean (SD)	65.44 (8.94)	65.67 (9.16)
Median	66.00	66.00
Q1, Q3	60.00, 72.00	60.00, 72.00
Age group (years) category		
18 - 44 years	49 (1.7%)	65 (2.3%)
45 - 64 years	1156 (40.8%)	1109 (39.0%)
65 - 74 years	1197 (42.3%)	1203 (42.3%)
≥ 75 years	431 (15.2%)	464 (16.3%)
Baseline BMI (kg/m^2)		
n	2821	2836
Mean (SD)	31.13 (6.03)	31.10 (6.00)
Median	30.40	30.30
Q1, Q3	26.80, 34.30	26.90, 34.50
Baseline BMI (kg/m^2) category		
missing	12 (0.4%)	5 (0.2%)
< 20 kg/m^2	22 (0.8%)	28 (1.0%)
≥ 20 - < 25 kg/m^2	348 (12.3%)	348 (12.2%)
≥ 25 - < 30 kg/m^2	950 (33.5%)	966 (34.0%)
≥ 30 - < 35 kg/m^2	866 (30.6%)	846 (29.8%)
≥ 35 kg/m^2	635 (22.4%)	648 (22.8%)
Baseline waist-hip ratio		
n	2821	2827
Mean (SD)	1.00 (0.11)	1.00 (0.12)
Median	0.99	0.99
Q1, Q3	0.94, 1.05	0.94, 1.05
Smoking History		
NEVER	1375 (48.5%)	1371 (48.3%)
FORMER	1044 (36.9%)	1078 (37.9%)
CURRENT	414 (14.6%)	392 (13.8%)
Alcohol Use, missing	0	1 (<0.1%)
ABSTINENT	1733 (61.2%)	1722 (60.6%)
LIGHT	946 (33.4%)	947 (33.3%)
MODERATE	143 (5.0%)	155 (5.5%)
HEAVY	11 (0.4%)	16 (0.6%)

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

Table 19. Baseline characteristics (FAS) for FIDELIO-DKD.

	Finerenone N=2833 (100%)	Placebo N=2841 (100%)
Baseline serum potassium (mmol/L)		
n	2832	2840
Arithm.Mean (Arithm.SD)	4.37 (0.46)	4.38 (0.46)
Median	4.40	4.40
Q1, Q3	4.10, 4.70	4.10, 4.70
Baseline serum potassium (mmol/L) category		
Missing	1 (<0.1%)	1 (<0.1%)
≤4.5 mmol/L	1881 (66.4%)	1861 (65.5%)

	Finerenone N=2833 (100%)	Placebo N=2841 (100%)
>4.5 mmol/L	951 (33.6%)	979 (34.5%)
Baseline serum potassium (mmol/L) category		
Missing	1 (<0.1%)	1 (<0.1%)
<4.8 mmol/L	2302 (81.3%)	2295 (80.8%)
≥4.8 to 5.0 mmol/L	333 (11.8%)	349 (12.3%)
>5.0 mmol/L	197 (7.0%)	196 (6.9%)
Baseline systolic blood pressure (mmHg)		
n	2830	2839
Arithm.Mean (Arithm.SD)	138.05 (14.32)	138.01 (14.42)
Median	138.33	138.33
Q1, Q3	128.67, 147.67	128.67, 148.33
Baseline systolic blood pressure (mmHg) category		
missing	3 (0.1%)	2 (<0.1%)
<130 mmHg	788 (27.8%)	778 (27.4%)
≥130 -<160 mmHg	1900 (67.1%)	1922 (67.7%)
≥160 mmHg	142 (5.0%)	139 (4.9%)
Baseline eGFR (mL/min/1.73m^2)		
n	2832	2840
Arithm. Mean (Arithm.SD)	44.36 (12.54)	44.32 (12.57)
Median	43.00	43.00
Q1, Q3	34.55, 52.50	34.70, 52.50
Baseline eGFR (mL/min/1.73m^2) category		
Missing	1 (<0.1%)	1 (<0.1%)
<25 mL/min/1.73m^2	66 (2.3%)	69 (2.4%)
25 - <45 mL/min/1.73m^2	1476 (52.1%)	1505 (53.0%)
45 -<60 mL/min/1.73m^2	972 (34.3%)	928 (32.7%)
≥60 mL/min/1.73m^2	318 (11.2%)	338 (11.9%)
Baseline albuminuria (mg/g) category		
missing	2 (<0.1%)	1 (<0.1%)
Normalbuminuria (UACR <30 mg/g)	11 (0.4%)	12 (0.4%)
High albuminuria (≥30 - <300 mg/g)	350 (12.4%)	335 (11.8%)
Very high albuminuria (≥300 mg/g)	2470 (87.2%)	2493 (87.8%)
Baseline UACR (mg/g)		
n	2831	2840
Geom.Mean (Geom.SD)	798.79 (2.65)	814.73 (2.67)
Median	832.72	867.01
Q1, Q3	441.00, 1628.14	453.11, 1644.58
UACR at baseline (below median and above median in the FAS)		
Missing	2 (<0.1%)	1 (<0.1%)
≤851.9 mg/g (median in FAS)	1442 (50.9%)	1394 (49.1%)
>851.9 mg/g (median in FAS)	1389 (49.0%)	1446 (50.9%)
Baseline Haemoglobin A1C (%)		
n	2826	2837
Arithm.Mean (Arithm.SD)	7.66 (1.33)	7.69 (1.36)
Median	7.50	7.50
Q1, Q3	6.70, 8.50	6.70, 8.50
History of CV disease, present [a]	1303 (46.0%)	1302 (45.8%)
Duration of diabetes (in years)		
N	2827	2836
Arithm. Mean (Arithm. SD)	16.58 (8.77)	16.55 (8.77)
Median	16.12	16.15
Q1, Q3	10.16, 21.22	10.14, 21.32
Use of the following at baseline:		
ARB	1879 (66.3%)	1846 (65.0%)
ACEI	950 (33.5%)	992 (34.9%)
Beta-blocker	1462 (51.6%)	1506 (53.0%)
Diuretic	1577 (55.7%)	1637 (57.6%)
Statin	2105 (74.3%)	2110 (74.3%)
Anti-diabetic treatment	2747 (97.0%)	2777 (97.7%)
Insulins and analogues	1843 (65.1%)	1794 (63.1%)
Dipeptidyl peptidase 4 inhibitors	764 (27.0%)	758 (26.7%)
GLP-1 receptor agonists	189 (6.7%)	205 (7.2%)
SGLT2 inhibitors	124 (4.4%)	135 (4.8%)
Biguanides	1251 (44.2%)	1239 (43.6%)

	Finerenone N=2833 (100%)	Placebo N=2841 (100%)
Sulfonamides	654 (23.1%)	673 (23.7%)
Alpha glucosidase inhibitors	163 (5.8%)	161 (5.7%)
Meglitinides	168 (5.9%)	155 (5.5%)
Thiazolidinediones	124 (4.4%)	105 (3.7%)
Potassium supplement	85 (3.0%)	85 (3.0%)
Potassium lowering agent (including binders) [b]	70 (2.5%)	66 (2.3%)

Table 20. Number of subjects with medical history findings of interest (FAS) in FIDELIO-DKD.

	Finerenone N = 2833 (100%)	Placebo N = 2841 (100%)
Chronic kidney disease [a]	2833 (100.0%)	2841 (100.0%)
Type 2 diabetes mellitus [a]	2832 (>99.9%)	2840 (>99.9%)
Hypertension [b]	2737 (96.6%)	2768 (97.4%)
Diabetic retinopathy [a]	1312 (46.3%)	1351 (47.6%)
Hyperlipidemia [b]	1281 (45.2%)	1280 (45.1%)
Diabetic neuropathy [c]	742 (26.2%)	722 (25.4%)
Peripheral arterial occlusive disease [a]	470 (16.6%)	453 (15.9%)
Coronary artery disease [a]	842 (29.7%)	860 (30.3%)
Myocardial infarction [a]	378 (13.3%)	388 (13.7%)
Ischaemic stroke [a]	329 (11.6%)	360 (12.7%)
Atrial fibrillation and atrial flutter [c]	240 (8.5%)	221 (7.8%)
Cardiac failure [b]	195 (6.9%)	241 (8.5%)
Percutaneous coronary intervention [c]	151 (5.3%)	135 (4.8%)
Coronary artery bypass graft [c]	141 (5.0%)	149 (5.2%)
Periodontal disease [a]	104 (3.7%)	128 (4.5%)
Carotid endarterectomy [a]	33 (1.2%)	38 (1.3%)

Table 21. New concomitant medication of interest (FAS) under study FIDELIO-DKD.

	Finerenone N = 2833 (100%)	Placebo N = 2841 (100%)
Number (%) of subjects with at least one new non-antidiabetic concomitant medication of interest	**2310 (81.5%)**	**2342 (82.4%)**
ACEI	428 (15.1%)	430 (15.1%)
ARB	747 (26.4%)	822 (28.9%)
Beta-blocker	767 (27.1%)	855 (30.1%)
Diuretics	1213 (42.8%)	1290 (45.4%)
Loop diuretics	921 (32.5%)	989 (34.8%)
Thiazide diuretics	296 (10.4%)	324 (11.4%)
Potassium supplements	190 (6.7%)	246 (8.7%)
Potassium lowering agents (including binders)	307 (10.8%)	184 (6.5%)
Alpha blocking agents	806 (28.5%)	881 (31.0%)
Calcium channel blockers	999 (35.3%)	1178 (41.5%)
Centrally acting antihypertensives	197 (7.0%)	254 (8.9%)
CYP3A4 inhibitors		
Strong	163 (5.8%)	150 (5.3%)
Moderate	360 (12.7%)	373 (13.1%)
Weak	1144 (40.4%)	1210 (42.6%)
Unclassified	129 (4.6%)	136 (4.8%)
CYP3A4 inducers		
Strong	33 (1.2%)	34 (1.2%)
Moderate	178 (6.3%)	209 (7.4%)
Weak	192 (6.8%)	206 (7.3%)
Unclassified	130 (4.6%)	122 (4.3%)
Oral anticoagulants	218 (7.7%)	223 (7.8%)
Acetylsalicylic acid and its salts	448 (15.8%)	482 (17.0%)
Statins	833 (29.4%)	862 (30.3%)
Erythropoietin stimulating agents	177 (6.2%)	210 (7.4%)
NSAIDs (excluding acetylsalicylic acid)	719 (25.4%)	759 (26.7%)
ARNIs	8 (0.3%)	13 (0.5%)
Potassium-sparing diuretics	141 (5.0%)	172 (6.1%)
Platelet aggregation inhibitors (excluding heparin)	670 (23.6%)	693 (24.4%)
Number (%) of subjects with at least one new anti-diabetic medication of interest	**1792 (63.3%)**	**1841 (64.8%)**
Insulins and analogues	1335 (47.1%)	1384 (48.7%)
Dipeptidyl peptidase 4 inhibitors	472 (16.7%)	474 (16.7%)
GLP-1 agonists	260 (9.2%)	264 (9.3%)
SGLT-2 inhibitors	186 (6.6%)	216 (7.6%)
Biguanides	516 (18.2%)	495 (17.4%)
Sulfonylureas	301 (10.6%)	334 (11.8%)
Alpha glucosidase inhibitors	119 (4.2%)	116 (4.1%)
Meglitinides	128 (4.5%)	143 (5.0%)
Thiazolidinediones	80 (2.8%)	82 (2.9%)

ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker, ARNIs = angiotensin receptor neprilysin inhibitors, FAS = full analysis set, GLP-1 = glucagon-like peptide-1, N = number of subjects, NSAIDs =non-steroidal anti-inflammatory drugs, SGLT-2 = sodium-glucose co-transporter-2
Source: Table 14.1.7/15, Table 14.1.7/17

- **Numbers analysed**

The primary efficacy analysis was based on the full analysis set (all randomised subjects without critical GCP violations) (*Table 22*).

Table 22. Analysis sets in FIDELIO-DKD.

	Finerenone N = 2866 (100%)	Placebo N = 2868 (100%)
Subjects valid for full analysis	**2833 (98.8%)**	**2841 (99.1%)**
Subjects valid for safety analysis	**2827 (98.6%)**	**2831 (98.7%)**
Subjects valid for per protocol analysis	**2391 (83.4%)**	**2451 (85.5%)**
Subjects valid for pharmacokinetic analysis	**2515 (87.8%)**	**0**

- **Outcomes and estimation**

Primary endpoint

Treatment with finerenone significantly reduced the risk of the primary renal composite endpoint when compared with placebo with a HR of 0.825 (95% CI 0.732; 0.928, log rank test p=0.0014) (*Table 23*).

Table 23. Summary of results for the primary endpoint and its components (FAS) in FIDELIO-DKD.

	Finerenone N = 2833 n (%)	**Placebo** N = 2841 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 renal composite endpoint	**504 (17.8%)**	**600 (21.1%)**	**7.59 (6.94;8.27)**	**9.08 (8.37;9.82)**	**0.825 [0.732; 0.928]**	**0.0014**
Components:						
Kidney failure	208 (7.3%)	235 (8.3%)	2.99 (2.60;3.41)	3.39 (2.97;3.83)	0.869 [0.721; 1.048]	0.1409
ESRD	119 (4.2%)	139 (4.9%)	1.60 (1.33;1.90)	1.87 (1.57;2.20)	0.858 [0.672; 1.096]	0.2191
Sustained decrease in eGFR to <15 mL/min	167 (5.9%)	199 (7.0%)	2.40 (2.05;2.78)	2.87 (2.48;3.28)	0.824 [0.671; 1.013]	0.0646
Sustained decrease in eGFR ≥40% (relative to baseline)	479 (16.9%)	577 (20.3%)	7.21 (6.58;7.87)	8.73 (8.03;9.46)	0.815 [0.722; 0.920]	0.0009
Renal death	2 (<0.1%)	2 (<0.1%)	-	-	-	-

Kaplan-Meier curves for finerenone and placebo are similar up until Month 12 and diverge thereafter (*Figure 10*), indicating a treatment effect for finerenone over the course of this trial. The stepwise appearance of the finerenone and placebo curves indicate the substantial contribution of the eGFR component that was primarily determined at visits every 4th month.

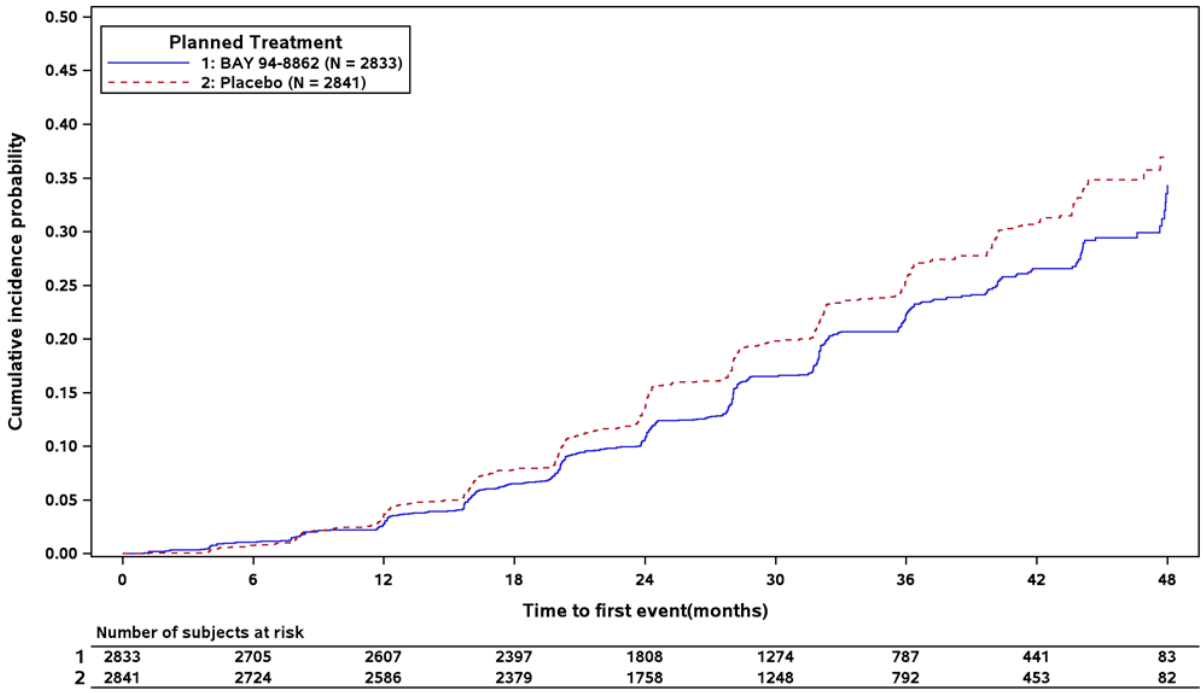


Figure 11. Kaplan-Meier curves for time to first occurrence of the renal composite endpoint (FAS)

In both treatment arms a comparably low number of events occurred during the first year after randomisation (*Table 24*). The absolute risk reduction based on Kaplan-Meier cumulative incidences for the primary renal composite endpoint was 2.9% at Month 24 and 3.4% at Month 36 with finerenone compared to placebo, corresponding to NNTs to prevent one primary endpoint event of 34 and 29 subjects, respectively. Numbers of subjects at risk at Month 48 (83 in the finerenone arm, 82 in the placebo arm, see *Figure 10*) are too low for any meaningful interpretation.

Table 24. Kaplan-Meier cumulative incidence probability, risk difference and NNT by time point for the renal composite endpoint (FAS) in FIDELIO-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	0.028 [0.022;0.034]	0.037 [0.030;0.044]	-0.009 [-0.018;0.000]	111
At Month 18	0.065 [0.056;0.075]	0.078 [0.068;0.088]	-0.013 [-0.027;0.001]	77
At Month 24	0.108 [0.096;0.120]	0.137 [0.123;0.151]	-0.029 [-0.047;-0.011]	34 [21;91]
At Month 30	0.165 [0.149;0.181]	0.198 [0.181;0.215]	-0.033 [-0.056;-0.010]	30 [17;100]
At Month 36	0.223 [0.204;0.243]	0.258 [0.237;0.278]	-0.034 [-0.062;-0.006]	29 [16;166]
At Month 42	0.266 [0.242;0.289]	0.308 [0.285;0.332]	-0.043 [-0.076;-0.009]	23 [13;107]

NNT = 1/(difference of Kaplan-Meier estimates), rounded to integer.

a Confidence intervals for NNT are only calculated if the confidence interval for the difference of Kaplan-Meier estimates does not encompass zero.

CI = confidence interval, eGFR = estimated glomerular filtration rate, FAS = full analysis set, NNT = number needed to treat, renal composite endpoint = kidney failure, sustained decrease of eGFR ≥40% from baseline over at least 4 weeks, or renal death

Subgroup analyses of the primary endpoint

Randomisation and analyses were stratified by the factors region, type of albuminuria and eGFR category at screening. There were no statistical interactions in the different stratification groups (*Figure 11*). However, for region, there appears to be a more pronounced effect in Asia than the other regions and the effect in Europe was more modest (HR=0.92).

The following subgroups had treatment interaction p-values <0.05: history of CV disease, baseline BMI and baseline waist circumference (*Figure 12*). Data suggests that patient without history of CVD has a less pronounced response than patients with a history of CVD (HR 0.94 [0.80; 1.09)] vs. HR 0.70 [0.58;0.84]).

Furthermore, patients with a baseline BMI above 30 kg/m^2 had a less pronounced response (HR 0.98 [0.83; 1.17]) than patients with a BMI under 30 kg/m^2 (HR 0.68 [0.58; 0.81]).

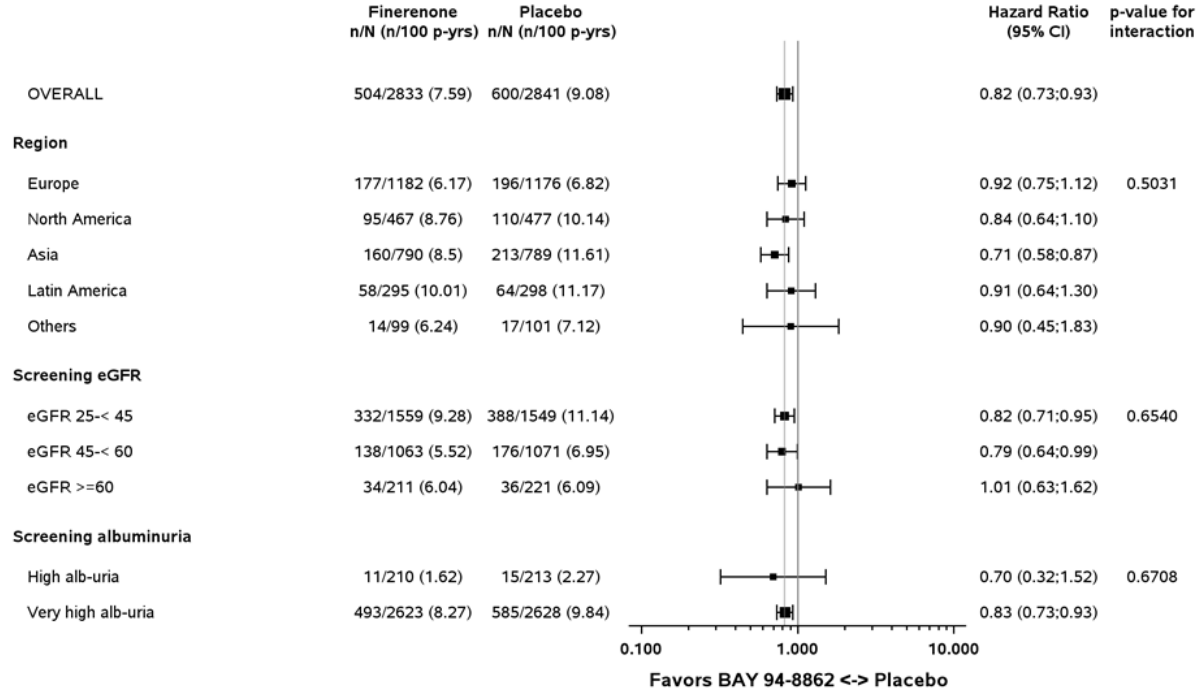


Figure 12. Forest plot for the primary endpoint by stratification factors (FAS)

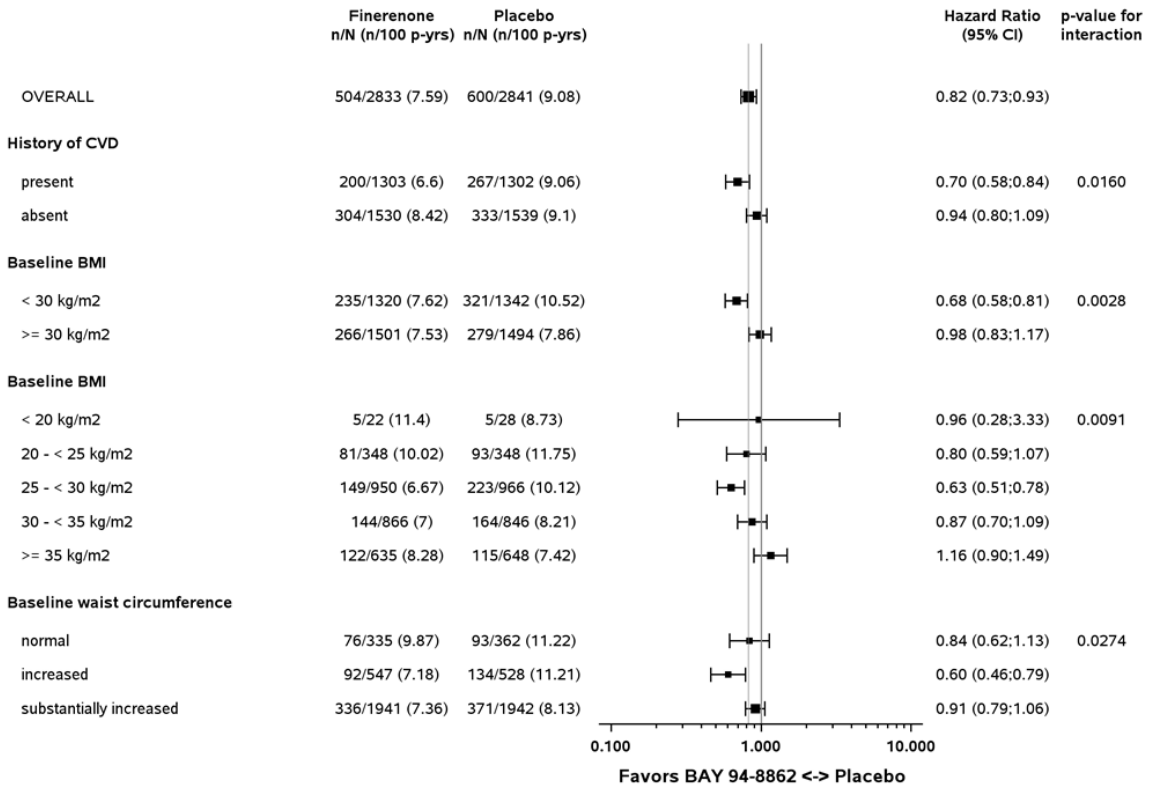


Figure 13. Forest plots for the primary renal composite for subgroups with interaction p-values <0.05 (FAS) in FIDELIO-CKD.

Secondary endpoints

Key secondary CV composite endpoint

Treatment with finerenone reduced the risk of the key secondary CV composite endpoint when compared with placebo with a HR of 0.860 (95% CI 0.747; 0.989, log rank test p=0.0339). The components of the composite are presented in Table 25. The Kaplan-Meier curves for finerenone and placebo diverge from Month 1 onwards with a consistent course throughout the study (Figure 13). The treatment effect of finerenone is supported by the FAS on treatment sensitivity analysis (HR 0.781, [95% CI 0.664;0.918], nominal p-value=0.0026).

Table 25. Key secondary CV composite endpoint: results for adjudicated events (FAS) in FIDELIO-DKD.

	Finerenone N = 2833 n (%)	Placebo N = 2841 n (%)	Finerenone n/100 p-yrs (95% CI)	Placebo n/100 p-yrs (95% CI)	HR (95% CI)	p-value
CV composite	**367 (13.0%)**	**420 (14.8%)**	**5.11 (4.60;5.64)**	**5.92 (5.37;6.50)**	**0.860 [0.747; 0.989]**	**0.0339**
Components:						
CV death	128 (4.5%)	150 (5.3%)	1.69 (1.41;2.00)	1.99 (1.68;2.32)	0.855 [0.675; 1.083]	0.1927
Non-fatal MI	70 (2.5%)	87 (3.1%)	0.94 (0.73;1.17)	1.17 (0.94;1.43)	0.796 [0.581; 1.090]	0.1540
Non-fatal stroke	90 (3.2%)	87 (3.1%)	1.21 (0.97;1.47)	1.18 (0.94;1.44)	1.027 [0.765; 1.380]	0.8579
Hospitalization due to heart failure	139 (4.9%)	162 (5.7%)	1.89 (1.59;2.21)	2.21 (1.89;2.57)	0.857 [0.683; 1.076]	0.1821

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 endpoint = CV death, non-fatal myocardial infarction, 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-39746, Table 14.2.2.1/1, Table 14.2.2.1/7, Table 14.2.3.1/23, Table 14.2.3.1/26 to Table 14.2.3.1/28

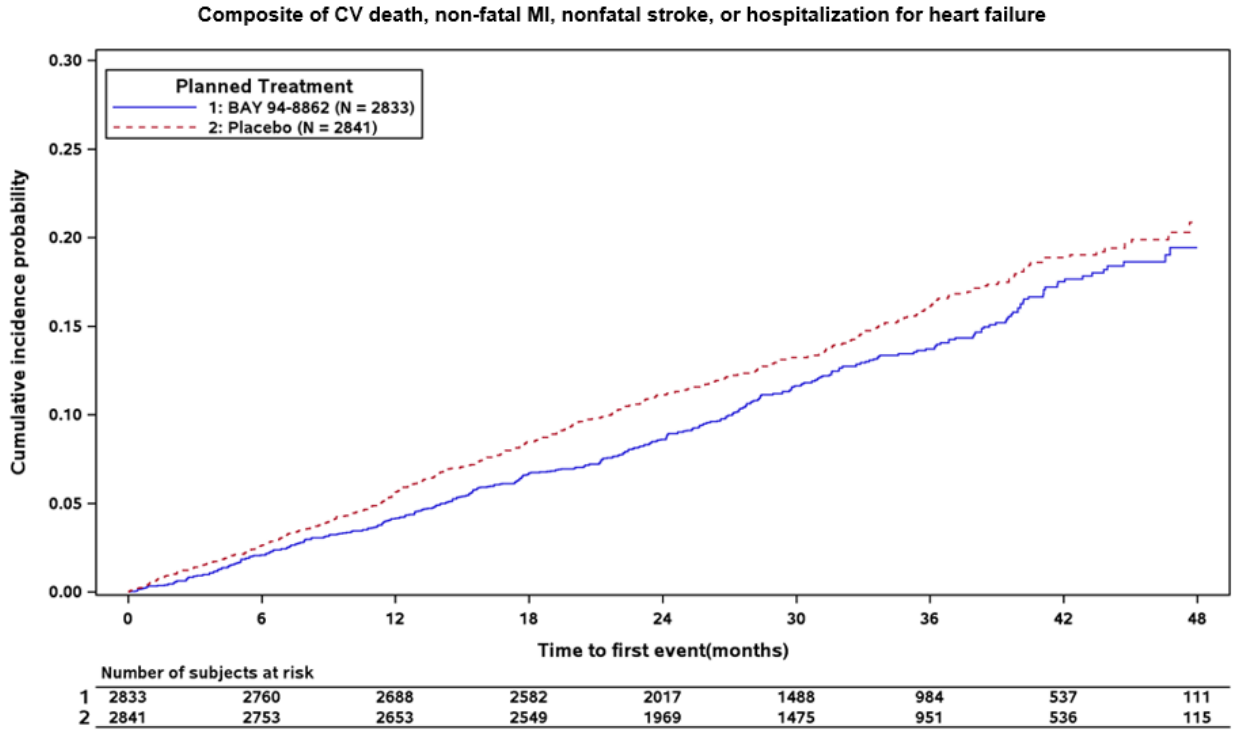


Figure 14. Key secondary composite endpoint: Kaplan-Meier plot for time to first occurrence (FAS).

Subgroup analyses of the key secondary endpoint

Point estimates of the HRs in the various subgroups were generally consistent with the overall result of the key secondary CV composite, with the majority having HRs <1. No treatment interaction p-values <0.05 were observed.

All-cause mortality

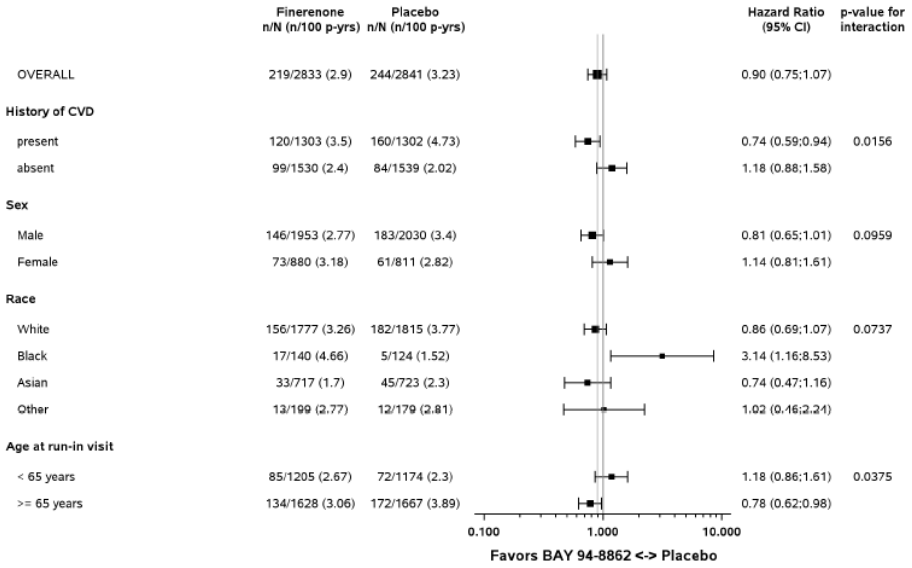
Finerenone treatment resulted in a 10.5% RRR in the time to all-cause mortality compared to placebo. Although not statistically significant (HR of 0.895, [95% CI 0.746; 1.075], p=0.2348), this result was directionally consistent with the primary and key secondary endpoints. Since the result for all-cause mortality did not reach statistical significance, the hierarchical testing sequence was stopped per protocol and statistical testing was performed in an exploratory manner. The components of the composite are presented in

Table **26**. A forest plot on subgroups with low p-values for interactions are presented in *Figure 14*.

Kaplan-Meier curves for finerenone and placebo are provided in *Figure 15*. The absolute risk reduction was 0.6% at Month 24 and 1.0% at Month 36.

The result described above for the FAS was supported by the PPS analysis (for which only events occurring up to 30 days after treatment discontinuation were considered) which showed a 29.5% RRR in the time to all-cause mortality (HR of 0.705, [95% CI 0.535; 0.928], p=0.0122) in subjects who were not excluded due to pre-defined validity criteria related to non-compliance to study drug or protocol requirements and procedures.

Subgroup analysis indicated interactions in the subgroups 'History of CVD' and 'Age at run-in visit'.



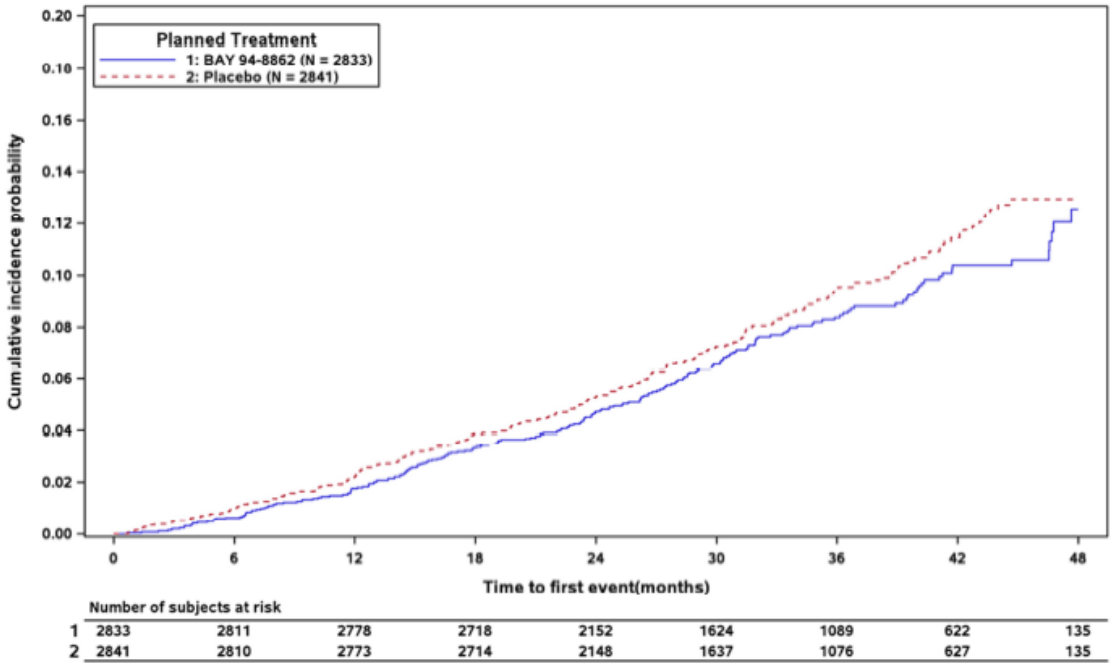
Hazard ratios (95% confidence interval) and interaction p-values (two-sided) are based on stratified Cox proportional hazards models including treatment, subgroup and a subgroup by treatment interaction term as fixed effects.
Subgroup category Other for factor Race includes Native Hawaiian or Other Pacific Islander, American Indian or Alaska Native, Multiple and Not Reported.

Figure 15. Forest plot of all-cause mortality: Hazard Ratio by key subgroups (FAS)

Table 26. Summary of results for adjudicated all-cause mortality (FAS)

	Finerenone N = 2833 n (%)	Placebo N = 2841 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	**219 (7.7%)**	**244 (8.6%)**	**2.90 (2.53;3.29)**	**3.23 (2.84;3.65)**	**0.895 [0.746; 1.075]**	**0.2348**
Components:						
CV death	128 (4.5%)	150 (5.3%)	1.69 (1.41;2.00)	1.99 (1.68;2.32)	0.855 [0.675; 1.083]	0.1927
Renal death	2 (<0.1%)	2 (<0.1%)	-	-	-	-
Fatal, non-CV/non-renal	89 (3.1%)	92 (3.2%)	1.18 (0.95;1.43)	1.22 (0.98;1.48)	0.958 [0.716; 1.283]	0.7751

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-39746, Table 14.2.2.2/1, Table 14.2.2.2/6, Table 14.2.3.1/23, Table 14.2.3.1/24



FAS = full analysis set, N = number of subjects
Source: Module 5.3.5.1, Report PH-39746, Figure 14.2.2.2/1

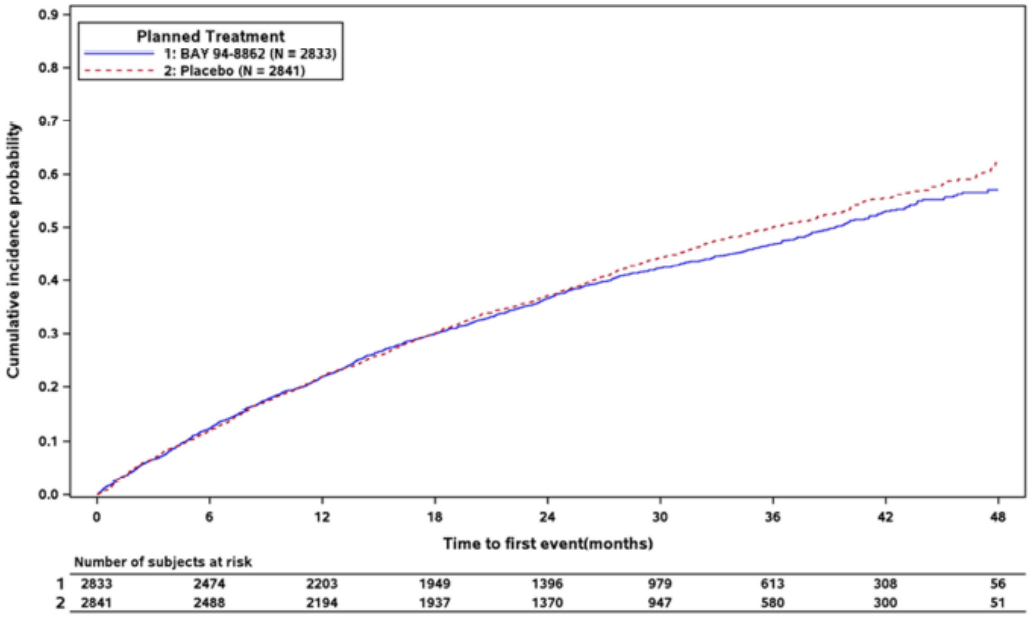
Figure 16. Kaplan-Meier curves for time to all-cause mortality (FAS).

All-cause hospitalisation

For all-cause hospitalisation, the comparison of finerenone with placebo showed a HR of 0.946 (95% CI 0.876; 1.022, log rank test p=0.1623). Statistical testing was performed in an explorative manner given that the hierarchical testing sequence was stopped in the previous step.

1263 subjects (44.6%) in the finerenone arm and 1321 subjects (46.5%) in the placebo arm were hospitalised for any cause. The incidence rates for all-cause hospitalisation were 22.56/100 patient-years (finerenone) and 23.87/100 patient-years (placebo).

Kaplan-Meier curves for finerenone and placebo are presented in *Figure 16*.



FAS = full analysis set, N = number of subjects
Source: Module 5.3.5.1, Report PH-39746, Figure 14.2.2.3/1

Figure 17. Kaplan-Meier curves for time to all-cause hospitalisation (FAS)

Change in UACR from baseline to Month 4

Treatment with finerenone led to a larger UACR reduction from baseline to Month 4 than placebo.

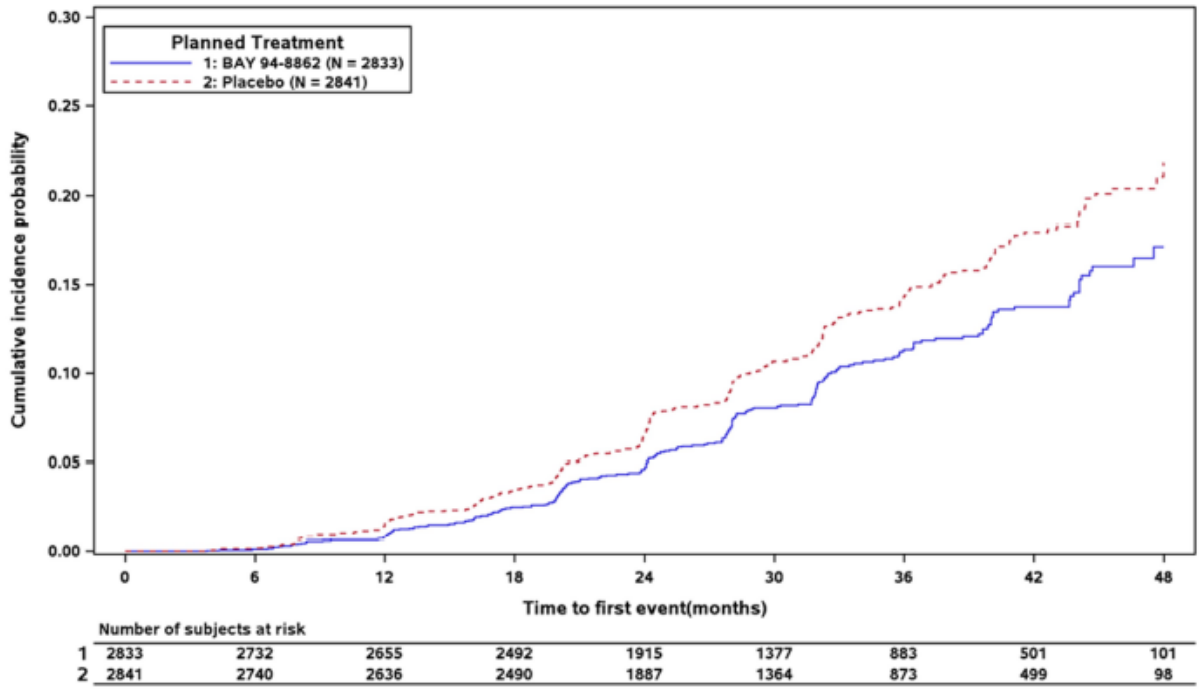
The LS means ratio with an ANCOVA was 0.688 (95% CI 0.662; 0.715, p<0.0001), which corresponds to a placebo-corrected relative reduction in UACR from baseline to Month 4 of 31.2%. Statistical testing was performed in an explorative manner given that the hierarchical testing sequence was stopped in the previous steps.

Secondary renal composite (with component decrease in eGFR ≥57%)

Compared to the primary renal composite endpoint, which consisted of the component 'sustained decrease in eGFR of ≥40%', the secondary renal composite endpoint replaced this component with a 'sustained decrease in eGFR of ≥57%' (equivalent to a doubling of serum creatinine).

Finerenone treatment resulted in a 23.7% RRR in the first event of the adjudicated secondary renal composite of kidney failure, a sustained decrease of eGFR ≥57% from baseline over at least 4 weeks, or renal death (HR of 0.763 [95% CI 0.648; 0.900], p=0.0012). Statistical testing was performed in an explorative manner given that the hierarchical testing sequence was stopped in the previous steps.

For the secondary renal composite endpoint, Kaplan-Meier curves for finerenone and placebo started to diverge from around Month 12 onwards (*Figure 17*). The observed treatment effect supports the findings of the primary renal endpoint.



eGFR = estimated glomerular filtration rate, eGFR = estimated glomerular filtration rate, FAS = full analysis set, N = number of subjects, secondary renal composite endpoint = kidney failure, sustained decrease of eGFR ≥57% from baseline over at least 4 weeks, or renal death
Source: Module 5.3.5.1, Report PH-39746, Figure 14.2.2.5/1

Figure 18. Kaplan-Meier curves for time to first occurrence of the secondary renal composite endpoint (FAS).

Explorative endpoints

Change in eGFR from baseline

Prespecified evaluations of eGFR included analyses of values by visit (below), and numbers of subjects with relative eGFR decreases by category (e.g. ≥57% decrease from baseline).

In finerenone-treated subjects, an initial ('acute') reduction in eGFR was observed compared to placebo, with a difference in LS means (finerenone minus placebo) of 2.38 mL/min/1.73 m^2 from baseline to Month 4; thereafter, a more attenuated decline over time in the eGFR ('chronic') slope was observed in finerenone-treated subjects compared to those on placebo (*Figure 18*).

An ANCOVA of the chronic eGFR slope (from Month 4 until the PD or EOS visit) also describes a slower decline in eGFR over time with finerenone: the annualised difference in LS means (finerenone minus placebo) was 1.310 mL/min/1.73 m^2 (p<0.0001). Further analyses across both treatment arms show that in the FAS, the acute and chronic slopes are negatively correlated (Pearson correlation coefficient -0.227, [95% CI 0.255; 0.198], p <0.0001) i.e. a more pronounced initial decline was associated with a better chronic preservation of renal function.

Due to the initial decreased eGFR in subjects treated with finerenone, eGFR values were numerically lower in the finerenone arm until Month 24. After this timepoint, eGFR values were numerically higher in the finerenone arm.

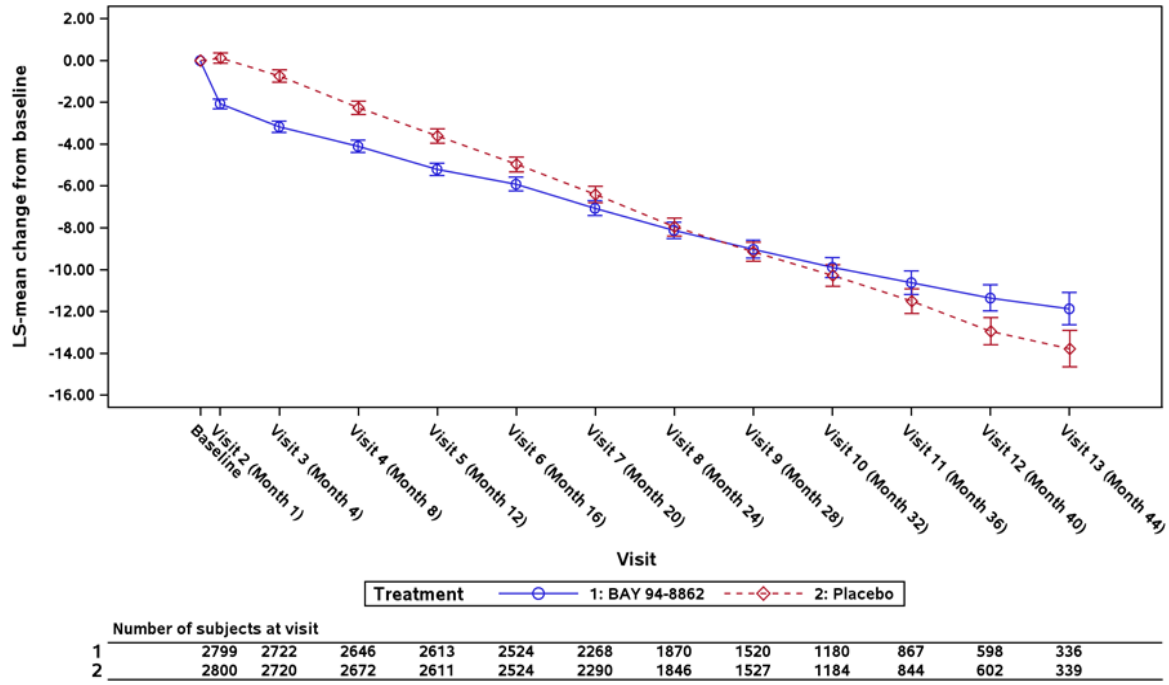


Figure 19. eGFR change by visit: LS means for absolute change from baseline (FAS).

Ratio to baseline of UACR

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 was sustained over the duration of the study. The LS mean ratio finerenone vs placebo did not exceed 0.683 (*Figure 19*).

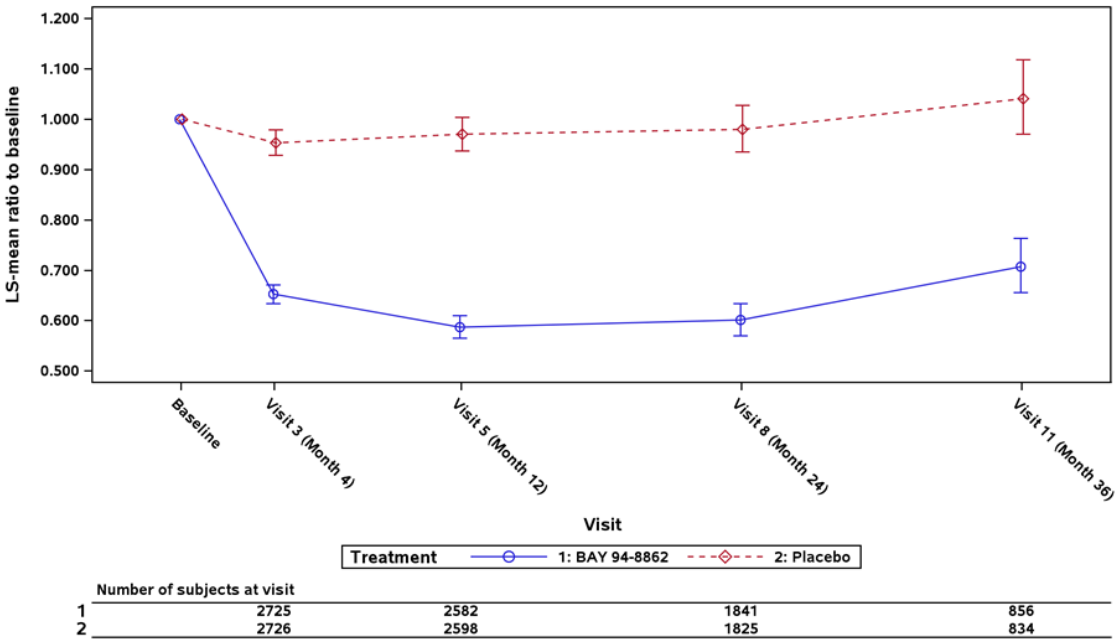


Figure 20. Line plots for LS means for ratio to baseline of UACR values by visit (FAS).

Subgroups of interest: SGLT2 inhibitors /GLP-1 receptor agonists

The effects of finerenone in patients treated with the novel blood glucose lowering agents SGLTi and GLP1-agonists are of interest. Overall, there was small subsets of patients that were treated with SGLT2 inhibitors and GLP-1 agonists at baseline. Consequently, there were very few events for the primary endpoint (*Figure 20*).

The applicant conducted an analysis in these subgroups concerning changes in UACR from baseline to month 4 where the response was similar which is indicative of an additive effect. The same observations were made when evaluating the subgroup of GLP 1 receptor agonist users at baseline. (*Figure 21*)

In addition, long-term data on UACR was provided for the SGLT2 and GLP-1 subgroups where finerenone showed a comparable effect on UACR as observed in the FAS.

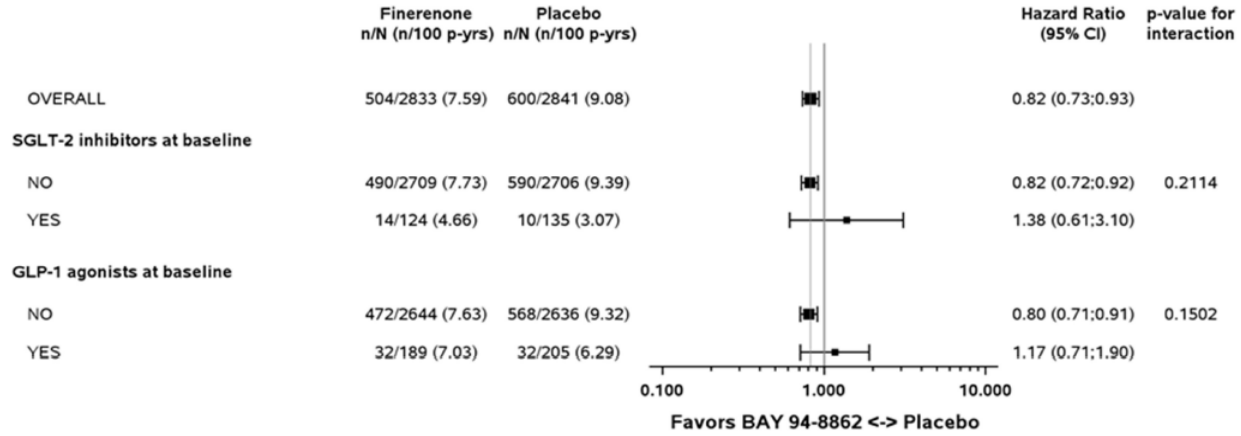


Figure 21. Forest plots for subgroups by SGLT2 inhibitor and GLP-1 receptor agonist use at baseline for the primary efficacy endpoint.

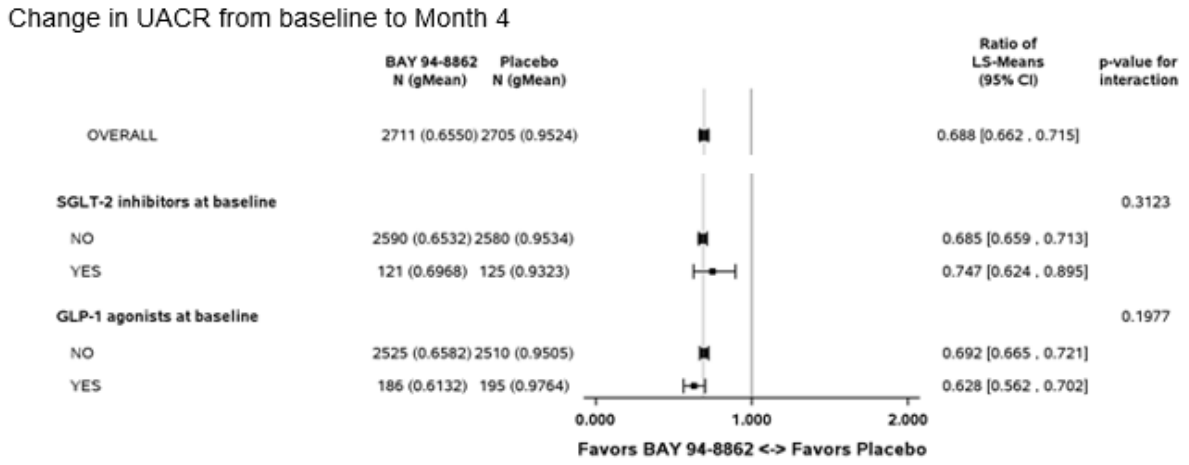


Figure 22. Forest plots for subgroups by SGLT2 inhibitor and GLP-1 receptor agonist use at baseline for UACR change at Month 4.

New diagnosis of atrial fibrillation or atrial flutter

A new diagnosis of atrial fibrillation or atrial flutter, which was independently adjudicated by the Clinical Event Committee, occurred less frequently in the finerenone arm (for 82 of 2593 subjects with no known history of atrial fibrillation or flutter, 3.2%) than in the placebo arm (for 117 of 2620 subjects, 4.5%) (Odds ratio 0.698, p=0.0146)

- **Ancillary analyses**

Not applicable.

- **Summary of main efficacy results**

The following table summarise the efficacy results from the main study 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).

Summary of efficacy for trial FIDELIO-DKD

Title: A randomized, double-blind, placebo-controlled, parallel-group, multicenter, event-driven Phase 3 study to investigate the efficacy and safety of finerenone, in addition to standard of care, on the progression of kidney disease in subjects with type 2 diabetes mellitus and the clinical diagnosis of diabetic kidney disease			
Study identifier	EudraCT: 2015-000990-11		
Design	1:1 randomised, double-blind, placebo-controlled, parallel-group, multicentre, event-driven Phase 3 study testing finerenone vs placebo as add-on to SoC		
	Duration of main phase: Duration of Run-in phase: Duration of Extension		From 17 SEP 2015 to 14 APR 2020 4-16 weeks not applicable
Hypothesis	Superiority		
Treatments groups	Finerenone Starting dose of 10 mg OD or 20 mg OD depending on eGFR with up- or down-titration based on potassium levels		randomised patients: 2866 analysed patients (FAS): 2833 duration: 27.039 months in median
	Placebo		randomised patients: 2868 analysed patients (FAS): 2841 duration: 27.203 months in median
Endpoints and definitions	Primary endpoint	RENAL	Composite of onset of kidney failure, a sustained decrease of eGFR ⩾40% from baseline over at least 4 weeks, or renal death
	Key Secondary endpoint	CV	Composite of CV death, non-fatal myocardial infarction, non-fatal stroke, or hospitalisation for heart failure
	Secondary endpoint	All-cause mortality	Time to mortality by any cause
	Exploratory	UACR	Change in UACR from baseline
		eGFR	Change in eGFR from baseline
Database lock	29 JUL 2020		
Results and Analysis			

Analysis description	**Primary Analysis**		
Analysis population and time point description	FAS-based analysis Events were adjudicated by an independent committee up to the end of study visit		
Descriptive statistics and estimate variability	Treatment group	Finerenone	Placebo
	Subjects N	2833	2841
	RENAL composite endpoint		
	Subjects with first event N (%)	504 (17.8%)	600 (21.1%)
	CV composite endpoint		
	Subjects with first event N (%)	367 (13%)	420 (14.8%)
	UACR change		
	LS mean range to baseline at Mth 36	0.707 (0.656;0.763)	1.041 (0.970;1.118)
	eGFR change		
	Annualised change	-4.064 (-4.553; -3.574)	-4.330 (-4.820; -3.841)
Effect estimate per comparison		**Comparison groups**	**Finerenone vs placebo**
	RENAL Primary endpoint	HR (95% CI) P value	0.825 (0.732;0.928) 0.0014
	CV Secondary endpoint	HR (95% CI) P value	0.860 (0.747;0.989) 0.0339
	Secondary: All-cause mortality	HR (95% CI) P value	0.895 (0.746;1.075) 0.2348
Notes	Statistically significant superiority of finerenone vs placebo was demonstrated for the primary renal composite endpoint and secondary CV endpoint.		

2.6.5.3. Clinical studies in special populations

The pivotal study included patients with renal impairment. No other dedicated studies were performed in special populations. A summary on the age distribution in the clinical programme is provided in Table 27.

Table 27. Participating subjects (SAF).

	Number of subjects in age subgroup			
Study phase and indication Study intervention received				
Age subgroup:	**<65 years**	**65–74 years**	**75–84 years**	**85+ years**
Controlled trials				
Phase 3, CKD in T2D (FIDELIO-DKD)				
Finerenone (N=2827, 100%)	1201 (42.5%)	1195 (42.3%)	413 (14.6%)	18 (0.6%)
Placebo (N=2831, 100%)	1171 (41.4%)	1199 (42.4%)	436 (15.4%)	25 (0.9%)
Phase 2b, CKD in T2D (ARTS-DN + ARTS-DN Japan)				
Finerenone (N=811, 100%)	382 (47.1%)	339 (41.8%)	86 (10.6%)	4 (0.5%)
Placebo (N=106, 100%)	56 (52.8%)	39 (36.8%)	11 (10.4%)	0
Phase 2b, Worsening of CHF (ARTS-HF + ARTS-HF Japan)				
Finerenone (N=893, 100%)	227 (25.4%)	291 (32.6%)	322 (36.1%)	53 (5.9%)
Eplerenone (N=234. 100%)	53 (22.6%)	74 (31.6%)	85 (36.3%)	22 (9.4%)
Phase 2a, Stable CHF (ARTS)				
Finerenone (N=313, 100%)	65 (20.8%)	127 (40.6%)	110 (35.1%)	11 (3.5%)
Placebo (N=81, 100%)	16 (19.8%)	36 (44.4%)	28 (34.6%)	1 (1.2%)
Spironolactone (N=63, 100%)	8 (12.7%)	24 (38.1%)	28 (44.4%)	3 (4.8%)
Non-controlled trials [a]				
Phase 1, renal impairment				
Finerenone (N = 33, 100%)	16 (48.5%)	14 (42.4%)	3 (9.1%)	0
Phase 1, Hepatic impairment				
Finerenone (N = 27, 100%)	18 (66.7%)	8 (29.6%)	1 (3.7%)	0

a Manual calculation
Abbreviations: CHF = Chronic heart failure, CKD = Chronic kidney disease, DKD = diabetic kidney disease, N = total number of subjects, SAF=safety analysis set, T2D = Type 2 diabetes mellitus

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

Not applicable.

2.6.5.5. Supportive studies

In support, the applicant has submitted the ARTS-HF (Study 14564), ARTS-HF Japan (Study 16815) and ARTS (Study 14563) conducted in patients with a different clinical condition than the proposed indication for Kerendia.

ARTS-HF and ARTS-HF Japan were conducted in patients with worsening chronic heart failure (WCHF) and either type 2 DM with or without CKD or moderate CKD alone whereas ARTS was conducted in patients with clinical diagnosis of CHF and CKD.

ARTS-HF (Study 14564)

The ARTS HF study was a Phase 2b randomised, adaptive, double blind, double dummy, comparator controlled, parallel group, multi-centre study with a planned treatment duration of 90 days.

Participants were adult male and female subjects with a clinical diagnosis of worsening chronic heart failure (WCHF) requiring emergency presentation to hospital and treatment with intravenous (IV) diuretics, and either type 2 DM with or without CKD or moderate CKD alone, who were New York Heart Association (NYHA) class II to IV and treated with evidence based therapy for heart failure (HF) for at least 3 months prior to emergency presentation to hospital.

The primary objective was to investigate efficacy (percentage of subjects with a relative decrease in N-terminal prohormone B-type natriuretic peptide [NT-proBNP] of more than 30% from baseline to Visit 9 [Day 90±2]) and safety of different oral doses of finerenone given once daily.

Initially, 2 doses of finerenone – 2.5 mg OD and 5 mg OD – and eplerenone were administered in a double-blind manner. After the safety and tolerability of these doses had been assessed by an independent Data Monitoring Committee (DMC), 3 further doses of finerenone were introduced: 7.5 mg, 10 mg, and 15 mg OD.

Results

The treatment groups were generally comparable with respect to demographic characteristics. In the SAF, between 74.3 and 81.0% of subjects in each treatment group were men. The majority (89.5 to 93.9%) of subjects was white; the next largest race group was Asian (3.1 to 5.8%). Age ranged from 33 to 92 years, with median age ranging from 70 to 74.5 years. Nearly three-quarters of subjects (72.3%) had a BMI of ≥25 kg/m2. Over half of the subjects in each treatment group were current or former smokers, and almost all subjects reported abstinence from alcohol or light alcohol use.

The primary efficacy variable, the percentage of subjects with a relative decrease in NT-proBNP of >30% from baseline to Day 90, showed that all doses of finerenone were comparable to eplerenone. The responder rate was not statistically significantly higher in any finerenone dose group compared with eplerenone.

An exploratory efficacy objective of the study was to assess the effects on a composite clinical endpoint of death from any cause, CV hospitalisations, or emergency presentations for worsening CHF until Day 90. Further exploratory efficacy variables included this composite and its components.

The composite clinical endpoint and its components showed a broad dose-dependent trend across the finerenone doses from 2.5-5 mg OD to 10 20 mg OD. Survival analyses showed a decrease for finerenone (starting from 5-10 mg OD), with an improved outcome for the 10-20 mg dose arm vs. eplerenone (e.g. composite endpoint with HR of 0.56, 95% CI 0.35; 0.90, p-value 0.0157).

ARTS-HF Japan (Study 16815)

The ARTS HF study was a Phase 2b randomised, adaptive, double blind, double dummy, comparator controlled, parallel group, multicentre study with a planned treatment duration of 90 days with a similar design as ARTS-HF but in a Japanese population.

Participants were adult male and female subjects with a clinical diagnosis of WCHF requiring emergency presentation to hospital.

The primary efficacy objective of this study was to investigate the responder rate, defined as the percentage of subjects with a relative decrease in NT-proBNP of more than 30% from baseline to Day 90.

Initially, 2 doses of finerenone 2.5 mg OD and 5 mg OD and eplerenone were administered in a double-blind manner. After the safety and tolerability of these doses had been assessed by an independent DMC (the first dose recommendation meeting), 3 higher dose arm of finerenone (7.5 mg, 10mg and 15mg OD) could be introduced.

Results

The responder rate at Day 90 was higher in the 3 highest finerenone dose groups (7.5-15 mg OD 45.5%; 10-20 mg OD, 27.3% and 15-20 mg OD groups, 45.5%) compared with the eplerenone group (23.1%).

Further analyses included a composite clinical endpoint of all-cause death, CV hospitalisation or emergency presentation due to worsening CHF until Day 90. Summary statistics of numbers of subjects for the individual components of this clinical endpoint show no clear trend across the finerenone dose groups; the incidences of composite endpoint events and CV hospitalisations were lower in the eplerenone group than in the finerenone dose groups on Day 90. No definitive conclusion can be drawn because of the low number of events and subjects.

ARTS (Study 14563)

The ARTS Study 14563 was a Phase 2a, randomised, double blind, placebo controlled, parallel group, multi centre safety study (Parts A and B), with an additional open-label active comparator for Part B. The planned treatment duration was 4 weeks.

Participants were adult male subjects and female subjects without childbearing potential with clinical diagnosis of CHF New York Heart Association (NYHA) class II - III, treated with evidenced-based therapy for CHF [e.g. treatment with beta-blockers and angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB) as well as diuretics, unless contraindicated or not tolerated and CKD, mild (Part A) or moderate (Part B) chronic kidney disease.

In Part A, 2.5 mg, 5 mg, and 10 mg BAY 94-8862 OD were compared to placebo in a double-blind manner. In Part B, 2.5 mg, 5 mg, 10 mg BAY 94-8862 OD (plus placebo dose in the evening), and 5 mg BID were compared to placebo BID in a double-blind manner and to open-label spironolactone 25 mg or 50 mg OD.

Results

All doses of BAY 94-8862 were assessed as safe and well tolerable. Thus, Part B was initiated.

Based on the primary analysis of the primary variable in Part B, 10 mg finerenone OD as well as 5 mg finerenone BID demonstrated a significantly higher increase in serum potassium than the placebo group. Compared to the spironolactone group, 2.5 mg, 5 mg, and 10 mg finerenone OD as well as 5 mg finerenone BID demonstrated a significantly smaller increase in serum potassium than the spironolactone group (

Table **28**).

Summary statistics for UACR (Table 29) showed that for all finerenone dose groups the geometric mean of the ratio to baseline was consistently <1.00, suggesting that finerenone reduced albuminuria when compared to placebo.

Table 28. Adjusted mean change in serum potassium [mmol/L] from baseline to the average of Visit 6 (Day 22±2) and Visit 7 (Day 29±2) in Part B (ANCOVA model, no imputation performed; full analysis set).

Treatment group	Adjusted mean	Standard error	95% confidence interval Lower limit	Upper limit
2.5 mg BAY 94-8862 OD	0.04	0.04	-0.04	0.13
5 mg BAY 94-8862 OD	0.16	0.04	0.07	0.24
10 mg BAY 94-8862 OD	0.21	0.04	0.13	0.29
5 mg BAY 94-8862 BID	0.30	0.04	0.21	0.38
Spironolactone	0.45	0.05	0.36	0.54
Placebo	0.08	0.04	-0.01	0.16

Source: Table 14.3.4 / 89

Table 29. UACR – Summary statistics and ratio compared to baseline on Day 29 - FAS, Part B ARTS Study 14563.

			Value at Day 29 (mg/g)			Ratio to baseline			
Treatment	N	≥LLOQ	Geom. Mean	(Geom. SD)	N	Geom. mean	(Geom. SD)	Median	[Min-Max]
Placebo	56	47	20.8	(6.63)	56	1.04	(2.66)	1.00	[0.1-12.2]
2.5 mg OD	54	46	18.9	(5.69)	54	0.77	(3.20)	0.88	[0.0-17.0]
5 mg OD	56	45	12.8	(4.28)	56	0.69	(2.94)	0.75	[0.0-5.1]
10 mg OD	59	50	17.1	(4.73)	59	0.72	(2.34)	0.75	[0.1-4.5]
5 mg BID	55	44	13.0	(4.02)	55	0.86	(2.14)	0.83	[0.1-10.1]
Spironolactone	51	39	14.3	(4.41)	51	0.61	(2.63)	0.66	[0.0-7.2]

Means were only calculated if at least 2/3 of the individual data were measured and were ≥ LLOQ. Values <LLOQ were set to 0.5 * LLOQ for the calculation of summary statistics.
ARTS = minerAlocorticoid-Receptor antagonist Tolerability Study, BID = twice daily, OD = once daily, FAS = full analysis set, LLOQ = lower limit of quantitation, Max = maximum, Min = minimum, SD = standard deviation, UACR = urinary albumin-to-creatinine ratio
Source: Module 5.3.5.1, Report A52945, Table 14.3.4/82

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The application is based on efficacy data from a single pivotal phase III study, FIDELIO-DKD and the phase II dose finding studies ARTS-DN and ARTS-DN Japan in patients with CKD and T2D. In addition, supportive data has been submitted from the ARTS-HF, ARTS-HF Japan and ARTS studies in patients with CHF. These studies provide some mechanistic information on finerenone, but given that they encompass a different patient population, they are of less importance for the current application. However, some comparative data versus eplerenone and spironolactone is provided. The design of the pivotal study is adequate and is in general in line with CHMP scientific advice provided in 2015.

Dose selection

The starting dose for the pivotal study was derived from the ARTS-DN, ARTS-DN Japan studies. The ARTS-DN study was a randomised, adaptive, double-blind, placebo-controlled, parallel-group, multi-centre study with a treatment duration of 90 days. Participants were male and female subjects (≥18 years of age) with type 2 diabetes mellitus and a clinical diagnosis of DN treated with an ACEI and/ or ARB for at least 3 months. The primary objective of this study was to investigate the change in UACR

from baseline to day 90 after treatment with 7 different dosing regimens of finerenone (1.25-20 mg OD) given once daily. UACR is commonly used as a dose-finding endpoint in CKD, given that reduction in UACR with ACE/ARBs have been shown to delay the progression of renal impairment in CKD and T2D. The study demonstrated a dose-dependent reduction in UACR compared with placebo from 7.5 mg to 20 mg OD. Post-hoc analysis in these groups demonstrated a significant reduction in UACR from day 30 and onwards. The study thus shows that finerenone reduces UACR in patients with CKD and T2D on top of a RAS inhibitor, in a dose-dependent manner with the most pronounced effect observed in the highest dose studied (20 mg OD) while the increase in plasma potassium was modest.

The ARTS-DN Japan had a similar design as ARTS-DN but in a Japanese population. The results from the ARTS-DN study together with data from the ARTS-DN Japan and the ARTS-HF study guided the applicant's decision to proceed to phase III studies with the 10 and 20 mg OD dose.

Main study (FIDELIO-DKD)

The FIDELIO-DKD was a randomised, double-blind, placebo-controlled, parallel-group, multicentre, event-driven Phase 3 study to study the efficacy and safety of finerenone in patients with T2D and CKD.

Subjects with CKD and T2D were enrolled. Eligible patients had to be treated with the individual maximum tolerated labelled dose of either an ACEI or an ARB and had persistent high albuminuria (UACR ≥30 to <300 mg/g) and eGFR 25-60 ml/min and presence of diabetic retinopathy or very high albuminuria (UACR ≥300 mg/g) and eGFR 25-75 mL/min. Thus, the study population reflects the target population according to the proposed indication. The study design included a run-in-period between 4-16 weeks to allow optimisation of SoC with RAAS inhibitors before finerenone initiation. The mean length of treatment with either ACEIs or ARBs before recruitment was around 4 years for both the finerenone and placebo group (2 years in median). The run-in-period lasted 48 days on average in both arms (48.14 and 48.33 days in the finerenone and placebo group, respectively), and only a negligible portion of patients were not on tolerated maximum dose before screening (1.7% and 1.1% in the finerenone and placebo group, respectively). The applicant showed that variation between the run-in and screening visit for the clinical parameters of major interest was generally comparable between the finerenone and placebo groups and regardless of run-in length, thus suggesting similar short-term effects of therapy adjustments in the two arms. The portion of patients who required optimisation of the ACE-I/ARBs therapy during the Run-in Period accounted for a minority of the study population (5.5%). Only 5.2% in the finerenone arm and 4.3% in the placebo arm were administered an ACEI or ARB below the minimum labelled dose. The dose and type of the different drugs were both balanced between treatment groups. This reassures on the validity of data as the inference of treatment was evaluated on top of a well-established and optimised long-standing therapy equally distributed between finerenone and placebo arm, thus limiting the possibility that a delayed effect of ACE-Is/ARBs or unbalanced therapy optimisation between groups could have introduced a bias in data analysis and interpretation.

Renal biopsy was not required as an entry criterium, which is in line with the EMA Guideline on the clinical investigation of medicinal products to prevent development/slow progression of chronic renal insufficiency (EMA/CHMP/500825/2016) where the following is included: "As a general rule, the renal biopsy is not required if not used in general practice to set diagnosis in case of pivotal studies, e. g diabetic nephropathy". However, CKD in type 2 diabetics encompasses both DKD and non-diabetic CKD as well as a mixed form of the two clinical entities. The clinical data in support of the current application are limited to CKD in T2D, without distinguishing between DKD and non-diabetic causes, however, patients with known significant non-diabetic disease were excluded, thus the study was intended to include mainly patients with DKD. The efficacy and safety of finerenone, in addition to standard of care, on the progression of kidney disease in patients with non-diabetic chronic kidney

disease is studied in the ongoing study Finerenone in non-diabetic CKD (FIND-CKD) with expected last patient last visit in December 2025.

Patients with symptomatic heart failure (NYHA class II-IV) and reduced ejection fraction at the run-in visit were excluded from the trial (due to class 1A recommendation for MRAs) but patients with reduced ejection fraction at NYHA class I or symptomatic patients with mildly reduced or preserved EF (HFmrEF / HFpEF) were included. However, the applicant claims that the ARTS-HF phase IIb study provides data on the use of finerenone in comparison with eplerenone in subjects with HFrEF. However, the study did not provide effect of treatment on clinical outcomes, and the posology scheme is not consistent with the study design of the FIDELIO-DKD trial. The pursued indication is for treatment of CKD based on the primary renal endpoints from the pivotal FIDELIO-DKD trial. Therefore, the available clinical data do not support the treatment of CHF patients. The applicant has included a labelling in section 5.1 of the SmPC on the exclusion of these heart failure patients and a specific warning was included in the SmPC section 4.4 to inform physicians on the absence of data in patients with diagnosed heart failure with reduced ejection fraction and NYHA class II-IV in the event that commercially available MRAs should be considered.

Subjects were randomly assigned to treatments. Although treatment was blinded, the effect of finerenone on potassium level might have unmasked it. However, increases in potassium level were common events in both arms given the underlying disease. It is recognised that CKD associates with potassium fluctuations; however, data clearly demonstrate a more frequent rate and high degree of potassium increase in finerenone-treated patients than placebo. In the applicant's view, this phenomenon was not a concern at the individual level considering the advanced CKD of the FIDELIO-DKD population. No causes of inadvertent unblinding due to finerenone-dependent potassium level modifications were envisaged, so no strategy was needed to retain the risk of unblinding. The applicant's justification is acknowledged.

The starting dose of study drug (10 or 20 mg) depended on the eGFR level at the screening visit. 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 potassium response and investigators were encouraged to reach the maximum dose of 20 mg without compromising safety. The dose selection rationale was based on the fixed dose Phase 2 programme, in particular the Phase 2b ARTS-DN study where a dose-dependency was demonstrated for UACR (the primary efficacy parameter in that study). A dose-exposure-responses modelling and simulation indicated a saturated effect at 20 mg. In terms of safety, no clear dose-dependency was seen for serum potassium in either healthy subjects in phase I studies or the patients in the ARTS-DN study. Analyses of different groups based on baseline GFR in the ARTS-DN study demonstrated that in patients with baseline GFR ≤60 mL/min a higher increase in serum potassium was observed in the 20 mg group compared to the 10 mg group. This difference was not seen in patients with baseline GFR >60ml/min. The varying response in terms of potassium guided the dose titration rationale for the phase 3 study. The dose selection rationale is acknowledged and the posology is adequately reflected in the SmPC.

The primary endpoint was the time to the first occurrence of the composite endpoint of onset of kidney failure, a sustained decrease of eGFR ≥40% from baseline over at least 4 weeks, or renal death which is considered appropriate and in line with scientific advice from CHMP.

The key secondary endpoint was the time to first occurrence of the composite endpoint CV death, non-fatal MI, non-fatal stroke, or hospitalisation for heart failure, again in line with the scientific advice by the CHMP. Other secondary endpoints focused on all-cause mortality, hospitalisation 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 primary and secondary endpoints are considered clinically relevant.

The sample size was calculated based on the assumption that a 20% relative risk reduction for the primary endpoint was observed with finerenone considering a 12% annual event rate in the placebo group. However, the hypothesis was based upon an overestimation of event rate in the placebo group. As a consequence, the number of enrolled patients (13911) largely exceeded the originally planned number of screenings (9600), due to both a higher than expected screening failure rate (originally estimated in the order of 50% but reaching 58.8%) and the lower rate of events compared to the protocol assumption (a total of 5734 patients were recruited, compared to the expected 4600 to achieve the planned number of event). The majority of screening failures were attributed to lack of a clinical diagnosis of DKD at the Run-in and Screening Visit, based on either persistent high albuminuria and presence of diabetic retinopathy OR persistent very high albuminuria (65.7%) or potassium levels above cut-off levels at the Run-in and Screening Visit (31.3%). No concerns arise from these data. With Amendment no.3, rescreening of previous failures was allowed, even if initial screen failure was due to elevated blood potassium values. The applicant also conducted an analysis to identify cases of rescreening and identified a total of 505 subjects firstly screened in FIDELIO and then re-screened in FIDELIO of which 181 were randomised to FIDELIO, and an additional 102 subjects firstly screened in FIGARO and then re-screened in FIDELIO, of which 56 were randomised to FIDELIO. Main raisons for the initial screen failures were levels of potassium above cut-off levels and uncontrolled hypertension. Drug modification occurred within 3 months from re-screening in 5 subjects in the finerenone arm and 10 subjects in the placebo arm. Given the limited number of patients undergoing background therapy modifications before re-screening, this is not considered to have relevant impact on either the study results or the conduct of the clinical trial.

The statistical analysis as planned could overall be agreed. No major concerns have been identified although there were analysis features that could be questioned. One concerned the corrected stratification and the other the corrected database. Additional analyses were requested and in response the applicant performed analyses based on the original database released on June 19, 2020 with the re-release dated July 29, 2020. The re-release implied an update to the number of events. The primary and secondary renal composites and change in UACR to month 4 was not affected while small changes were observed in the key secondary CV composite endpoint, all-cause mortality and all-cause hospitalisation. Importantly, none of the updates had any impact on primary conclusions and thereby could the analyses based on the re-released DB be accepted. Further, an analysis of the original database using original stratification groups (including stratification errors) was performed. Only for the key secondary CV composite the HR was slightly changed. The minor change does not affect the interpretation of the results. All important endpoints but one was time-to-event endpoints. The censoring mechanism of subjects without an event of the primary composite endpoint at the time of analysis was assumed to be non-informative (implying a missing at random assumption). In the end a high proportion of subjects completed the study hence, the number of subjects lost to follow-up or with withdrawn consent were very few. Subjects having withdrawn from study drug permanently were expected to continue to attend all protocol specified study visits. The proportion of subjects who discontinued study drug permanently was approximately 29% and similar in the two arms. The completion of follow-up on the primary endpoint was however lower than the study completion which, according to the applicant, was mainly due to censoring rules. Follow-up on the primary renal composite endpoint that included a laboratory measurement to determine the eGFR decrease, was incomplete/missing for 16.1% (457/2833) of the subjects in the finerenone arm and 14.3% (406/2841) among subjects randomised to placebo. Tipping Point (TP) analyses were performed (primary endpoint, key secondary endpoint) and as described for the primary endpoint, shows how much higher the hazard rate after the last non-missing eGFR measurement would need to be for subjects in the finerenone arm without complete endpoint follow-up so that statistical significance is

lost. Based on the TP analysis it is agreed that the primary outcome appears robust. For the key secondary endpoint on CV-events the proportion of subjects with incomplete follow-up was low (approximately 2.5%) and comparable between the arms.

A weighted Bonferroni-Holm procedure was used for the primary and key secondary endpoints, followed by hierarchical testing of four additional secondary efficacy endpoints. The multiple testing procedure is agreed. As further discussed below, statistically significance was not achieved for the second secondary endpoint why the testing of the remaining secondary efficacy variables was performed in an explorative manner.

The conduct of the study raised important concerns on GCP aspects. Indeed, sixty patients in total were excluded from the analysis due to serious GCP issues, related to investigator fraud and patient duplicate randomisations. Moreover, a substantial number of important protocol violations occurred in the study (>50% of total population, equally distributed between treatment arms). The applicant has provided a review of serious GCP findings and important protocol deviations and discussed the impact of these protocol breaches on patient safety and data reliability of the trial. The applicant appears to have undertaken proper action concerning the serious GCP findings. With reference to important protocol deviations, a list of breaches was provided with an associate description of more frequent events. Based on the provided information, no safety concerns arise around the possibility that these protocol breaches might have influenced the wellbeing of study participants; the quality and reliability of data do not appear to have been compromised.

Overall, FIDELIO-DKD is considered as a well-conducted study.

Efficacy data and additional analyses

The percentage of randomised subjects that completed the study was high, above 98% in both arms.

Baseline characteristics were similar in the two treatment arms and reflect a population representative for the condition. Patients in general had elevated BMI and a medical history of hypertension. Approximately half of the patients had a medical history of diabetic retinopathy and hyperlipidaemia, 30% had coronary heart disease and 25% had diabetic neuropathy. Although the exclusion criteria allowed inclusion of patients in very poor metabolic control (i.e. with a HbA1c < 12%), the baseline mean haemoglobin A1C was 7.7%.

The degree of blood pressure control in the study population was generally not optimal since above 60% of recruited participants had SBP levels ranging between 130-160 mmHg. Data suggests a contribution of finerenone to BP control that starts soon after treatment initiation which resulted in more patients in the experimental arm achieving on-target BP values compared to placebo (30.8% vs 24.3% with BP<130 mmHg at Month 1 in the finerenone and placebo arm, respectively). However, in both arms an increase in the use of anti-hypertensives over time was observed, with a rise in the number of patients treated with >4 drugs in both groups (from 40.1% and 41.1% in the finerenone and placebo arm at baseline to 50.5% and 52.5% in the finerenone and placebo arm at Month 36). Based on these observations, the contribution to BP control exerted by finerenone can be considered modest.

In the first 12 months of treatment, the mean reduction in SBP was approximately 3 to 4 mmHg greater in the finerenone arm compared to placebo, and the reduction was more pronounced in the subgroup of subjects with a baseline SBP >160 mmHg (5 to 7 mmHg). Although of modest entity, the effect can be considered clinically beneficial, based on the association between BP reduction and CV risk reduction. Accordingly, the applicant showed that a proportion of the treatment effect on cardiorenal outcomes could be attributed to BP reduction. This proportion equals to 14.0%, 12.5%

and 31.2% for the primary renal, secondary renal and key secondary CV endpoint, respectively, using a Cox proportional hazards model adjusted for baseline SBP and SBP change from baseline to Month 4, and of 13.8%, 13.2% and 12.6% in a Cox proportional hazards model adjusted for time-varying SBP. The fact that the use of anti-hypertensive drugs was similar between groups, together with the therapy optimisation during the run-in-period, provide reassurance on the similarity in BP management adopted in both groups, thus limiting the risk of bias. The use of finerenone on top of SoC led to an improvement in BP control compared to placebo, which was maximum for patients with uncontrolled BP. As expected, patients with on-target BP levels at baseline presented with a reduced incidence of renal events compared to those with off-target BP irrespective of treatment. This is in line with the well-established renoprotection deriving from BP control. Finerenone independently adds a beneficial action to the background therapy since a reduction in renal endpoints was observable regardless of BP category at baseline. The current data support the concept that the target population is expected to benefit from finerenone regardless of BP control status, with no impact on the pursued indication.

The primary endpoint was intended to support the first part of the initially proposed indication, i.e. *"to delay progression of kidney disease"*. Treatment with finerenone resulted in a 17.5% relative hazard reduction compared with placebo for the composite endpoint time to first occurrence of kidney failure, a sustained decrease of eGFR ≥40% from baseline over at least 4 weeks, or renal death (HR 0.825 [95% CI 0.732; 0.928]; p=0.0014). The primary endpoint of the FIDELIO-DKD study was thus met.

The Kaplan-Meier curves did separate starting 12 months after treatment initiation, indicating a sustained effect. The absolute risk reduction based on Kaplan-Meier cumulative incidences for the primary renal composite endpoint was 2.9% at 24 months and 3.4% at 36 months with finerenone compared to placebo, corresponding to NNTs to prevent one primary endpoint event of 34 and 29 subjects, respectively.

The effect on the primary endpoint appears to be mainly driven by the component sustained decrease in eGFR ≥40% relative baseline (HR 0.815 [95% CI 0.722; 0.920]; nominally p-value=0.0009) while no efficacy was reported on other clinical endpoints (kidney failure and death).

In finerenone-treated subjects, an initial ('acute') reduction in eGFR was observed compared to placebo, with a difference in LS means (finerenone minus placebo) of 2.38 mL/min/1.73 m^2 from baseline to Month 4. According to the applicant this finding reflects a reduced intraglomerular pressure due to finerenone treatment rather than intrinsic structural damage to the kidneys. The initial reduction in eGFR is anticipated based on the mode of action of finerenone and consistent with that observed in ARTS DN, where these changes were observed to be reversible following treatment discontinuation. Thereafter, a more attenuated decline over time in the eGFR ('chronic') slope was observed in finerenone-treated subjects compared to those on placebo. From the FIDELIO-DKD study, no reliable post-treatment data is available given the study design.

Due to the initial decreased eGFR in subjects treated with finerenone, eGFR values were numerically lower in the finerenone arm until Month 24. After this timepoint, eGFR values were numerically higher in the finerenone arm. An ANCOVA of the chronic eGFR slope (from Month 4 until the PD or EOS visit) describes a slower decline in eGFR over time with finerenone: the annualised difference in LS means (finerenone minus placebo) was 1.310 mL/min/1.73 m^2 (p<0.0001). Further analyses across both treatment arms show that in the FAS, the acute and chronic slopes are negatively correlated (Pearson correlation coefficient -0.227, [95% CI 0.255; 0.198], p <0.0001) i.e. a more pronounced initial decline was associated with a better chronic preservation of renal function, indicating that the decline has no negative long-term consequences on eGFR.

Based on subgroup analyses, variability in magnitude of effect for the primary endpoint is noted across geographic areas, with Asia displaying the highest beneficial response to treatment (HR=0.71; 95% CI: 0.58, 0.87) and Europe showing only a marginal effect (HR=0.92; 0.75, 1.12). However, the

secondary renal endpoint of time to first occurrence of kidney failure, sustained decrease of eGFR ≥ 57% from baseline over at least 4 weeks or renal death showed a lower HR in Europe (0.61; 95% CI 0.44-0.83) than Asia (0.75; 95% CI 0.57-0.99). Clearly the point estimates lack precision in the subgroup analysis, and there is no biological plausibility as to why the two renal outcomes should be discordant; it can be concluded that kidney benefit did not differ between regions.

There is a net differentiation of response in the primary endpoint when looking at efficacy data by BMI levels (HR=0.68 for BMI<30 vs HR=0.98 for BMI≥30); it should however be noted that the control arm within the BMI≥30 performed unexpectedly better than the placebo group in the counterpart, this discrepancy potentially introducing a bias in data interpretation as the rate of events in patients on finerenone were similar for the two BMI subcategories. An additional data analysis by Cox proportional hazards model indicates no benefit for patients with a BMI>35 kg/m^2 (HR consistently above 1) which supports the previously observed lack of beneficial effect of finerenone in obese diabetics (BMI>30). In comparing baseline characteristics across BMI quartiles, the only notable difference can be attributed to concomitant medications. In the analysis of results by concomitant medications as presented in the original submission, and with reference to ACE-Is, ARBs and Beta-blockers, all of them exerting feedback on the compensatory RAAS activation status, there were no observable differences between users and non-users in terms of finerenone response to treatment for the primary outcome.

History of CVD demonstrated a significant interaction with treatment so that efficacy in patients without prior events can be deemed absent (HR 0.94 [0.80; 1.09)] vs. HR 0.70 [0.58; 0.84]) however the effect on the key secondary cardiovascular outcome was consistent in patients with (HR 0.85 [0.71; 1.01]) and without (HR 0.87 [0.69; 1.09] a history of CVD. The comparison between groups (i.e. CVD present or absent) revealed similarity in terms of clinical characteristics, the only difference being the use of concomitant drugs at baseline (particularly, beta-blockers were more frequently prescribed in patients with prior CVD). The portion of patients who experienced a CV events within 12 weeks from study recruitment was limited to 1.5% in the finerenone arm (42/2833 subjects) and 1.2% in the placebo arm (35/2841 subjects), thus accounting for only a minority of the group of patients with history of CVD (42/1303 and 35/1302; 3.2% in the finerenone arm and 35/1302; 2.7% in the placebo arm). The majority of patients with CVD (96.5% and 97.3% in the finerenone and placebo arm, respectively) had a period from events and recruitment >12 weeks, thus reassuring on the stability of the clinical conditions and background therapy of these patient subcategory.

About one third (34.4%) of the total study population was treated with a combination of diuretics and beta-blockers as concomitant medications. Within this subgroup of patients, the treatment effect of finerenone on the primary renal endpoint was attenuated (HR of 0.93 [95% CI 0.76; 1.12]) for subjects with a combined therapy with diuretic and beta-blocker at baseline; vs a HR of 0.77 [95% CI 0.66; 0.90] for subjects without a combined therapy with diuretic and beta-blocker at baseline) although no significant interaction of treatment was observed. Concerning the secondary renal endpoint, the effect of finerenone was consistent among groups regardless of concomitant medications (i.e. users and non-users of beta-blockers, either alone or in combination with diuretics). No distinct recommendations can be made based on this efficacy data for finerenone depending on concomitant medications.

No benefit was reported for the primary endpoint in the subgroup with eGFR ≥60 ml/min/1.73 m^2; this is not cause of concern considering that the proposed indication is restricted to CKD stage 3 and 4. Furthermore, given the small number of participants in the subgroup, the point estimate lacks precision. There is limited evidence to the potential advantage of finerenone on top of SoC for patients with high albuminuria (compared to very high albuminuria), not only because of their limited representativeness within the overall study population but also in view of a consistent variability in response that makes the benefit of treatment on primary outcomes quite dubitable in this subgroup. While a HR < 1 was observed consistently across different ranges, confidence intervals are wide

particularly for UACR values < 300 mg/g. The strongest beneficial effect appears for patients in the highest UACR quartile given a nominal value of HR and 95% CI < 1. In comparing patient characteristics, patients in the highest UACR quartile seem to present with a more advanced stage of disease as suggested by a higher mean systolic and diastolic blood pressure, a lower mean eGFR and higher mean serum creatinine compared to those in the lowest quartiles. On the other side, the precision of the point estimates is likely influenced by the numerosity of the different subgroups as well as the event rate, which is more frequent in the "very high" albuminuria group compared to the "high" albuminuria group. Given the potential for confounding factors, data interpretation is not univocal.

The secondary renal composite defined a more pronounced eGFR decrease compared to the primary endpoint (≥57% vs. ≥40%). Treatment with finerenone resulted in a 23.7% relative hazard reduction compared with placebo (RR 0.763 [95% 0.648; 0.900]. Statistical testing was considered explorative (p=0.0012) given that the hierarchical testing sequence had been broken in the previous steps.

Treatment with finerenone resulted in a reduced UACR from baseline to month 4 (RR 0.688 [95% CI 0.662, 0.715]; p<0.0001 explorative). This is in line with results from the ARTS-DN phase II study and supports the reno-protective mode of action of finerenone. An ancillary analysis indicates that this effect is sustained throughout the study.

SGLT2 inhibitors have recently been shown to have benefit for patients with T2D and CKD. The effect of finerenone in patients treated with SGLT2i is therefore of interest. Long-term data on UACR was requested for these subgroups given that the estimate for the primary endpoint is unreliable in small subgroups. The applicant has provided data on UACR up to 36 months in the subgroups of patients treated with SGLT-2 inhibitors and GLP1 agonists, respectively. In both these subgroups, finerenone showed a comparable effect on UACR as observed in the FAS. Although no definitive conclusions can be made on clinical benefit of finerenone in these patients, data exclude harm deriving from the therapy.

In summary, a statistically significant and clinically relevant effect on CKD has been shown in support of the first part of the indication, i.e. "to delay progression of kidney disease".

The key secondary endpoint was intended to support the second part of the initially proposed indication, i.e. *"to reduce the risk of cardiovascular mortality and morbidity"*. Treatment with finerenone resulted in a 14% relative hazard reduction compared with placebo of the key secondary CV composite endpoint, i.e. time to CV death, non-fatal MI, non-fatal stroke, or hospitalisation for heart failure (HR 0.860 [95% CI 0.747; 0.989]; p=0.0339). When analysing the components, there are numerical differences in favour of finerenone in CV death, non-fatal MI and hospitalisation for heart failure (although the nominal p-values were above 0.05) whereas the occurrence of stroke in the two treatment arms were very similar. Although this risk reduction observed in this endpoint is formally significant, the treatment effect is not convincing. According to EMA guidance (CPMP/EWP/2330/99), applications based on one pivotal study needs to be particularly compelling with respect to clinical relevance and statistical significance. For the key secondary (cardiovascular) endpoint, the upper limit of the 95% CI is close to unity and the p-value (0.0339) relatively close to the pre-specified alpha level. Consequently, evidence do not demonstrate a compelling benefit of finerenone in terms of CV protection; this, in any case, can be at least partly ascribed to the renal effects of the drug given the intrinsic relationship between kidney disease and CV risk.

In the prior SA, CHMP recommended the submission of both the FIDELIO-DKD and the FIGARO trials to support the dual indication. The applicant has explained that the strategy was changed given that significant results were obtained for both the primary and the secondary endpoint in the FIDELIO-DKD study. The applicant has provided a high-level summary of the FIGARO-DKD trial. In this trial, the primary cardiovascular endpoint was met but not the secondary renal endpoint, although a positive trend was shown. It was considered that an assessment of the final results of the FIGARO-DKD study

is required before the CHMP could come to a conclusion with respect to a CV indication, in line with previous scientific advice. The outcome based on the single pivotal study is not considered compelling and is therefore not sufficient to support the indication "to reduce the risk of cardiovascular mortality and morbidity in adults with CKD". Nevertheless, the currently available evidence reassures on the lack of harm deriving from treatment in a population of patients who are classified at high CV risk given the underlying renal disease. In this regard, the cardiovascular data from the FIDELIO-DKD study supports the use of finerenone for the renal indication and therefore are reflected in section 5.1 of the SmPC. In the present submission, the cardiovascular part of the initially proposed indication has been removed.

All-cause mortality was numerically reduced in the finerenone arm (HR 0.895 [95% CI 0.746; 1.075]) but not statistically significant (p=0.2348). The risk reduction appears to be driven by a decrease in CV death. This finding is important given that it supports that there is no general detrimental effect of finerenone on mortality, but it does not provide additional support for the claimed reduction of cardiovascular mortality.

Among the exclusion criteria, thirty days between a prior CV event and screening visit implies that a more vulnerable population than generally contemplated was recruited into the study (i.e. 12 weeks since prior CV events, especially of cardiac origin, are the usual limit for patient recruitment in clinical trials evaluating stable patients with chronic CV conditions). Almost half of the recruited population had history of CV events however the portion of patients who experienced a CV events within 12 weeks from study recruitment was limited to 1.5% in the finerenone arm (42/2833 subjects) and 1.2% in the placebo arm (35/2841 subjects), thus accounting for only a minority of the group of patients with history of CVD (42/1303 and 35/1302; 3.2% in the finerenone arm and 35/1302; 2.7% in the placebo arm). The majority of patients with CVD (96.5% and 97.3% in the finerenone and placebo arm, respectively) had a length period from events and recruitment >12 weeks, thus reassuring on the stability of the clinical conditions and background therapy of these patient subcategory. Moreover, a similar trend in primary and secondary endpoints can be recognised between the >12 weeks and <12 weeks subgroups.

Patients with symptomatic heart failure and reduced ejection fraction were excluded from the trial but patients with reduced ejection fraction at NYHA class I or symptomatic patients with mildly reduced or preserved EF (HFmrEF/HFpEF) were included. The number of included patients with a history of cardiac failure present was 195 (6.9%) in the finerenone group and 241 (8.5%) in the placebo group. The applicant has performed an exploratory analysis of the primary endpoint and its components. Comparable HR:s for both the composite and the components were found. Thus, based on the present data, history of cardiac failure does not appear to influence the treatment effect of finerenone on renal function.

A similar analysis was performed for the key secondary CV composite endpoint. As may be expected, the number of events were higher in the subgroup with a history of cardiac failure, but the outcome for the composite endpoint remained numerically in favour of finerenone. The outcome was largely driven by a lower rate of non-fatal MIs and hospitalisations due to heart failure among patients with a history of cardiac failure.

Efficacy data from supportive studies

ARTS-HF and ARTS-HF Japan phase 2 studies were conducted in patients with worsening chronic heart failure and either type 2 DM with or without CKD or moderate CKD alone. The results indicate a comparable effect of finerenone as eplerenone on the responder rate of NT-proBNP after 90 days treatment. The ARTS study was conducted in patients with clinical diagnosis of CHF. After 28 days of finerenone treatment, UACR was reduced while serum potassium was increased. Directionally consistent changes were observed with the comparator spironolactone. Taken together, the data supports a positive effect on kidney and cardiac function in a different population.

2.6.7. Conclusions on the clinical efficacy

The application is based on the FIDELIO-DKD study, encompassing 5674 patients with CKD and T2D treated with maximum tolerable dose of ACEi or an ARB. The primary endpoint was intended to support the first part of the initially proposed indication, i.e. "to delay progression of kidney disease". Treatment with finerenone resulted in a 17.5% relative hazard reduction compared with placebo for the composite endpoint time to first occurrence of kidney failure, a sustained decrease of eGFR ≥40% from baseline over at least 4 weeks, or renal death. A decline in 57% eGFR i.e., doubling of serum creatinine, was incorporated in the secondary renal composite which showed a more pronounced effect of the treatment (RR 0.763 [95% 0.648; 0.900]; nominally p-value=0.0012). Thus, a statistically significant effect on CKD has been shown in support of the first part of the indication that is considered clinically relevant. However, the effect size was relatively modest and driven by a reduction in the number of eGFR>40% or 57% decays.

The key secondary endpoint was intended to support the second part of the initially proposed indication, i.e. "to reduce the risk of cardiovascular mortality and morbidity". Treatment with finerenone resulted in a 14% relative hazard reduction compared with placebo of the key secondary CV composite endpoint, i.e. time to CV death, non-fatal MI, non-fatal stroke, or hospitalisation for heart failure. Although this risk reduction observed in this endpoint is formally significant, the treatment effect is not convincing but provide reassurance on lack of harm deriving from therapy when used for a renal indication. In the prior scientific advise procedure, CHMP recommended the submission of both the FIDELIO-DKD and the FIGARO trials to support the dual indication. With the present submission, the applicant has provided only a high-level summary of the FIGARO-DKD trial. It was considered that an assessment of the final results of the FIGARO-DKD study is required before the CHMP could come to a conclusion with respect to a CV protection part of the initially proposed indication, in line with previous scientific advice. The outcome based on the single pivotal study is not considered compelling and is therefore not sufficient to support the proposed cardiovascular protection part of the initially proposed indication. In the present submission, the cardiovascular protection part of the indication has therefore been removed.

In summary, a statistically significant effect on CKD has been shown in support of the indication: "treatment of chronic kidney disease", that is considered clinically relevant, although the effect size was relatively modest. The currently 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." is acceptable.

2.6.8. Clinical safety

The safety of finerenone is evaluated in the safety analysis set (or 'SAF' population), which included all randomised subjects who received at least 1 dose of study drug in the FIDELIO-DKD study. The evaluation of the FIDELIO-DKD study provides information on the safety profile of finerenone in subjects with CKD and T2D

2.6.8.1. Patient exposure

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, 1,632 subjects (58%) for at least 2 years. Mean and median duration of treatment in the SAF were similar in both treatment arms (about 27 months).

2.6.8.2. Adverse events

The number of TEAEs was balanced for finerenone (87.3%) and placebo (87.5%); however, the incidence of drug-related TEAEs was increased for finerenone (22.9%) compared with placebo (15.9%) (Table 30).

Table 30. Overall summary of AEs: number (%) of subjects (SAF) – FIDELIO-DKD.

	Finerenone	Placebo
Number (%) of subjects with	**N = 2827 (100%)**	**N = 2831 (100%)**
Any AE [a]	**2540 (89.8%)**	**2535 (89.5%)**
Any AE related to procedures required by protocol	63 (2.2%)	66 (2.3%)
Any AE leading to discontinuation of study drug	233 (8.2%)	188 (6.6%)
Any serious AE	1113 (39.4%)	1148 (40.6%)
Any AE with outcome death [d]	89 (3.1%)	105 (3.7%)
Any TEAE	**2468 (87.3%)**	**2478 (87.5%)**
Any study drug-related TEAE	646 (22.9%)	449 (15.9%)
Any TEAE related to procedures required by protocol	52 (1.8%)	54 (1.9%)
Any TEAE leading to discontinuation of study drug	207 (7.3%)	168 (5.9%)
Any serious TEAE	**902 (31.9%)**	**971 (34.3%)**
Any study drug-related serious TEAE	48 (1.7%)	34 (1.2%)
Any serious TEAE related to procedures required by protocol	2 (<0.1%)	4 (0.1%)
Any serious TEAE leading to discontinuation of study drug	75 (2.7%)	78 (2.8%)
Any TEAE with outcome death [d]	31 (1.1%)	51 (1.8%)
Any pre-randomisation [b] AE	**9 (0.3%)**	**8 (0.3%)**
Any AE related to procedures required by protocol	7 (0.2%)	7 (0.2%)
Any serious AE	1 (<0.1%)	0
Any AE with outcome death [d]	0	0
Any post-treatment [c] AEs	**919 (32.5%)**	**851 (30.1%)**
Any AE related to procedures required by protocol	5 (0.2%)	5 (0.2%)
Any serious AE	404 (14.3%)	415 (14.7%)
Any AE with outcome death [d]	58 (2.1%)	54 (1.9%)

Most frequently reported adverse events

The most commonly reported TEAEs that were reported more for frequently for finerenone than for placebo were hyperkalaemia including increased blood potassium (18.3% vs 9.0%), decreased GFR (6.3% vs 4.7%), anaemia (7.4% vs 6.7%), hypotension (4.5% vs 3.1%) and hyponatremia (1.3% vs 0.6%).

Table 31. Number of subjects with common (≥5% in any treatment arm) TEAEs by PT (SAF) – FIDELIO-DKD.

PT MedDRA version 23.0	Finerenone N=2827 (100%)	Placebo N=2831 (100%)
Hyperkalaemia	446 (15.8%)	221 (7.8%)
Nasopharyngitis	241 (8.5%)	250 (8.8%)
Hypertension	212 (7.5%)	273 (9.6%)
Anaemia	209 (7.4%)	191 (6.7%)
Oedema peripheral	186 (6.6%)	304 (10.7%)
Diarrhoea	184 (6.5%)	189 (6.7%)
Upper respiratory tract infection	181 (6.4%)	189 (6.7%)
Glomerular filtration rate decreased	179 (6.3%)	133 (4.7%)
Urinary tract infection	179 (6.3%)	192 (6.8%)
Back pain	175 (6.2%)	175 (6.2%)
Hypoglycaemia	151 (5.3%)	194 (6.9%)
Dizziness	146 (5.2%)	153 (5.4%)
Arthralgia	142 (5.0%)	149 (5.3%)
Bronchitis	134 (4.7%)	151 (5.3%)
Constipation	131 (4.6%)	163 (5.8%)
Pneumonia	128 (4.5%)	181 (6.4%)

Table 32. TEAEs with a difference in reporting of ≥1% of subjects between the treatment arms by PT (SAF) - FIDELIO-DKD.

PT MedDRA version 23.0	Finerenone N=2827 (100%)	Placebo N=2831 (100%)
Difference of ≥1% of subjects: higher frequency in the finerenone arm		
Hyperkalaemia	446 (15.8%)	221 (7.8%)
Glomerular filtration rate decreased	179 (6.3%)	133 (4.7%)
Hypotension	126 (4.5%)	87 (3.1%)
Pruritus	104 (3.7%)	73 (2.6%)
Blood potassium increased	81(2.9%)	40 (1.4%)
Difference of ≥1% of subjects: higher frequency in the placebo arm		
Hypertension	212 (7.5%)	273 (9.6%)
Oedema peripheral	186 (6.6%)	304 (10.7%)
Hypoglycaemia	151 (5.3%)	194 (6.9%)
Constipation	131 (4.6%)	163 (5.8%)
Pneumonia	128 (4.5%)	181 (6.4%)
Blood creatine phosphokinase increased	64 (2.3%)	102 (3.6%)
Hypokalaemia	28 (1.0%)	61 (2.2%)

"Hyperkalaemia", "hyponatraemia", "hypotension" and "GFR decreased" are adequately included in the proposed tabulated list of ADRs in section 4.8 of the SmPC. However, pruritus (common frequency) should also be included in the tabulated list in 4.8 (**SmPC**).

Adverse events of special interest

Hyperkalaemia

The hyperkalaemia related events were described using PTs Hyperkalaemia and Blood potassium increased.

The incidence of hyperkalaemia was 2 times increased for finerenone versus placebo (18.3% vs 9.0%). Drug-related hyperkalaemia were reported in 11.8% of the subjects in the finerenone group compared with 4.8% in the placebo group. Serious events of hyperkalaemia were reported more frequently for finerenone (1.6%) than for placebo (0.4%). Moreover, a higher incidence of hyperkalaemia leading to discontinuation (2.3% vs 0.9%) and hospitalisation (1.4% vs 0.3%) was reported for finerenone compared with placebo **(**Table 33).

More subjects treated with finerenone, compared with placebo, reported one AE (11.9% vs 6.6%), two AEs (4.3% vs 1.8%) and three AEs (1.5% vs 0.5%) of hyperkalaemia, respectively (Table 34).

A higher incidence for finerenone, than for placebo, had changes in serum potassium to >5.5 mmol/L (21.4% vs 9.2%) and to >6.0 mmol/L (4.5% vs 1.4%), respectively, at any time during treatment (Table 33).

The majority of cases with hyperkalaemia/ blood potassium increased recovered; however, in about 12% (62/527) of the cases of hyperkalaemia the outcome was reported as not recovered/not resolved **(**Table 35)

The incidence of hyperkalaemia (including hospitalisation due to hyperkalaemia) increased with decreasing renal function. The risk for serious events of hyperkalaemia could be handled with precautionary measures addressed in the SmPC, i.e. routine risk minimisation.

Table 33. Number of subjects with treatment-emergent hyperkalaemia including serum laboratory potassium values by category (SAF) - FIDELIO-DKD.

	Finerenone N = 2827 (100%)	Placebo N = 2831 (100%)
Any hyperkalaemia TEAE	**516 (18.3%)**	**255 (9.0%)**
Drug-related	333 (11.8%)	135 (4.8%)
Leading to hospitalisation	40 (1.4%)	8 (0.3%)
Leading to permanent discontinuation of study drug	64 (2.3%)	25 (0.9%)
Serious	44 (1.6%)	12 (0.4%)
Leading to death	0 (0.0%)	0 (0.0%)
PT hyperkalaemia	**446 (15.8%)**	**221 (7.8%)**
Drug-related	286 (10.1%)	114 (4.0%)
Severe	33 (1.2%)	9 (0.3%)
Drug-related, severe	20 (0.7%)	5 (0.2%)
Serious	42 (1.5%)	12 (0.4%)
Drug-related serious	24 (0.8%)	5 (0.2%)
Severe serious	20 (0.7%)	5 (0.2%)
PT blood potassium increased	**81 (2.9%)**	**40 (1.4%)**
Drug-related	53 (1.9%)	22 (0.8%)
Severe	2 (<0.1%)	0
Drug-related, severe	0	0
Serious	2 (<0.1%)	0
Drug-related serious	2 (<0.1%)	0
Severe serious	0	0
Serum potassium [a]	**Num/Den (%)**	**Num/Den (%)**
>5.5 mmol/L	597/2785 (21.4%)	256/2775 (9.2%)
>6 mmol/L	126/2802 (4.5%)	38/2796 (1.4%)

Table 34. Treatment-emergent adverse events: number of events in MLG Hyperkalaemia by treatment group (SAF)- FIDELIO-DKD.

	Finerenone N = 2827 (100%)	Placebo N = 2831 (100%)
Number (%) of subjects with at least 1 adverse event	516 (18.3%)	255 (9.0%)
Total number of events	793	342
Number of events per subject		
1	335 (11.9%)	188 (6.6%)
2	121 (4.3%)	51 (1.8%)
3	42 (1.5%)	13 (0.5%)
4	9 (0.3%)	2 (<0.1%)
5	3 (0.1%)	1 (<0.1%)
6	4 (0.1%)	0
7	1 (<0.1%)	0
8	1 (<0.1%)	0

Table 35. Number of subjects with treatment-emergent hyperkalaemia events by worst outcome (SAF)- FIDELIO-DKD.

Preferred term MedDRA version 23.0	**Worst Outcome**	**Finerenone N=2827 (100%)**	**Placebo N=2831 (100%)**
Hyperkalaemia	Unknown	1 (<0.1%)	0
	Recovered/resolved	372 (13.2%)	174 (6.1%)
	Recovering/resolving	21 (0.7%)	16 (0.6%)
	Recovered/resolved with sequelae	1 (<0.1%)	2 (<0.1%)
	Not recovered/not resolved	51 (1.8%)	29 (1.0%)
	Total	446 (15.8%)	221 (7.8%)
Blood potassium increased	Recovered/resolved	68 (2.4%)	34 (1.2%)
	Recovering/resolving	2 (<0.1%)	3 (0.1%)
	Not recovered/not resolved	11 (0.4%)	3 (0.1%)
	Total	81 (2.9%)	40 (1.4%)

Worsening of renal function

The incidence of 'eGFR decreased' was increased for finerenone (6.3%) compared with placebo (4.7%). The incidence of AEs from the SOC Renal and urinary disorders (18.5% vs 19.5%) was slightly higher for placebo, of which the incidence of acute kidney injury (4.6% vs 4.8%) was balanced. However, the incidence of *drug-related* events of 'eGFR decreased' (1.4% vs 0.5%) and AEs from the SOC Renal and urinary disorders (3.0% vs 2.3%), including acute kidney injury (1.2% vs 0.6%), was increased for finerenone versus placebo (Table 36). The outcome was reported as resolved/recovered in the majority of finerenone drug-related cases of AKI. The action taken was "no dose change" in half of the cases (17/34) and a "dose change" in 2 of the cases. The drug was interrupted in 11 cases and was withdrawn in 4 of the cases.

Treatment emergent SAEs from the SOC Renal and urinary disorders of renal events (4.7% vs 5.1%), including acute kidney injury (2.0% vs 1.8%) was balanced. The incidence of treatment emergent serious events of eGFR decreased was low but numerically higher for finerenone (0.2%) than for placebo (0.1%).

Information on decreased eGFR is included in section 4.8 of the SmPC.

Table 36. Number of subjects with treatment-emergent worsening of renal function including laboratory eGFR values by category (SAF).

	Finerenone N = 2827 (100%)	Placebo N = 2831 (100%)
Any worsening of renal function TEAE		
Leading to hospitalisation	68 (2.4%)	66 (2.3%)
Leading to permanent discontinuation of study drug	28 (1.0%)	32 (1.1%)
Relevant PTs		
Glomerular filtration rate decreased	**179 (6.3%)**	**133 (4.7%)**
Drug-related	39 (1.4%)	15 (0.5%)
Severe	12 (0.4%)	9 (0.3%)
Drug-related, severe	2 (<0.1%)	0
Serious	5 (0.2%)	4 (0.1%)
Drug-related serious	0	1 (<0.1%)
Severe serious	1 (<0.1%)	2 (<0.1%)
Acute kidney injury	**129 (4.6%)**	**136 (4.8%)**
Drug-related	34 (1.2%)	18 (0.6%)
Severe	29 (1.0%)	36 (1.3%)
Drug-related, severe	6 (0.2%)	5 (0.2%)
Serious	56 (2.0%)	51 (1.8%)
Drug-related serious	9 (0.3%)	6 (0.2%)
Severe serious	23 (0.8)	30 (1.1%)
Treatment emergent relative eGFR decrease [a]	**Num/Den (%)**	**Num/Den (%)**
≥30%	1277/2802 (45.6%)	1209/2797 (43.2%)
≥40%	695/2802 (24.8%)	695/2797 (24.8%)
≥50%	340/2802 (12.1%)	392/2797 (14.0%)
≥57%	171/2802 (6.1%)	242/2797 (8.7%)

2.6.8.3. Serious adverse event/deaths/other significant events

Serious adverse events

The incidence of treatment emergent SAEs was slightly higher in the placebo group (34.3%) than in the finerenone group (31.9%) and drug-related treatment emergent SAEs slightly higher for finerenone (1.7%) than for placebo (1.2%). The most frequently reported treatment emergent SAEs for finerenone versus placebo were pneumonia (2.5% vs 3.6%), acute kidney injury (2.0% vs 1.8%) and hyperkalaemia (1.5% vs 0.4%).

Table 37. Serious TEAE: 10 most frequent PTs in each treatment group - number (%) of subjects (SAF)- FIDELIO-DKD.

PT MedDRA Version 23.0	Finerenone N = 2827 (100%)	Placebo N = 2931 (100%)
Number (%) of subjects with at least 1 such adverse event	**902 (31.9%)**	**971 (34.3%)**
Pneumonia	70 (2.5%)	103 (3.6%)
Acute kidney injury	56 (2.0%)	51 (1.8%)
Hyperkalaemia	42 (1.5%)	12 (0.4%)
Cellulitis	26 (0.9%)	22 (0.8%)
Hypoglycaemia	21 (0.7%)	31 (1.1%)
Urinary tract infection	21 (0.7%)	23 (0.8%)
Cataract	19 (0.7%)	12 (0.4%)
Diabetic nephropathy	18 (0.6%)	16 (0.6%)
Hyperglycaemia	17 (0.6%)	23 (0.8%)
Hypertension	15 (0.5%)	23 (0.8%)
Sepsis	15 (0.5%)	17 (0.6%)
Type 2 diabetes mellitus	14 (0.5%)	22 (0.8%)
Chronic kidney disease	12 (0.4%)	22 (0.8%)
Syncope	12 (0.4%)	22 (0.8%)

Deaths

There were more fatal cases in the placebo group compared with the finerenone group (4.8% vs 3.1%).

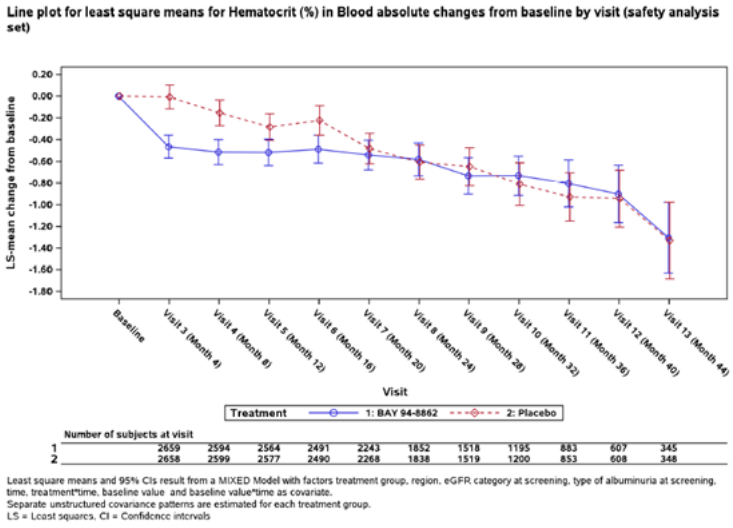
2.6.8.4. Laboratory findings

Laboratory findings

Haematology

A decrease in mean haemoglobin (<0.15 g/dL) and mean haematocrit (<0.45%) levels was observed in the first 4 months in the finerenone arm compared to placebo (Figure 22). Decreased haemoglobin has been included in the tabulated list of adverse reactions in section 4.8 of the SmPC.

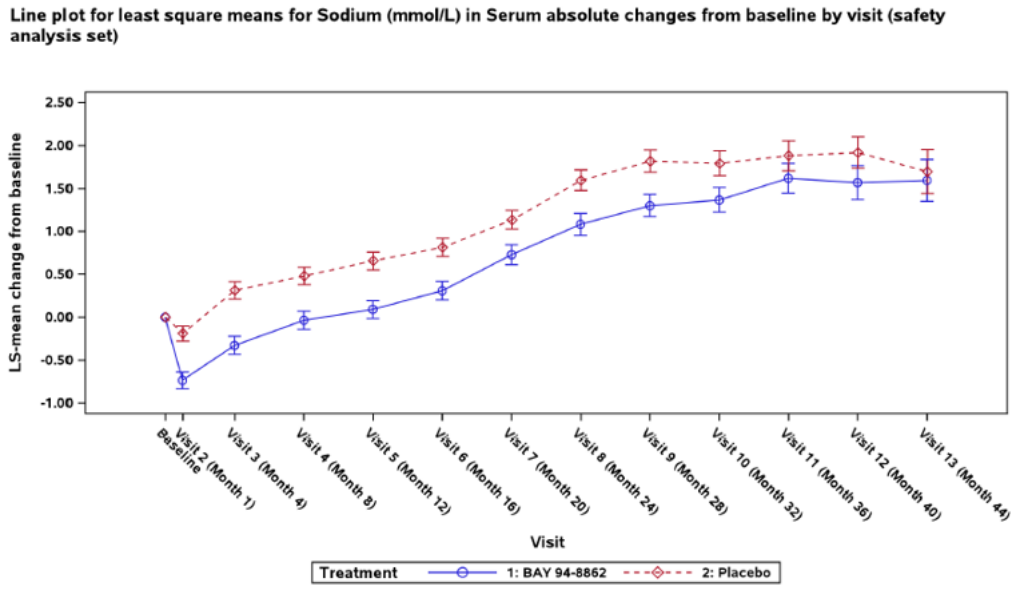
Figure 23. Line plot for LS means for haematocrit absolute changes from baseline by visit (safety analysis set).



Serum sodium

An initial decrease in mean serum sodium (approximately 0.7 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 groups, although the increase observed was smaller in the finerenone group (Figure 23).

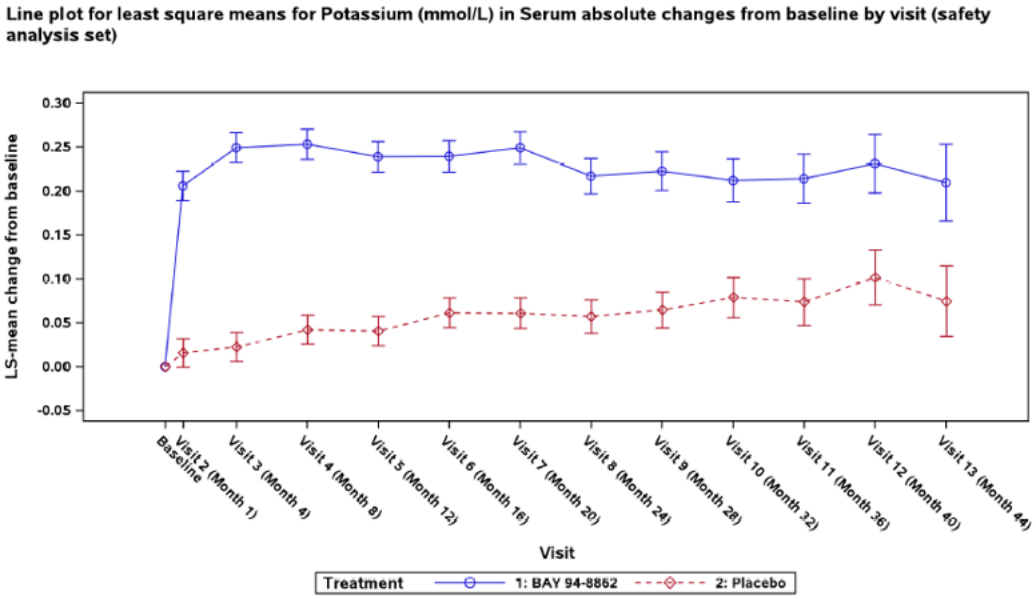
Figure 24. Line plot for LS means for sodium absolute changes from baseline by visit (safety analysis set).



Serum potassium

An increase from baseline in mean serum potassium in the first month of treatment of approximately 0.2 mmol/L was observed in the finerenone arm compared to placebo, with a maximum between-group difference of 0.23 mmol/L observed at Month 4, and stable mean measurements thereafter in the finerenone arm.

Figure 25. Line plot for LS means for potassium absolute changes from baseline by visit (safety analysis set).



Vital signs

Blood pressure

Treatment with finerenone resulted in mean reductions in SBP and DBP from baseline compared to placebo. Placebo-adjusted LS-mean difference for finerenone was consistent over time: -3.84/-1,74 mmHg (month 4), -3,27/-1,18 mmHg (month 16), -3,08/-1.09 mmHg (month 28), -2.49/-0.62 (month 40) and -2.21/-1,52 (month 44). Mean reductions in SBP were approximately 2 to 4 mmHg greater in finerenone-treated subjects compared with placebo and mean reductions in DBP approximately 1 to 2 mmHg greater in the finerenone group compared to placebo (Table 38**,** Table 39).

Table 38. Mixed model analysis of systolic blood pressure (FAS).

Visit	p-Value for main factors (a)			p-Value for interaction (b)	LS-mean difference	95% CI for difference	
Overall	<.0001, <.0001, 0.0028, 0.0119, <.0001, <.0001			0.0596, <.0001	-2.71	[-3.29 , -2.12]	
	Treatment	**N**	**LS-mean change from baseline**	**95% CI for change from baseline**	**LS-mean difference**	**95% CI for difference**	**p-value of treatment group comparison**
Visit 2 (Month 1)	Finerenone	2811	-3.00	[-3.46 , -2.54]	-2.92	[-3.58 , -2.27]	<.0001
	Placebo	2809	-0.09	[-0.56 , 0.37]			
Visit 3 (Month 4)	Finerenone	2745	-3.20	[-3.73 , -2.67]	-3.84	[-4.59 , -3.10]	<.0001
	Placebo	2754	0.67	[0.15 , 1.19]			
Visit 4 (Month 8)	Finerenone	2670	-1.62	[-2.19 , -1.05]	-3.11	[-3.89 , -2.32]	<.0001
	Placebo	2700	1.43	[0.90 , 1.97]			
Visit 5 (Month 12)	Finerenone	2628	-2.07	[-2.63 , -1.51]	-2.97	[-3.76 , -2.18]	<.0001
	Placebo	2640	0.85	[0.29 , 1.41]			
Visit 6 (Month 16)	Finerenone	2553	-2.45	[-3.03 , -1.86]	-3.27	[-4.09 , -2.45]	<.0001
	Placebo	2563	0.72	[0.14 , 1.29]			
Visit 7 (Month 20)	Finerenone	2310	-1.76	[-2.39 , -1.13]	-2.44	[-3.32 , -1.56]	<.0001
	Placebo	2330	0.58	[-0.03 , 1.20]			
Visit 8 (Month 24)	Finerenone	1907	-1.61	[-2.27 , -0.95]	at	[-3.46 , -1.58]	<.0001
	Placebo	1895	0.62	[-0.05 , 1.29]			
Visit 9 (Month 28)	Finerenone	1559	-2.13	[-2.86 , -1.40]	-3.08	[-4.12 , -2.04]	<.0001
	Placebo	1568	0.84	[0.10 , 1.58]			
Visit 10 (Month 32)	Finerenone	1223	-0.65	[-1.47 , 0.16]	-1.47	[-2.62 , -0.32]	0.0121
	Placebo	1224	0.66	[-0.16 , 1.47]			
Visit 11 (Month 36)	Finerenone	903	-1.82	[-2.79 , -0.85]	-2.18	[-3.54 , -0.82]	0.0017
	Placebo	884	0.37	[-0.59 , 1.33]			
Visit 12 (Month 40)	Finerenone	620	-2.32	[-3.46 , -1.18]	-2.49	[-4.09 , -0.89]	0.0023
	Placebo	622	-0.02	[-1.16 , 1.12]			
Visit 13 (Month 44)	Finerenone	348	-2.01	[-3.54 , -0.48]	-2.21	[-4.33 , -0.10]	0.0404
	Placebo	353	0.13	[-1.35 , 1.62]			

Table 39. Mixed model analysis of diastolic blood pressure (FAS).

Visit	p-Value for main factors (a)			p-Value for interaction (b)	LS-mean difference	95% CI for difference	
Overall	<.0001, <.0001, 0.0243, 0.0520, <.0001, <.0001			0.0126, <.0001	-1.03	[-1.37 , -0.69]	
	Treatment	N	LS-mean change from baseline	95% CI for change from baseline	LS-mean difference	95% CI for difference	p-value of treatment group comparison
Visit 2 (Month 1)	Finerenone	2811	-1.48	[-1.75 , -1.21]	-1.36	[-1.74 , -0.98]	<.0001
	Placebo	2809	-0.15	[-0.42 , 0.12]			
Visit 3 (Month 4)	Finerenone	2745	-1.77	[-2.06 , -1.47]	-1.74	[-2.17 , -1.32]	<.0001
	Placebo	2754	-0.06	[-0.36 , 0.24]			
Visit 4 (Month 8)	Finerenone	2670	-1.12	[-1.44 , -0.80]	-1.18	[-1.62 , -0.73]	<.0001
	Placebo	2700	0.00	[-0.31 , 0.31]			
Visit 5 (Month 12)	Finerenone	2628	-1.46	[-1.77 , -1.16]	-1.11	[-1.55 , -0.67]	<.0001
	Placebo	2640	-0.42	[-0.74 , -0.10]			
Visit 6 (Month 16)	Finerenone	2553	-1.62	[-1.95 , -1.29]	-1.18	[-1.65 , -0.71]	<.0001
	Placebo	2563	-0.52	[-0.86 , -0.19]			
Visit 7 (Month 20)	Finerenone	2310	-1.27	[-1.62 , -0.92]	-0.67	[-1.16 , -0.18]	0.0078
	Placebo	2330	-0.69	[-1.04 , -0.35]			
Visit 8 (Month 24)	Finerenone	1907	-1.44	[-1.81 , -1.07]	-0.89	[-1.41 , -0.37]	0.0009
	Placebo	1895	-0.70	[-1.08 , -0.33]			
Visit 9 (Month 28)	Finerenone	1559	-1.73	[-2.13 , -1.32]	-1.09	[-1.67 , -0.51]	0.0002
	Placebo	1568	-0.82	[-1.23 , -0.41]			
Visit 10 (Month 32)	Finerenone	1223	-1.14	[-1.59 , -0.69]	-0.45	[-1.09 , 0.19]	0.1686
	Placebo	1224	-0.98	[-1.44 , -0.53]			
Visit 11 (Month 36)	Finerenone	903	-1.51	[-2.04 , -0.97]	-0.52	[-1.28 , 0.23]	0.1711
	Placebo	884	-1.35	[-1.88 , -0.82]			
Visit 12 (Month 40)	Finerenone	620	-1.69	[-2.32 , -1.06]	-0.62	[-1.51 , 0.27]	0.1703
	Placebo	622	-1.58	[-2.21 , -0.95]			
Visit 13 (Month 44)	Finerenone	348	-2.30	[-3.11 , -1.49]	-1.52	[-2.71 , -0.33]	0.0121
	Placebo	353	-1.37	[-2.25 , -0.50]			

Heart rate

Overall, 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

In the FIDELO-DKD study, a 12-lead ECG was to be obtained if serum potassium levels exceeded 6.5 mmol/L. In the study, 60 subjects (41 on finerenone and 19 subjects on placebo) were identified with serum potassium >6.5 mmol/L and were further obtained with ECG measurements. ECG findings of "normal or normal variant" were reported in 25 subjects (19/41 subjects on finerenone vs 6/19 on placebo) and "sinus rhythm" were reported in 55 subjects (38/41 on finerenone vs 17/19 on placebo). Abnormal findings were reported in 35 subjects (22/41 on finerenone vs 13/19 on placebo), and the following ECG findings were considered likely to be related to hyperkalaemia: e.g. peaked T-waves, bundle branch block, bradycardia, sinus bradycardia and 1st degree AV block.

Of the 60 subjects in total (41 on finerenone and 19 subjects on placebo), 6 subjects had more than one ECG within three days of reported hyperkalaemia of which 3 in the finerenone group; 2 subjects had two ECG recordings, one reported as "normal sinus rhythm" and one reported "sinus rhythm and right bundle branch block" and 1 subject had 3 ECGs reported as "normal sinus rhythm". The revealed "sinus rhythm and right bundle branch block" was recorded in the medical history and was confirmed at baseline in that patient.

Table 40. Number of subjects with ECG findings within +/-3 days from treatment emergent (local or central) laboratory value of serum potassium >6.5 mmol/l (safety analysis set).

ECG findings within +/-3 days from treatment emergent (local or central) laboratory value of serum potassium >6.5 mmol/l	Finerenone N=41 (100%)	Placebo N=19 (100%)	Total N=60 (100%)
Normal or normal variant	19 (46.3%)	6 (31.6%)	25 (41.7%)
Sinus rhythm	38 (92.7%)	17 (89.5%)	55 (91.7%)
Abnormal	22 (53.7%)	13 (68.4%)	35 (58.3%)
1st degree AV block*	5 (12.2%)	2 (10.5%)	7 (11.7%)
Sinus bradycardia*	3 (7.3%)	2 (10.5%)	5 (8.3%)
Bradycardia*	0	1 (5.3%)	1 (1.7%)
Incomplete left bundle branch block*	0	1 (5.3%)	1 (1.7%)
Incomplete right bundle branch block*	1 (2.4%)	1 (5.3%)	2 (3.3%)
Intraventricular conduction delay, nonspecific*	0	1 (5.3%)	1 (1.7%)
Left anterior fascicular block*	0	1 (5.3%)	1 (1.7%)
Left bundle branch block*	2 (4.9%)	1 (5.3%)	3 (5.0%)
Right bundle branch block*	3 (7.3%)	0	3 (5.0%)
T wave peaked*	2 (4.9%)	2 (10.5%)	4 (6.7%)
Atrial fibrillation	1 (2.4%)	2 (10.5%)	3 (5.0%)
Left atrial abnormality	1 (2.4%)	1 (5.3%)	2 (3.3%)
Left ventricular hypertrophy	1 (2.4%)	3 (15.8%)	4 (6.7%)
Low QRS voltage	0	2 (10.5%)	2 (3.3%)
Non-specific ST-T changes	2 (4.9%)	0	2 (3.3%)
Old or age indeterminate anteroseptal wall myocardial infarction	1 (2.4%)	0	1 (1.7%)
Old or age indeterminate inferior wall myocardial infarction	2 (4.9%)	0	2 (3.3%)
Old or age indeterminate septal wall myocardial infarction	2 (4.9%)	0	2 (3.3%)
Poor R wave progression	0	1 (5.3%)	1 (1.7%)
Premature atrial complexes	0	1 (5.3%)	1 (1.7%)
Premature atrial complexes blocked	0	1 (5.3%)	1 (1.7%)
Q axis, left axis deviation	2 (4.9%)	0	2 (3.3%)
Q axis, right axis deviation	1 (2.4%)	0	1 (1.7%)
Repolarisation abnormality	1 (2.4%)	0	1 (1.7%)
T wave inversion	3 (7.3%)	0	3 (5.0%)

Body weight/BMI

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.

2.6.8.5. Safety in special populations

Effect by age

In FIDELIO-DKD, TEAE categories were analysed by age group <65 (n=2,372), 65 to 74 (n=2,394) and ≥75 years (n=892).

The reporting rate was overall similar across the age groups. Slightly more SAEs were reported in the age group ≥75 years (35.0% vs 38.0%) compared to subjects 65-74 years (32.6% vs 32.7%) and <65 years (30.1% vs 34.1%); however, the incidence of SAEs was higher for placebo than for finerenone in all age groups. More subjects discontinued due to an AE in for finerenone compared with placebo in the subgroups ≥75 years (9.5% vs 5.6%) and 65-74 years (8.1% vs 6.3%); however, the discontinuation rate due to AEs was balanced (5.7% vs 5.6%) in subjects <65 years (*Table* 41).

The incidence of subjects discontinuing permanently due to hyperkalaemia was increased for finerenone compared to placebo across age groups with the highest incidence in the subgroup ≥75 years (3.9% vs 0.7%) (Table 42).

Table 41. Overall summary of number of subjects with TEAE by age group (years) (SAF).

Number (%) of subjects with TEAE	Age <65 years		Age 65 - 74 years		Age ≥75 years	
	Finerenone N=1201 (100%)	Placebo N=1171 (100%)	Finerenone N=1195 (100%)	Placebo N=1199 (100%)	Finerenone N=431 (100%)	Placebo N=461 (100%)
Any AE	1039 (86.5%)	1033 (88.2%)	1052 (88.0%)	1039 (86.7%)	377 (87.5%)	406 (88.1%)
Maximum intensity for any AE						
Mild	366 (30.5%)	327 (27.9%)	341 (28.5%)	325 (27.1%)	115 (26.7%)	112 (24.3%)
Moderate	477 (39.7%)	485 (41.4%)	489 (40.9%)	483 (40.3%)	179 (41.5%)	189 (41.0%)
Severe	196 (16.3%)	221 (18.9%)	222 (18.6%)	231 (19.3%)	83 (19.3%)	105 (22.8%)
Any study drug-related AE	270 (22.5%)	195 (16.7%)	290 (24.3%)	183 (15.3%)	86 (20.0%)	71 (15.4%)
Maximum intensity for study drug-related AE						
Mild	157 (13.1%)	114 (9.7%)	164 (13.7%)	104 (8.7%)	47 (10.9%)	39 (8.5%)
Moderate	94 (7.8%)	73 (6.2%)	99 (8.3%)	65 (5.4%)	33 (7.7%)	26 (5.6%)
Severe	19 (1.6%)	8 (0.7%)	27 (2.3%)	14 (1.2%)	6 (1.4%)	6 (1.3%)
Any AE related to procedures required by the protocol	22 (1.8%)	25 (2.1%)	26 (2.2%)	23 (1.9%)	4 (0.9%)	6 (1.3%)
Any AE leading to discontinuation of study drug	69 (5.7%)	66 (5.6%)	97 (8.1%)	76 (6.3%)	41 (9.5%)	26 (5.6%)
Any SAE	361 (30.1%)	404 (34.5%)	390 (32.6%)	392 (32.7%)	151 (35.0%)	175 (38.0%)
Any study drug-related SAE	22 (1.8%)	16 (1.4%)	19 (1.6%)	10 (0.8%)	7 (1.6%)	8 (1.7%)
Any SAE related to procedures required by the protocol	1 (<0.1%)	1 (<0.1%)	1 (<0.1%)	2 (0.2%)	0	1 (0.2%)
Any SAE leading to discontinuation of study drug	20 (1.7%)	28 (2.4%)	36 (3.0%)	34 (2.8%)	19 (4.4%)	16 (3.5%)
AE with outcome death	11 (0.9%)	13 (1.1%)	12 (1.0%)	24 (2.0%)	8 (1.9%)	14 (3.0%)

Source: Table 4-1, Summary of clinical safety

Table 42. Number of subjects discontinuing study drug permanently due to treatment-emergent hyperkalemia by safety subgroups (SAF).

Safety subgroups	Finerenone Number of subjects with event	N	Placebo Number of subjects with event	N
Age group				
<45 years	**1 (2.0%)**	**49**	**0**	**65**
45 -<65 years	**19 (1.6%)**	**1152**	**9 (0.8%)**	**1106**

65 - <75 years	28 (2.3%)	1195	13 (1.1%)	1199
75 - <85 years	16 (3.9%)	413	3 (0.7%)	436
≥85 years	0	18	0	25

Effect by sex

No notable differences between males and females, apart from that the incidence of subjects that discontinued due to an AE was increased for finerenone compared with placebo (8.0% vs 5.8%) in males and was more balanced in females (5.9% than 6.2%).

Effect by race

The rate of AEs was similar between the treatment arms across the race groups; however, the incidence of AEs was about 85%-89% in White, Black and Other subjects and was slightly higher in Asian subjects (93%). The difference was mainly driven by a higher number of subjects with AEs of mild intensity in the Asian race group (38%-41%) compared to the other race groups (19%-27%).

Effect by hepatic impairment

The applicant has presented an overall summary by hepatic impairment: "subjects with no hepatic impairment" (n=4,764) and "subjects with hepatic impairment" (n=894) (Table 43). Subjects with hepatic impairment had an overall slightly higher incidence of AEs (92.3% vs 92.0%) and SAEs (39.1% vs 40.1%) compared with subjects with no hepatic impairment (86.4% vs 86.2% and 30.6% vs 33.2%).

Table 43. Overall summary of number of subjects with TEAE by hepatic impairment (SAF).

	No		Yes	
Number (%) of subjects with TEAE	Finerenone N=2384 (100%)	Placebo N=2380 (100%)	Finerenone N=443 (100%)	Placebo N=451 (100%)
Any AE	2059 (86.4%)	2063 (86.7%)	409 (92.3%)	415 (92.0%)
Maximum intensity for any AE				
Mild	685 (28.7%)	636 (26.7%)	137 (30.9%)	128 (28.4%)
Moderate	967 (40.6%)	968 (40.7%)	178 (40.2%)	189 (41.9%)
Severe	407 (17.1%)	459 (19.3%)	94 (21.2%)	98 (21.7%)
Any study drug-related AE	544 (22.8%)	367 (15.4%)	102 (23.0%)	82 (18.2%)
Maximum intensity for study drug-related AE				
Mild	315 (13.2%)	211 (8.9%)	53 (12.0%)	46 (10.2%)
Moderate	186 (7.8%)	134 (5.6%)	40 (9.0%)	30 (6.7%)
Severe	43 (1.8%)	22 (0.9%)	9 (2.0%)	6 (1.3%)
Any AE related to procedures required by the protocol	40 (1.7%)	45 (1.9%)	12 (2.7%)	9 (2.0%)
Any AE leading to discontinuation of study drug	167 (7.0%)	137 (5.8%)	40 (9.0%)	31 (6.9%)
Any SAE	729 (30.6%)	790 (33.2%)	173 (39.1%)	181 (40.1%)
Any study drug-related SAE	39 (1.6%)	27 (1.1%)	9 (2.0%)	7 (1.6%)
Any SAE related to procedures required by the protocol	2 (<0.1%)	3 (0.1%)	0	1 (0.2%)
Any SAE leading to discontinuation of study drug	61 (2.6%)	66 (2.8%)	14 (3.2%)	12 (2.7%)
AE with outcome death	28 (1.2%)	43 (1.8%)	3 (0.7%)	8 (1.8%)

Effect by renal impairment

In the study population, approximately 2.3% of the subjects had baseline eGFR<25 mL/min/1.73m^2, 53% eGFR 25 -<45 mL/min/1.73m^2, 34% eGFR 45 - <60 mL/min/1.73m^2 and 12% eGFR eGFR>60 mL/min/1.73m^2.

The incidence of AEs and SAEs for finerenone versus placebo was similar in subjects with eGFR 25 - <45 mL/min/1.73m^2(88.2% vs 88.9% and 31.8% vs 35.3%) and eGFR 45 - <60 mL/min/1.73m^2 (86.8% vs 86.2% and 32.6% and 33.2%). However, the incidence of *study-drug related* AEs and SAEs was increased for finerenone compared with placebo and slightly higher in the subgroup with eGFR 25 -<45 mL/min/1.73m^2 (25.3% vs 17.4% and 2.0% vs 1.5%) than in the eGFR 45 - <60 mL/min/1.73m^2 (19.9% vs 13.9% and 1.4% vs 0.9%). Moreover, the incidence of subjects with any AE leading to discontinuation of study drug was increased for finerenone compared with placebo and slightly higher in subjects with eGFR 25 -<45 mL/min/1.73m^2 (8.2% vs 6.3%) than in subjects with eGFR 45 - <60 mL/min/1.73m^2 (6.0% vs 5.0%) (Table 44). Additionally, the risk of hyperkalaemia increased with decreasing renal function across eGFR strata: ≥60 (10.7% vs 8.6%), 45 -<60 (14.7% vs 6.3%) and 25 -45 (22.1% vs 10.6%) (Table 45). The FIDELIO-DKD study did not include any follow-up of eGFR after discontinuation of treatment. An off-treatment slope was calculated from available data, by assessing the difference between the last available eGFR measurement before last intake of study drug and the first available eGFR measurement after last intake of study drug, indicating reversibility of eGFR decline in the overall population but not for the subgroup with eGFR <25. Furthermore, follow-up data from the phase 2b ARTS-DN study did show that eGFR values tended to return to baseline after discontinuation of 3 months treatment.

Table 44, Number of subjects with any treatment-emergent hyperkalemia events (based on MLG) in selected safety subgroups (SAF),

	Finerenone		Placebo	
Safety subgroups	**Number of subjects with event**	**N**	**Number of subjects with event**	**N**
Baseline eGFR (CKD-EPI)				
<25 mL/min/1.73m^2	14 (21.2%)	66	9 (13.0%)	69
25 - <45 mL/min/1.73m^2	325 (22.1%)	1473	159 (10.6%)	499
45 - <60 mL/min/1.73m^2	143 (14.7%)	971	58 (6.3%)	926
≥60 mL/min/1.73m2	34 (10.7%)	317	29 (8.6%)	337

Table 45, Overall summary of number of subjects with TEAE by baseline eGFR category (CKD-EPI, SAF),

Number (%) of subjects with TEAE	<25 mL/min/1.73m^2		25 - <45 mL/min/1.73m^2		45 - <60 mL/min/1.73m^2		≥60 mL/min/1.73m^2	
	Finerenone N=66 (100%)	Placebo N=69 (100%)	Finerenone N=1473 (100%)	Placebo N=1499 (100%)	Finerenone N=971 (100%)	Placebo N=926 (100%)	Finerenone N=317 (100%)	Placebo N=337 (100%)
Any AE	60 (90.9%)	65 (94.2%)	1299 (88.2%)	1333 (88.9%)	843 (86.8%)	798 (86.2%)	266 (83.9%)	282 (83.7%)
Maximum intensity for any AE								
Mild	19 (28.8%)	13 (18.8%)	424 (28.8%)	400 (26.7%)	286 (29.5%)	262 (28.3%)	93 (29.3%)	89 (26.4%)
Moderate	26 (39.4%)	36 (52.2%)	604 (41.0%)	616 (41.1%)	393 (40.5%)	373 (40.3%)	122 (38.5%)	132 (39.2%)
Severe	15 (22.7%)	16 (23.2%)	271 (18.4%)	317 (21.1%)	164 (16.9%)	163 (17.6%)	51 (16.1%)	61 (18.1%)
Any study drug-related AE	21 (31.8%)	11 (15.9%)	372 (25.3%)	261 (17.4%)	193 (19.9%)	129 (13.9%)	60 (18.9%)	48 (14.2%)
Maximum intensity for study drug-related AE								
Mild	7 (10.6%)	6 (8.7%)	214 (14.5%)	141 (9.4%)	110 (11.3%)	85 (9.2%)	37 (11.7%)	25 (7.4%)
Moderate	10 (15.2%)	4 (5.8%)	129 (8.8%)	101 (6.7%)	66 (6.8%)	37 (4.0%)	21 (6.6%)	22 (6.5%)
Severe	4 (6.1%)	1 (1.4%)	29 (2.0%)	19 (1.3%)	17 (1.8%)	7 (0.8%)	2 (0.6%)	1 (0.3%)
Any AE related to procedures required by the protocol	1 (1.5%)	1 (1.4%)	26 (1.8%)	35 (2.3%)	17 (1.8%)	11 (1.2%)	8 (2.5%)	7 (2.1%)
Any AE leading to discontinuation of study drug	12 (18.2%)	8 (11.6%)	121 (8.2%)	95 (6.3%)	58 (6.0%)	46 (5.0%)	16 (5.0%)	19 (5.6%)
Any SAE	23 (34.8%)	36 (52.2%)	468 (31.8%)	529 (35.3%)	317 (32.6%)	307 (33.2%)	94 (29.7%)	99 (29.4%)
Any study drug-related SAE	2 (3.0%)	2 (2.9%)	30 (2.0%)	22 (1.5%)	14 (1.4%)	8 (0.9%)	2 (0.6%)	2 (0.6%)
Any SAE related to procedures required by the protocol	0	0	2 (0.1%)	4 (0.3%)	0	0	0	0
Any SAE leading to discontinuation of study drug	7 (10.6%)	6 (8.7%)	49 (3.3%)	46 (3.1%)	16 (1.6%)	18 (1.9%)	3 (0.9%)	8 (2.4%)
AE with outcome death	2 (3.0%)	2 (2.9%)	15 (1.0%)	27 (1.8%)	12 (1.2%)	18 (1.9%)	2 (0.6%)	4 (1.2%)

eGFR, UACR, frequency of ESRD across eGFR strata

An initial decrease in eGFR was observed for subjects in the finerenone arm with a mean difference between finerenone and placebo of approximately 2 to 3 mL/min/1.73 m^2 up to Month 4 and, thereafter, an attenuated decline in eGFR was observed in the finerenone group compared to placebo.

eGFR over time

Line graphs showing model-adjusted mean changes from baseline in eGFR over time are provided for the subgroups of patients with baseline eGFR >60, 45–≤60, 25–≤45 and < 25 mL/min/1.73 m^2 in Figures below.

Figure 26, Line plot for least square means of eGFR absolute changes values by visit and by baseline eGFR ≥60 mL/min/1.73m^2 (safety analysis set).

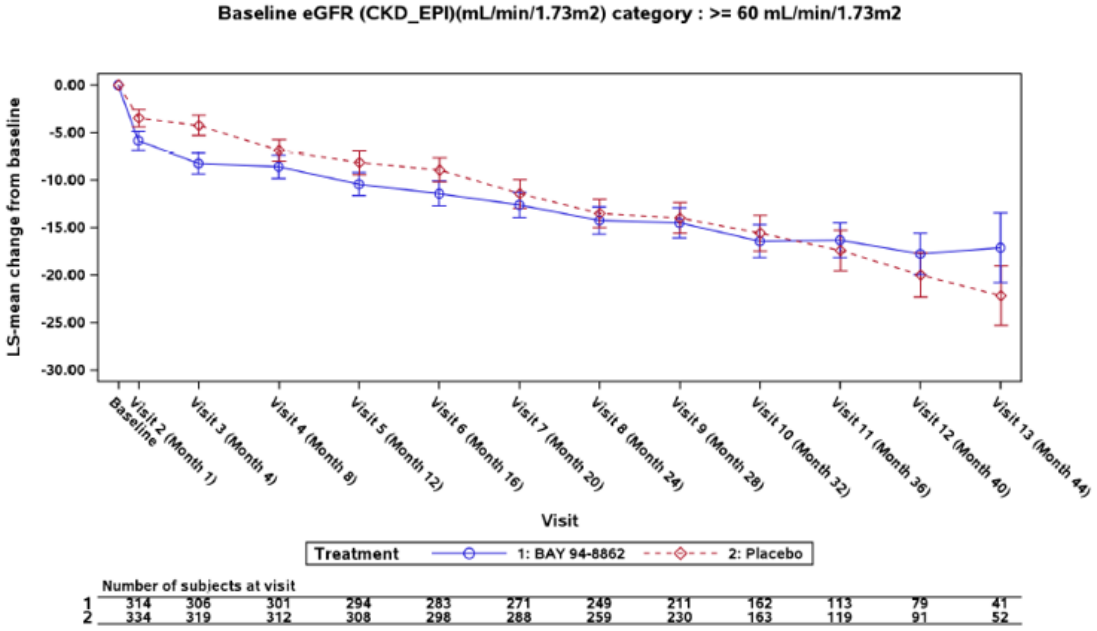


Figure 27. Line plot for least square means of eGFR absolute changes values by visit and by baseline eGFR 45 - <60 mL/min/1.73m^2 (safety analysis set).

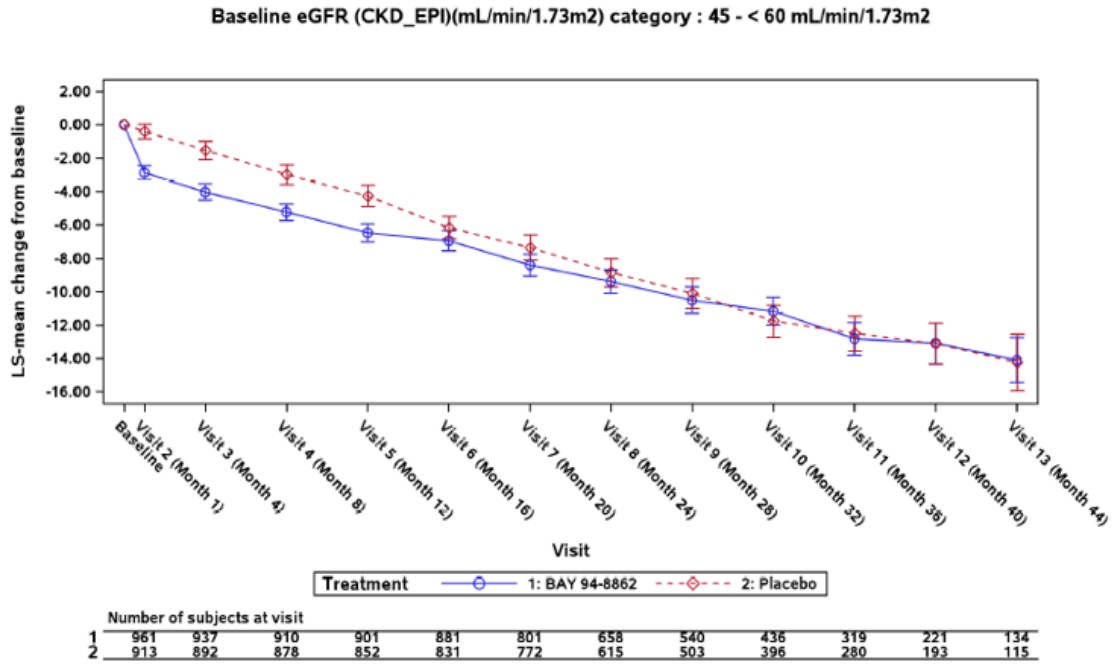


Figure 28. Line plot for least square means of eGFR absolute changes values by visit and by baseline eGFR 25 to <45 mL/min/1.73m^2 (safety analysis set).

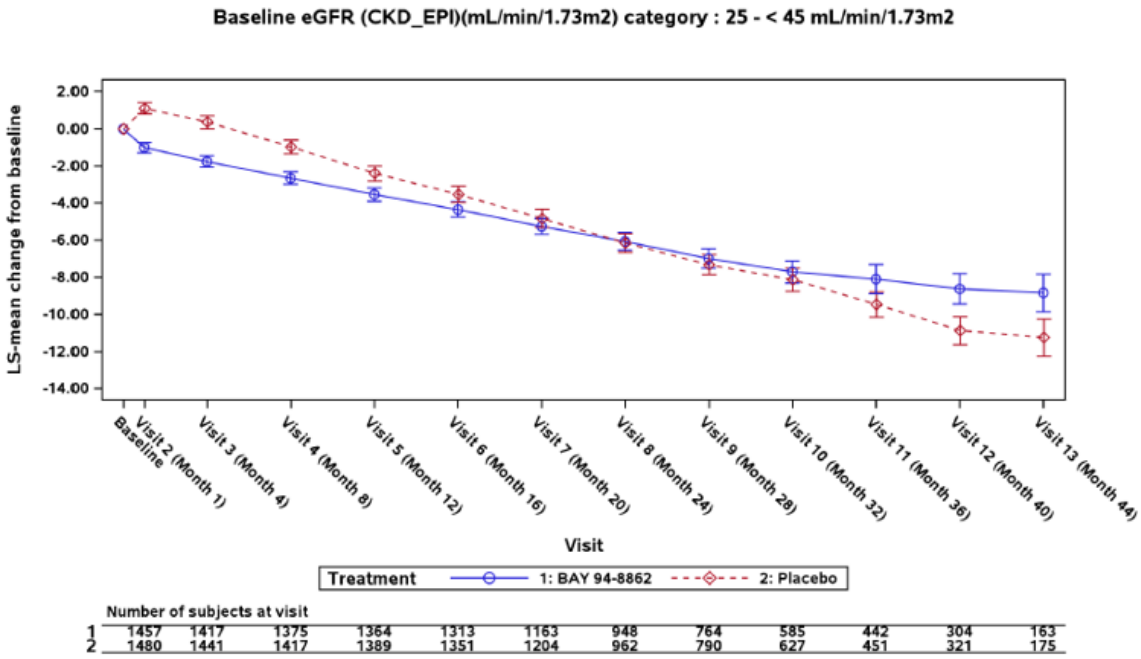
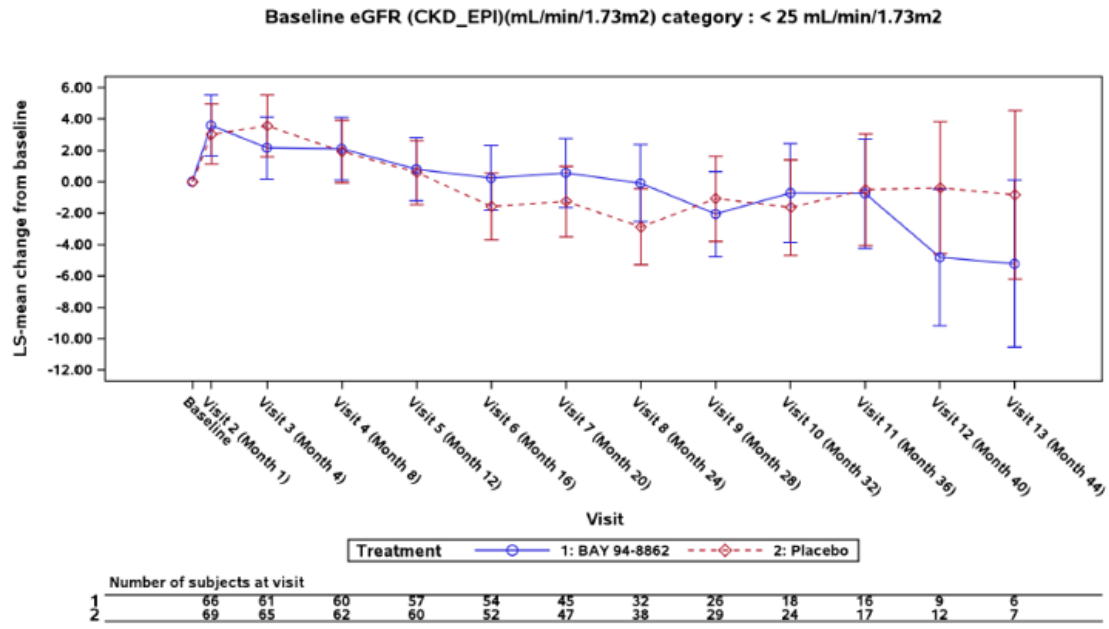


Figure 29. Line plot for least square means of eGFR absolute changes values by visit and by baseline eGFR <25 mL/min/1.73m^2 (safety analysis set).



There was an initial decrease in eGFR in the finerenone group compared with placebo group, across the subgroups eGFR >60, 45–≤60 and 25–≤45 mL/min/1.73 m^2, with a more pronounced magnitude in eGFR decrease in the subgroups with higher baseline eGFR, i.e. eGFR >60 and 45–≤60, compared with the eGFR 25–≤45 group. Over time, the eGFR declined more in the placebo group than in the finerenone group, apart from the subgroup eGFR 45–≤60 in which the eGFR seemed to decline similar for finerenone and placebo. The steepness of the eGFR plot in the finerenone group was attenuated over time across the eGFR subgroups; although, the eGFR decline was slightly steeper in the subgroup

eGFR 45 to ≤60 compared to the eGFR 25 to ≤45 and eGFR >60 from month 28 an onwards. However, treatment effects with regards to primary and secondary renal composite endpoints were reached, thus the data does not evoke any concerns regarding efficacy.

In the subjects with eGFR <25ml/min/1.73m^2, the eGFR for finerenone increased and remained above or near baseline until about month 24. Between month 24 and month 36 both finerenone and placebo remined close to baseline and thereafter the eGFR decreased in the finerenone group but remained at baseline in the placebo group. However, data in this subgroup should be interpreted with caution due to the low number of subjects.

UACR over time

Line graphs showing model-adjusted mean changes from baseline in UACR over time are provided for the subgroups of patients with baseline eGFR eGFR >60, 45–≤60, 25–≤45 and < 25 mL/min/1.73 m^2 in Figures below.

Figure 30. Line plot for least square means of ratio to baseline of UACR (mg/g) values by visit and by baseline eGFR ≥60 mL/min/1.73m^2 (safety analysis set).

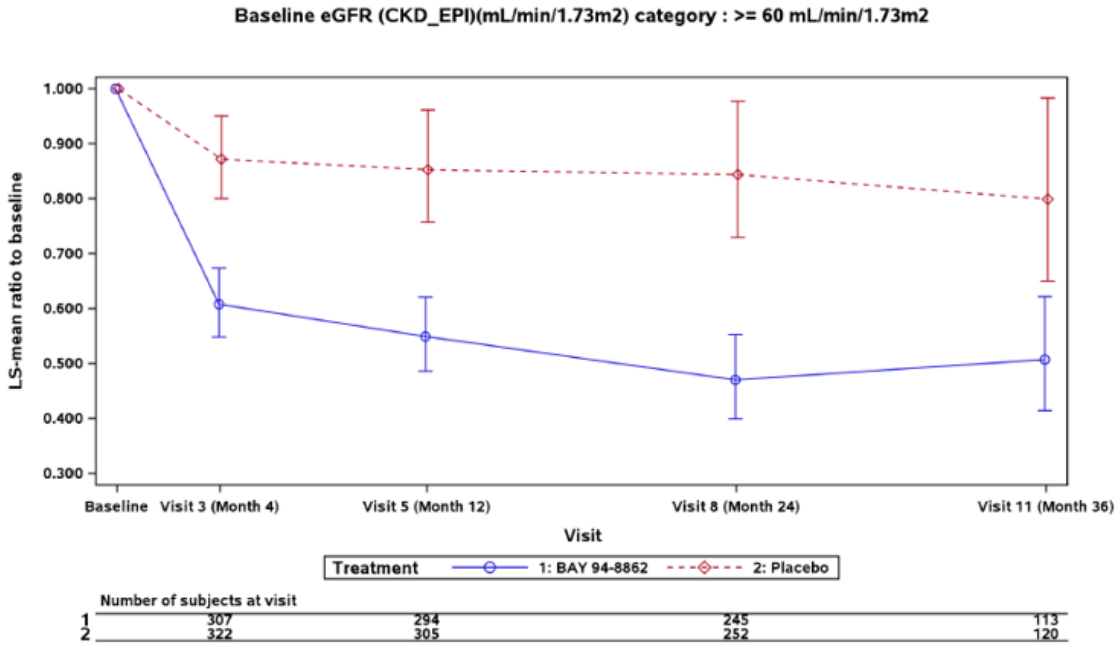


Figure 31. Line plot for least square means of UACR (mg/g) values by visit and by baseline eGFR 45 - <60 mL/min/1.73m^2 (safety analysis set).

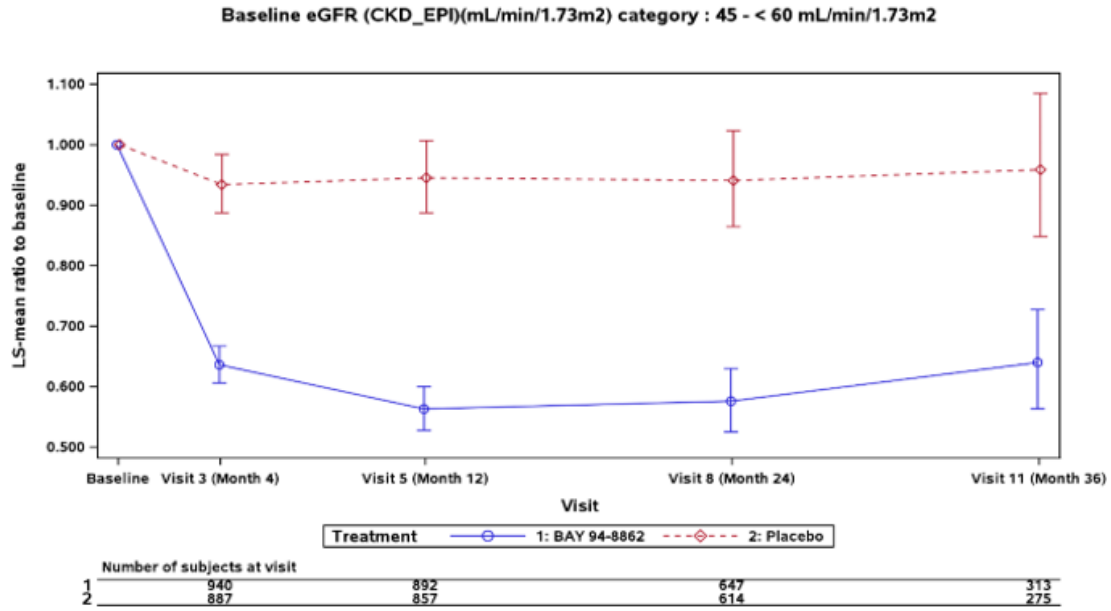


Figure 32. Line plot for least square means of UACR (mg/g) values by visit and by baseline eGFR <25 mL/min/1.73m^2 (safety analysis set).

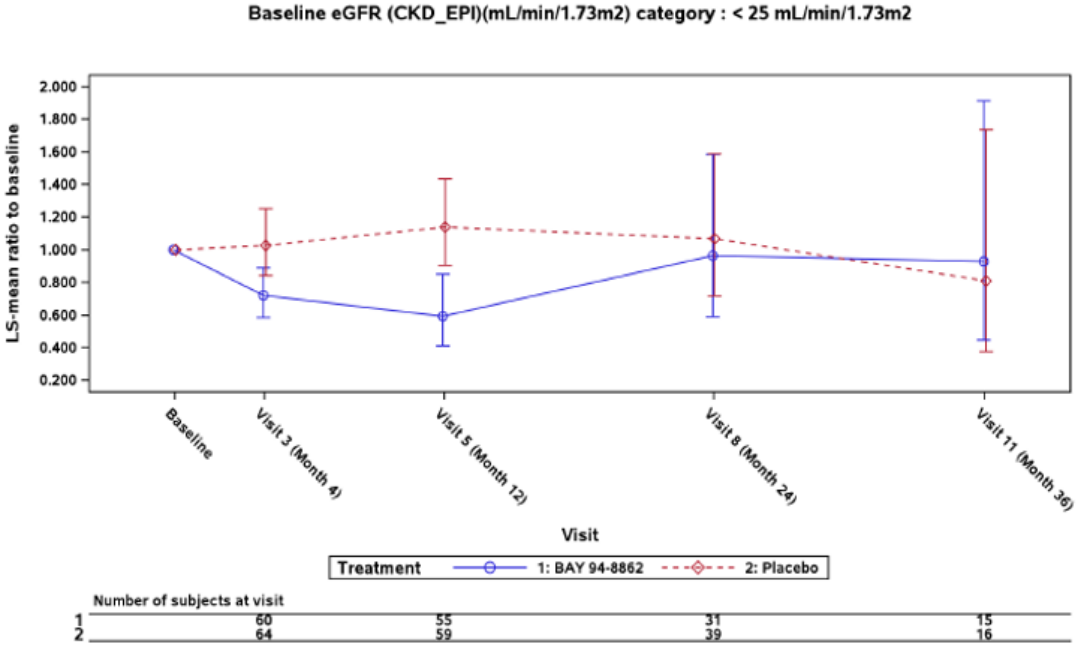
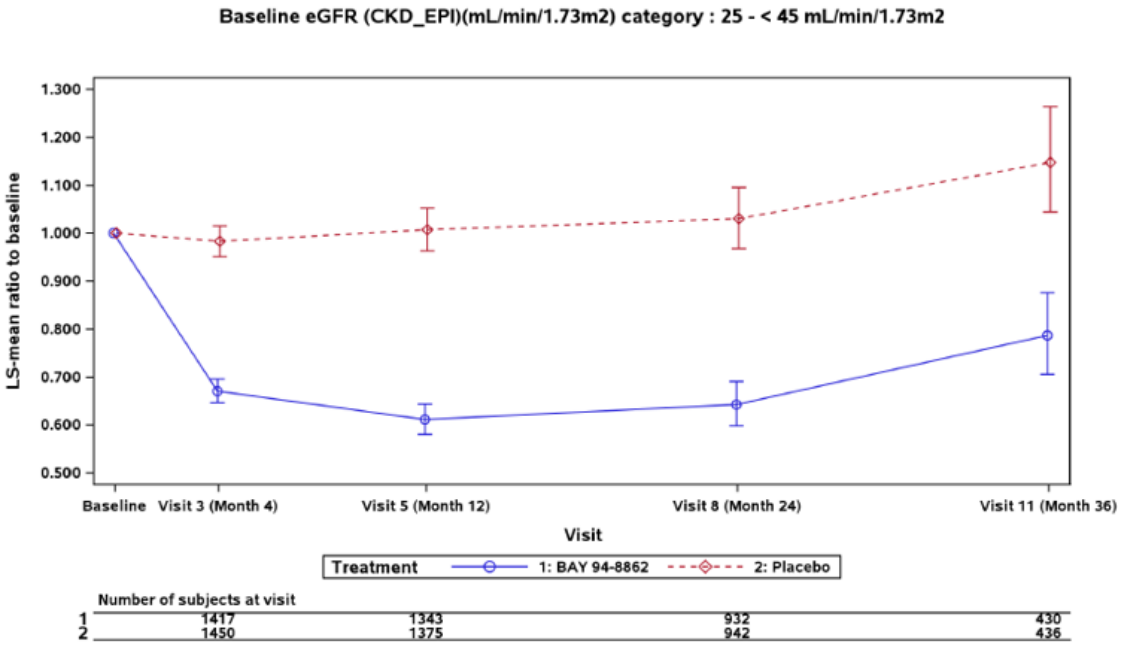


Figure 33. Line plot for least square means of UACR (mg/g) values by visit and by baseline eGFR 25 to <45 mL/min/1.73m^2 (safety analysis set).



Treatment with finerenone was associated with a greater reduction in UACR for finerenone compared with placebo across the subgroups; eGFR >60, eGFR 45—≤60 and eGFR 25—≤45. The difference in UACR between finerenone and placebo was maintained throughout the duration of the study. In the subgroup eGFR ≤25, the LS mean ratio to baseline of UACR was initially decreased for finerenone compared with placebo; however, from month 24 until month 36 the reduction in UACR was similar for finerenone and placebo.

Frequency of ESRD

The frequency of ESRD was increased in the subgroups eGFR <25 and eGFR 25—≤45 compared with the subgroups eGFR ≥45—≤60 and eGFR >60. The frequency of ESRD was higher in the placebo group compared with the finerenone group across the subgroups, except for the subgroup eGFR <25 where the frequency was higher for finerenone than for placebo (Table 46).

Table 46. Number of subjects with onset of kidney failure, a sustained decrease of eGFR ≥40% from baseline over at least 4 weeks, or renal death (renal censoring) by baseline eGFR (CKD-EPI) (mL/min/1.73m^2) category (FAS).

	Finerenone		Placebo	
Baseline eGFR category: < 25 mL/min/1.73m^2	**n (%) N=66 (100%)**	**n/100 p-yrs (95% CI)**	**n (%) N=69 (100%)**	**n/100 p-yrs (95% CI)**
Number of subjects with event	18 (27.3%)	13.35 (7.91;20.2)	23(33.3%)	16.53 (10.5;23.9)
Kidney failure	18 (27.3%)	13.35 (7.91;20.2)	23(33.3%)	16.53 (10.5;23.9)
End stage renal disease (ESRD)	14 (21.2%)	9.18 (5.02;14.6)	10(14.5%)	6.18 (2.96;10.6)
- initiation of chronic dialysis	13 (19.7%)		10 (14.5%)	
- renal transplantation	0		1 (1.4%)	
- other	1 (1.5%)		0	
Sustained decrease in eGFR to <15 ml/min	13 (19.7%)	9.69 (5.16;15.6)	22 (31.9%)	15.85 (9.93;23.1)
Sustained decrease in eGFR ≥40%	10 (15.2%)	7.31 (3.51;12.5)	16 (23.2%)	11.28 (6.45;17.4)
Renal death	0		0	
Baseline eGFR category: 25 - < 45 mL/min/1.73m^2	**n (%) N=1476 (100%)**	**n/100 p-yrs (95% CI)**	**n (%) N=1505 (100%)**	**n/100 p-yrs (95% CI)**
Number of subjects with event	295 (20.0%)	8.66 (7.70;9.68)	339 (22.5%)	9.81 (8.79;10.9)
Kidney failure	164 (11.1%)	4.62 (3.94;5.36)	180 (12.0%)	4.98 (4.28;5.74)
End stage renal disease (ESRD)	87 (5.9%)	2.29 (1.84;2.80)	105 (7.0%)	2.70 (2.21;3.24)
- initiation of chronic dialysis	79 (5.4%)		95 (6.3%)	
- renal transplantation	3 (0.2%)		4 (0.3%)	
- other	5 (0.3%)		8 (0.5%)	
Sustained decrease in eGFR to <15 ml/min	134 (9.1%)	3.78 (3.17;4.45)	153 (10.2%)	4.24 (3.59;4.94)
Sustained decrease in eGFR ≥40%	279 (18.9%)	8.20 (7.26;9.19)	326 (21.7%)	9.43 (8.44;10.5)
Renal death	2 (0.1%)		1 (<0.1%)	
Baseline eGFR category: 45 - < 60 mL/min/1.73m^2	**n (%) N=972 (100%)**	**n/100 p-yrs (95% CI)**	**n (%) N=928 (100%)**	**n/100 p-yrs (95% CI)**
Number of subjects with event	138 (14.2%)	5.96 (5.00;6.99)	168 (18.1%)	7.69 (6.57;8.90)
Kidney failure	22 (2.3%)	0.90 (0.57;1.32)	25 (2.7%)	1.09 (0.70;1.55)
End stage renal disease (ESRD)	15 (1.5%)	0.58 (0.32;0.90)	18 (1.9%)	0.74 (0.44;1.12)
- initiation of chronic dialysis	14 (1.4%)		14 (1.5%)	
- renal transplantation	0		0	
- other	1 (0.1%)		4 (0.4%)	
Sustained decrease in eGFR to <15 ml/min	17 (1.7%)	0.70 (0.41;1.07)	20 (2.2%)	0.87 (0.53;1.29)
Sustained decrease in eGFR ≥40%	137 (14.1%)	5.91 (4.96;6.94)	166 (17.9%)	7.60 (6.49;8.80)
Renal death	0		1 (0.1%)	
Baseline eGFR category: ≥60 mL/min/1.73m^2	**n (%) N=318 (100%)**	**n/100 p-yrs (95% CI)**	**n (%) N=338 (100%)**	**n/100 p-yrs (95% CI)**
Number of subjects with event	53 (16.7%)	6.77 (5.07;8.71)	70 (20.7%)	8.47 (6.61;10.6)

	Finerenone		Placebo	
Kidney failure	4 (1.3%)	0.48 (0.13;1.04)	7 (2.1%)	0.79 (0.32;1.47)
End stage renal disease (ESRD)	2 (0.6%)	0.22 (0.03;0.62)	5 (1.5%)	0.53 (0.17;1.08)
- initiation of chronic dialysis	1 (0.3%)		4 (1.2%)	
- renal transplantation	0		0	
- other	1 (0.3%)		1 (0.3%)	
Sustained decrease in eGFR to <15 ml/min	3 (0.9%)	0.36 (0.07;0.86)	4 (1.2%)	0.45 (0.12;0.99)
Sustained decrease in eGFR ≥40%	53 (16.7%)	6.77 (5.07;8.71)	69 (20.4%)	8.36 (6.50;10.4)
Renal death	0		0	

Subgroup eGFR <25 mL/min/1.73 m^2

Finerenone is not recommended in subjects with eGFR <25 mL/min/1.73m^2 due to limited data. The incidence of study-drug related AEs was further increased for finerenone compared with placebo in this subgroup (31.8% vs 15.9%) and study-drug related SAEs was increased for both finerenone and placebo (3.0% vs 2.9%). Moreover, a higher incidence of subjects, compared to subjects with eGFR >25 mL/min/1.73m^2, discontinued due to an AE (18.2% vs 11.6%) and an SAE (10.6% vs 8.7%) for finerenone compared with placebo in in this subgroup. Additionally, the incidence of ESRD was more frequent in the finerenone than in the placebo group and treatment with finerenone was not associated with a greater reduction in UACR compared with placebo over time (Table 46). Since no beneficial effects on CV events is observed in patients treated with finerenone who have developed renal failure, continued treatment of patients with eGFR<15 mL/min is not recommended. The posology was updated to state that treatment should be discontinued in patients who have progressed to ESRD (eGFR <15)**.**

2.6.8.6. Immunological events

N/A

2.6.8.7. Safety related to drug-drug interactions and other interactions

According to the applicant, concomitant use of finerenone with strong CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, ritonavir, nelfinavir, cobicistat, clarithromycin, telithromycin or nefazodone) is expected to result in greater than 5-fold increase in finerenone plasma concentration and is contraindicated. The concomitant use of moderate or strong CYP3A4 inducers (e.g. efavirenz, rifampicin, carbamazepine, phenytoin, phenobarbital, St John's Wort) is not recommended because finerenone plasma concentrations may be reduced and result in a decrease in efficacy.

Concomitant use of finerenone with medications that impair potassium excretion and increase serum potassium, may increase the risk of hyperkalemia. In FIDELIO-DKD, the following agents could be used with caution: trimethoprim, or trimethoprim and sulfamethoxazole and potassium supplements.

2.6.8.8. Discontinuation due to adverse events

Adverse events resulting in permanent discontinuation of study drug were reported more frequently in the finerenone group (7.3%) than in the placebo group (5.9%). The difference was driven by the higher number of subjects permanently discontinuing study drug due to hyperkalemia for finerenone (1.8%) compared with placebo (0.7%).

Table 47. Permanent discontinuation of study drug due to TEAE: 5 most frequent PTs in each treatment group with their associated SOCs - number (%) of subjects (SAF) - FIDELIO-DKD.

SOC PT MedDRA Version 23.0	Finerenone N = 2827 (100%)	Placebo N = 2831 (100%)
Number (%) of subjects with at least one such adverse event	**207 (7.3%)**	**168 (5.9%)**
Gastrointestinal disorders	**14 (0.5%)**	**16 (0.6%)**
Diarrhoea	4 (0.1%)	9 (0.3%)
Investigations	**26 (0.9%)**	**20 (0.7%)**
Blood potassium increased	13 (0.5%)	6 (0.2%)
Glomerular filtration rate decreased	7 (0.2%)	8 (0.3%)
Blood creatinine increased	5 (0.2%)	5 (0.2%)
Metabolism and nutrition disorders	**52 (1.8%)**	**22 (0.8%)**
Hyperkalaemia	51 (1.8%)	19 (0.7%)
Renal and urinary disorders	**27 (1.0%)**	**34 (1.2%)**
Renal impairment	8 (0.3%)	8 (0.3%)
Acute kidney injury	5 (0.2%)	7 (0.2%)
Chronic kidney disease	2 (<0.1%)	8 (0.3%)
Skin and subcutaneous tissue disorders	**12 (0.4%)**	**7 (0.2%)**
Pruritus	5 (0.2%)	1 (<0.1%)

2.6.8.9. Post marketing experience

N/A

2.6.9. Discussion on clinical safety

The safety of finerenone is evaluated in the safety analysis set (or 'SAF' population), which included all randomised subjects who received at least 1 dose of study drug in the FIDELIO-DKD study. The evaluation of the FIDELIO-DKD study provides information on the safety profile of finerenone in subjects with CKD and T2D.

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, 1,632 subjects (58%) for at least 2 years. Mean and median duration of treatment in the SAF were similar in both treatment arms (about 27 months).

The number of AEs was balanced for finerenone (87.3%) and placebo (87.5%); however, the incidence of drug-related AEs was increased for finerenone (22.9%) compared with placebo (15.9%). The most commonly reported AEs that were reported more for frequently for finerenone than for placebo were hyperkalaemia (18.3% vs 9.0%), decreased GFR (6.3% vs 4.7%), anaemia (7.4% vs 6.7%), hypotension (4.5% vs 3.1%) and hyponatremia (1.3% vs 0.6%).

The incidence of SAEs was slightly higher in the placebo group (34.3%) than in the finerenone group (31.9%) and drug-related SAEs slightly higher for finerenone (1.7%) than for placebo (1.2%). The most frequently reported SAEs for finerenone versus placebo were pneumonia (2.5% vs 3.6%), acute kidney injury (2.0% vs 1.8%) and hyperkalaemia (1.5% vs 0.4%). There were more fatal cases in the placebo group compared with the finerenone group (4.8% vs 3.1%).

Discontinuation rate due to AE was higher for finerenone (7.3%) than for placebo (5.9%) in the FIDELIO-DKD study. The most frequently reported AE leading to study drug discontinuation for finerenone vs placebo was hyperkalaemia (2.3% vs 0.9%).

Hyperkalaemia

The incidence of hyperkalaemia was 2 times increased for finerenone versus placebo (18.3% vs 9.0%). Drug-related hyperkalaemia were reported in 11.8% of the subjects in the finerenone group compared with 4.8% in the placebo group. Serious events of hyperkalaemia were reported more frequently for finerenone (1.6%) than for placebo (0.4%). Moreover, a higher incidence of hyperkalaemia leading to discontinuation (2.3% vs 0.9%) and hospitalisation (1.4% vs 0.3%) was reported for finerenone compared with placebo.

More subjects treated with finerenone, compared with placebo, reported one AE (11.9% vs 6.6%), two AEs (4.3% vs 1.8%) and three AEs (1.5% vs 0.5%) of hyperkalaemia, respectively.

A higher incidence for finerenone, than for placebo, had changes in serum potassium to >5.5 mmol/L (21.4% vs 9.2%) and to >6.0 mmol/L (4.5% vs 1.4%), respectively, at any time during treatment.

The majority of cases with hyperkalaemia/ blood potassium increased recovered/resolved; however, in about 12% (62/527) of the cases of hyperkalaemia the outcome was reported as not recovered/not resolved.

Hyponatraemia

Hyponatremia, although less frequent than hyperkalaemia, was more frequent for finerenone (1.3%) than for placebo (0.6%).

Decreased eGFR and renal events

The incidence of 'eGFR decreased' was increased for finerenone (6.3%) compared with placebo (4.7%). The incidence of AEs from the SOC Renal and urinary disorders (18.5% vs 19.5%) was slightly higher for placebo, of which the incidence of acute kidney injury (4.6% vs 4.8%) was balanced. However, the incidence of *drug-related* events of 'eGFR decreased' (1.4% vs 0.5%) and AEs from the SOC Renal and urinary disorders (3.0% vs 2.3%), including acute kidney injury (1.2% vs 0.6%), was increased for finerenone versus placebo.

TESAEs of renal events (4.7% vs 5.1%), including acute kidney injury (2.0% vs 1.8%) was balanced. The incidence of serious events of eGFR decreased was low but numerically higher for finerenone (0.2%) than for placebo (0.1%).

Hypotension

Hypotension occurred more frequently in subjects in the finerenone group (4.5%) than in the placebo group (3.1%). Events associated with hypotension such as dizziness (5.2% vs 5.4%), syncope (1.2% vs 2.0%) and events of fall (1.6% vs 2.0%) was balanced between the groups.

Serious hypotension was balanced between the groups (0.2% vs 0.2%).

Anaemia

Anaemia was slightly increased for finerenone (7.4%) compared with placebo (6.7%); see also section 3.5 laboratory findings. Serious anaemia, however, was low and balanced (0.5% vs 0.7%).

Gastrointestinal haemorrhage

More patients in the finerenone group compared to placebo had oral and gastrointestinal tract haemorrhage. In patients with history of GI disorders the incidence was 3.9% vs 2.5% for finerenone vs placebo, respectively; however, alternative explanations could be found in the majority of cases.

Malignancies

In the FIDELIO-DKD study, the incidence of AEs in the SOC Neoplasms (classified as benign, malignant or unspecified) was 7.3% for finerenone and 7.0% for placebo.

Laboratory findings, vital signs

Haematocrit

A decrease in mean haemoglobin (<0.15 g/dL) and mean haematocrit (<0.45%) levels was observed in the first 4 months in the finerenone arm compared to placebo. Decreased haemoglobin has been included in the tabulated list of adverse reactions in section 4.8 of the SmPC.

Blood pressure

In the first 12 months of treatment, the mean reduction in SBP was approximately 2 to 4 mmHg greater in finerenone-treated subjects compared with placebo, and the mean reduction in DBP approximately 1 to 2 mmHg greater in the finerenone group compared to placebo.

Subgroups

Effect by age

The reporting rate was overall similar across the age groups. Slightly more SAEs were reported in the age group ≥75 years (35.0% vs 38.0%) compared to subjects 65-74 years (32.6% vs 32.7%) and <65 years (30.1% vs 34.5%); however, the incidence of SAEs was higher for placebo than for finerenone in all age groups.

More subjects discontinued due to an AE in for finerenone compared with placebo in the subgroups ≥75 years (9.5% vs 5.6%) and 65-74 years (8.1% vs 6.3%); however, the discontinuation rate due to AEs was balanced (5.7% vs 5.6%) in subjects <65 years. The incidence of subjects discontinuing permanently due to hyperkalaemia was increased for finerenone compared to placebo across age groups with the highest incidence in the subgroup ≥75 years (3.9% vs 0.7%).

Effect by sex

No notable differences between males and females, apart from that the incidence of subjects that discontinued due to an AE was increased for finerenone compared with placebo (8.0% vs 5.8%) in males and was more balanced in females (5.9% than 6.2%).

Effect by race

The rate of AEs was similar between the treatment arms across the race groups; however, the incidence of AEs was about 85%-89% in White, Black and Other subjects and was slightly higher in Asian subjects (93%). The difference was mainly driven by a higher number of subjects with AEs of mild intensity in the Asian race group (38%-41%) compared to the other race groups (19%-27%)

Effect by renal function

In the study population, approximately 2.3% of the subjects had baseline eGFR<25 mL/min/1.73m^2, 53% eGFR 25 -<45 mL/min/1.73m^2, 34% eGFR 45 - <60 mL/min/1.73m^2 and 12% eGFR eGFR>60 mL/min/1.73m^2.

The incidence of AEs and SAEs for finerenone versus placebo was similar in subjects with eGFR 25 - <45 mL/min/1.73m^2 (AEs; 88.2% vs SAEs; 88.9% and 31.8% vs 35.3%) and eGFR 45 - <60 mL/min/1.73m^2 (AEs; 86.8% vs 86.2% and SAEs; 32.6% and 33.2%). However, the incidence of *study-drug related* AEs and SAEs was increased for finerenone compared with placebo and slightly higher in the subgroup with eGFR 25 -<45 mL/min/1.73m^2 (AEs; 25.3% vs 17.4% and SAEs; 2.0% vs 1.5%) than in the eGFR 45 - <60 mL/min/1.73m^2 (19.9% vs 13.9% and 1.4% vs 0.9%). Moreover,

the incidence of subjects with any AE leading to discontinuation of study drug was increased for finerenone compared with placebo and slightly higher in subjects with eGFR 25 -<45 mL/min/1.73m^2 (8.2% vs 6.3%) than in subjects with eGFR 45 - <60 mL/min/1.73m^2 (6.0% vs 5.0%).

Additionally, the risk of hyperkalaemia increased with decreasing renal function across eGFR strata: eGFR ≥60 (10.7% vs 8.6%), eGFR 45 -<60 (14.7% vs 6.3%) and eGFR 25 -45 (22.1% vs 10.6%).

Finerenone is not recommended in subjects with eGFR <25 mL/min/1.73m^2 due to limited data. The incidence of AEs was slightly higher placebo than for finerenone; however, the incidence of study-drug related AEs was two times increased for finerenone compared with placebo in this subgroup (31.8% vs 15.9%). SAEs were reported more frequently for placebo (52.2%) than for finerenone (34.8%) and drug-related SAEs was balanced for finerenone and placebo (3.0% vs 2.9%). A higher incidence of subjects, compared to subjects with eGFR >25 mL/min/1.73m^2, discontinued due to an AE (18.2% vs 11.6%) and an SAE (10.6% vs 8.7%) for finerenone compared with placebo in in this subgroup.

2.6.10. Conclusions on the clinical safety

The FIDELIO-DKD study provides information on the safety profile of finerenone in subjects with chronic kidney disease and T2D.

In the overall population, the number of AEs was balanced; however, the incidence of drug-related AEs was higher for finerenone than for placebo. The incidence of SAEs was slightly higher for placebo versus finerenone, and drug-related SAEs was slightly higher for finerenone versus placebo. There were more fatal cases in the placebo group than in the finerenone group.

The major safety concern is the increased incidence of hyperkalaemia in the overall population (18.3% vs 9.0%). The risk of hyperkalaemia increased with decreasing renal function. Moreover, 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. However, the risk for serious events of hyperkalaemia could be handled with precautionary measures addressed in the SmPC, i.e. routine risk minimisation.

The incidence of 'eGFR decreased' was increased for finerenone compared with placebo. The incidence of drug-related events of 'eGFR decreased' and drug-related renal AEs, including acute kidney injury, was increased for finerenone versus placebo. The outcome was reported as resolved/recovered in the majority of finerenone drug-related cases of AKI. The action taken was "no dose change" in half of the cases (17/34) and a "dose change" in 2 of the cases. The drug was interrupted in 11 cases and was withdrawn in 4 of the cases. Information on decreased eGFR is included in section 4.8 of the SmPC.

There was an initial decrease in eGFR in the finerenone group compared with placebo group, across the subgroups eGFR >60, 45—≤60 and 25—≤45 mL/min/1.73 m^2, with a more pronounced magnitude in eGFR decrease in the subgroups with higher baseline eGFR, i.e. eGFR >60 and 45—≤60, compared with the eGFR 25—≤45 group. Over time, the eGFR declined more in the placebo group than in the finerenone group, apart from the subgroup eGFR 45—≤60 in which the eGFR seemed to decline similar for finerenone and placebo. The steepness of the eGFR plot in the finerenone group was attenuated over time across the eGFR subgroups; although, the eGFR decline was slightly steeper in the subgroup eGFR 45 to ≤60 compared to the eGFR 25 to ≤45 and eGFR >60 from month 28 an onwards. However, treatment effects with regards to primary and secondary renal composite endpoints were reached, thus the data does not evoke any concerns regarding efficacy.

Finerenone is not recommended in subjects with eGFR <25 mL/min/1.73m^2 due to limited data. The posology states that treatment should be discontinued in patients who have progressed to ESRD (eGFR <15 mL/min/1.73 m^2).

The applicant has proposed to include hyperkalaemia as an important identified risk and embryo-foetal toxicity as an important potential risk in the RMP. Furthermore, "use during pregnancy and lactation" has been proposed as missing information. These proposals were accepted.

The application was considered approvable from clinical safety point of view.

2.7. Risk Management Plan

2.7.1. Safety concerns

Summary of the Safety Concerns

Important identified risks	Hyperkalemia
Important potential risks	Embryo-foetal toxicity
Missing information	Use in pregnancy and lactation

2.7.2. Pharmacovigilance plan

No additional pharmacovigilance activities are considered necessary for Kerendia. Routine pharmacovigilance is sufficient to further characterise the safety concerns associated with the product.

2.7.3. Risk minimisation measures

Safety concern	Risk minimisation measures
Important identified risk	
Hyperkalemia	**Routine risk minimisation measures:** • SmPC sections 4.2, 4.4, 4.5, and 4.8 • Kerendia® is a prescription-only medicine **Additional risk minimisation measures**: None
Important potential risk	
Embryo-foetal toxicity	**Routine risk minimisation measures:** • 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 • Kerendia® is a prescription-only medicine **Additional risk minimisation measures**: None
Missing information	
Use in pregnancy and lactation	**Routine risk minimisation measures:** • 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 • Kerendia® is a prescription-only medicine **Additional risk minimisation measures**: None

2.7.4. Conclusion

The CHMP considers that the risk management plan version 0.4 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 9th July 2021. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Kerendia (finerenone) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

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

The agreed therapeutic indication for finerenone is:

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

Chronic kidney disease (CKD) and type 2 diabetes (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. An estimated 20 to 40% of T2D patients develop CKD which is characterised 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. Worldwide rates of end stage renal disease (ESRD) are projected to rise in parallel with the substantial increase in T2D prevalence. CKD is also associated with increased risks of cardiovascular (CV) mortality and morbidity, as well as impaired quality of life.

3.1.2. Available therapies and unmet medical need

For the treatment of CKD associated with 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. 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.

Finerenone is a novel, non-steroidal and selective mineralocorticoid receptor (MR) 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.

3.1.3. Main clinical studies

The main evidence of efficacy submitted is a phase III randomised, placebo-controlled, multicentre study comparing finerenone (n=2833) with placebo (n=2841) in addition to standard of care in patients with T2D and CKD with albuminuria.

The study was event-driven and the primary objective was to demonstrate that finerenone is superior to placebo in delaying the progression of kidney disease, as measured by the primary 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 secondary objective was to demonstrate that finerenone is superior to placebo in reducing the risk of cardiovascular mortality and morbidity, as measured by the composite endpoint of *time to CV death, non-fatal MI, non-fatal stroke, or hospitalisation for heart failure*.

3.2. Favourable effects

Primary endpoint

Treatment with finerenone resulted in a 17.5% relative risk reduction compared with placebo of the composite primary endpoint (HR 0.825 [95% CI 0.732; 0.928]; p=0.0014). The primary endpoint of the FIDELIO-DKD study was thus met. The effect appears to be mainly driven by the component sustained decrease in eGFR ≥40% relative baseline (HR 0.815 [95% CI 0.722; 0.920]; p=0.0009). The other components were numerically reduced but the changes were not significant.

Kaplan-Meier curves for the primary endpoint for finerenone and placebo are similar up until Month 12 but diverge thereafter indicating a sustained treatment effect after this timepoint. The absolute risk reduction based on Kaplan-Meier cumulative incidences for the primary renal composite endpoint was 2.9% at Month 24 and 3.4% at Month 36 with finerenone compared to placebo, corresponding to NNTs to prevent one primary endpoint event of 34 and 29 subjects, respectively.

Secondary endpoints

Treatment with finerenone resulted in a 14% relative risk reduction compared with placebo for the key secondary CV composite endpoint *time to CV death, non-fatal MI, non-fatal stroke, or hospitalisation for heart failure* (HR 0.860 [95% CI 0.747; 0.989]; p=0.0339). When analysing the components, the effect appears to be equally driven by CV death, non-fatal MI and hospitalisation for heart failure (although the differences in any of the groups were not statically significant) whereas the occurrences of stroke in the two treatment arms were very similar.

The secondary renal composite endpoint defined a more pronounced eGFR decrease compared to the primary endpoint (≥57% vs. ≥40%). Treatment with finerenone resulted in a 23.7% relative risk reduction compared with placebo (RR 0.763 [95% 0.648; 0.900]; nominally p-value=0.0012) supporting the primary endpoint.

Treatment with finerenone resulted in a reduced UACR from baseline to month 4 (RR 0.688 [95% CI 0.662, 0.715]; nominally p-value<0.0001). This is in line with results from the ARTS-DN phase II study and supports the reno-protective mode of action of finerenone.

In summary, directionally consistent changes were observed for all secondary endpoints, but a statistically significant change in line with the hierarchical testing strategy was only found for the key secondary endpoint.

3.3. Uncertainties and limitations about favourable effects

In finerenone-treated subjects, an initial reduction in eGFR was observed compared to placebo. The initial reduction in eGFR is anticipated based on the mode of action of finerenone and consistent with that observed in ARTS DN, where these changes were observed to be reversible following treatment discontinuation. Thereafter, a more attenuated decline over time in the eGFR slope was observed in finerenone-treated subjects compared to those on placebo. When mean values of eGFR between the treatment arms are compared, eGFR is numerically lower in the finerenone arm up until two years after treatment initiation. After this timepoint, eGFR values were numerically higher in the finerenone arm. Analyses showed that a more pronounced initial decline was associated with a better chronic preservation of renal function, indicating that the decline has no negative long-term consequences on eGFR.

The data to support the second part of the initially proposed indication "to reduce the risk of cardiovascular mortality and morbidity" were not considered convincing. The risk reduction observed in the secondary endpoint ([HR 0.860; 95% CI 0.747; 0.989]) was statistically significant but not considered compelling, as required for applications based on one pivotal study (*Points to consider on application with 1. Meta-analyses; 2. One pivotal study [CPMP/EWP/2330/99]*). The upper limit of the 95% CI is close to unity and the p-value (0.0339) relatively close to the assigned alpha level. Furthermore, none of the components of the composite were significantly changed when tested individually. The CHMP considered that an assessment of the final results of the FIGARO-DKD study is required before a conclusion could be reached with respect to a CV indication, in line with previous scientific advice. The applicant agreed to remove the cardiovascular part of the indication from the wording of the final, approved indication.

3.4. Unfavourable effects

In FIDELIO-DKD study, 2,827 were treated with finerenone for a total exposure of 6,346 patient-years, with 2,446 subjects (87%) for at least 52 weeks, 1,632 subjects (58%) for at least 2 years. Mean and median duration of treatment in the safety analysis set (SAF) were similar in both treatment arms (about 27 months).

The number of TEAEs was balanced for finerenone (87.3%) and placebo (87.5%); however, the incidence of drug-related TEAEs was increased for finerenone (22.9%) compared with placebo (15.9%). The most commonly reported TEAEs that were reported more frequently for finerenone than for placebo were hyperkalaemia (18.3% vs 9.0%), decreased GFR (6.3% vs 4.7%), anaemia (7.4% vs 6.7%), hypotension (4.5% vs 3.1%) and hyponatremia (1.3% vs 0.6%).

The incidence of TESAEs was slightly higher in the placebo group (34.3%) than in the finerenone group (31.9%) and drug-related TESAEs slightly higher for finerenone (1.7%) than for placebo (1.2%). The most frequently reported TESAEs for finerenone versus placebo were pneumonia (2.5% vs 3.6%), acute kidney injury (2.0% vs 1.8%) and hyperkalaemia (1.5% vs 0.4%). There were more treatment emergent fatal cases in the placebo group compared with the finerenone group (4.8% vs 3.1%).

Discontinuation rate due to TEAE was higher for finerenone (7.3%) than for placebo (5.9%) in the FIDELIO-DKD study. The most frequently reported TEAE leading to study drug discontinuation for finerenone vs placebo was hyperkalaemia (2.3% vs 0.9%).

The incidence of *hyperkalaemia* was 2 times increased for finerenone versus placebo (18.3% vs 9.0%). TESAEs of hyperkalaemia were reported more frequently for finerenone (1.6%) than for placebo (0.4%). A higher incidence of hyperkalaemia leading to discontinuation (2.3% vs 0.9%) and hospitalisation (1.4% vs 0.3%) was reported for finerenone compared with placebo. More subjects treated with finerenone, compared with placebo, reported one AE (11.9% vs 6.6%), two AEs (4.3% vs 1.8%) and three AEs (1.5% vs 0.5%) of hypokalaemia, respectively. A higher incidence for finerenone, than for placebo, had changes in serum potassium to >5.5 mmol/L (21.4% vs 9.2%) and to >6.0 mmol/L (4.5% vs 1.4%), respectively, at any time during treatment.

Hyponatremia, although less frequent than hyperkalaemia, was more frequent for finerenone (1.3%) than for placebo (0.6%).

The incidence of *'eGFR decreased'* was increased for finerenone (6.3%) compared with placebo (4.7%). The incidence of *AEs* from the SOC Renal and urinary disorders (18.5% vs 19.5%) was slightly higher for placebo, of which the incidence of acute kidney injury (4.6% vs 4.8%) was balanced. However, the incidence of *drug-related* events of 'eGFR decreased' (1.4% vs 0.5%) and AEs from the SOC Renal and urinary disorders (3.0% vs 2.3%), including acute kidney injury (1.2% vs 0.6%), was increased for finerenone versus placebo. SAEs of events from the SOC Renal and urinary disorders (4.7% vs 5.1%), including acute kidney injury (2.0% vs 1.8%) was balanced. The incidence of serious events of eGFR decreased was low but numerically higher for finerenone (0.2%) than for placebo (0.1%).

Hypotension occurred more frequently in subjects in the finerenone group (4.8%) than in the placebo group (3.4%). Events associated with hypotension such as dizziness (5.2% vs 5.4%), syncope (1.2% vs 2.0%) and events of fall (1.6% vs 2.0%) were balanced between the groups.

Anaemia was slightly increased for finerenone (7.4%) compared with placebo (6.7%). Serious anaemia, however, was low and balanced (0.5% vs 0.7%).

A decrease in *mean haematocrit (<0.46%)* levels was observed in the first 4 months in the finerenone arm compared to placebo.

In the first 12 months of treatment, the *mean reduction in SBP* was approximately 2 to 4 mmHg greater in finerenone-treated subjects compared with placebo, and the *mean reduction in DBP* approximately 1 to 2 mmHg greater in the finerenone group compared to placebo.

All-cause mortality was numerically reduced in the finerenone arm (HR 0.946 [95% CI 0.876; 1.022]; 0.2348) which supports that there is no general detrimental effect of finerenone on mortality.

Subgroups

The reporting rate was overall similar across the age groups. Slightly more SAEs were reported in the age group ≥75 years (35.0% vs 38.0%) compared to subjects 65-74 years (32.6% vs 32.7%) and <65 years (30.1% vs 34.1%); however, the incidence of SAEs was higher for placebo than for finerenone in all age groups. More subjects discontinued due to an AE in for finerenone compared with placebo in the subgroups ≥75 years (9.5% vs 5.6%) and 65-74 years (8.1% vs 6.3%); however, the discontinuation rate due to AEs was balanced (5.7% vs 5.6%) in subjects <65 years. The incidence of

subjects discontinuing permanently due to hyperkalaemia was increased for finerenone compared to placebo across age groups with the highest incidence in the subgroup ≥75 years (3.9% vs 0.7%).

No notable differences between males and females, apart from that the incidence of subjects that discontinued due to an AE was increased for finerenone compared with placebo (8.0% vs 5.8%) in males and was more balanced in females (5.9% than 6.2%).

The rate of AEs was similar between the treatment arms across the race groups; however, the incidence of AEs was about 85%-89% in White, Black and Other subjects and was slightly higher in Asian subjects (93%). The difference was mainly driven by a higher number of subjects with AEs of mild intensity in the Asian race group (38%-41%) compared to the other race groups (19%-27%).

The incidence of AEs and SAEs for finerenone versus placebo was similar in subjects with eGFR 25 - <45 mL/min/1.73m^2 (AEs; 88.2% vs SAEs; 88.9% and 31.8% vs 35.3%) and eGFR 45 - <60 mL/min/1.73m^2 (AEs; 86.8% vs 86.2% and SAEs; 32.6% and 33.2%). The risk of hyperkalaemia increased with decreasing renal function across eGFR strata: eGFR ≥60 (10.7% vs 8.6%), eGFR 45 -<60 (14.7% vs 6.3%) and eGFR 25 -45 (22.1% vs 10.6%).

3.5. Uncertainties and limitations about unfavourable effects

The major safety concern is the increased incidence of hyperkalaemia in the overall population. The risk of hyperkalaemia increased with decreasing renal function. Moreover, 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 could be handled with routine risk minimisation.

The incidence of 'eGFR decreased' was increased for finerenone compared with placebo. The incidence of drug-related events of 'eGFR decreased' and drug-related renal AEs, including acute kidney injury, was increased for finerenone versus placebo. Information on decreased eGFR is included in section 4.8 of the SmPC. There was an initial decrease in eGFR in the finerenone group compared with placebo group, across the subgroups eGFR >60, 45–≤60 and 25–≤45 mL/min/1.73 m^2, with a more pronounced magnitude in eGFR decrease in the subgroups with higher baseline eGFR, i.e. eGFR >60 and 45–≤60, compared with the eGFR 25–≤45 group.

Finerenone is not recommended in subjects with eGFR <25 mL/min/1.73m^2 due to limited data. The posology was therefore updated to state that treatment should be discontinued in patients who have progressed to ESRD (eGFR <15 mL/min/1.73m2)**.**

The applicant has proposed and it was agreed to include "hyperkalaemia" as an important identified risk and "embryo-foetal toxicity" as an important potential risk. "Use in pregnancy and lactation" has been proposed to be included as missing information.

3.6. Effects table

Effects table for finerenone in patients with CKD and T2D (FIDELIO-CKD Study) (data cut-off: 29 Jul 2020).

Effect	Short Description	Unit	Finerenone	Placebo	Uncertainties/ Strength of evidence	References
Favourable Effects						
Primary endpoint	Composite of onset of kidney failure, a sustained decrease of eGFR ≥40% from baseline over at least 4 weeks, or renal death	n/N (%)	504/2833 (17.8%)	600/2841 (21.1%)	HR 0.825 [95% CI 0.732; 0.928] p=0.0014	FIDELIO-DKD study
Key secondary endpoint	Composite of CV death, non-fatal myocardial infarction, non-fatal stroke, or hospitalisation for heart failure	n/N (%)	367/2833 (13.0%)	420/2841 (14.8%)	0.860 [95% CI 0.747; 0.989] p=0.0339	
Secondary endpoints	All-cause mortality	n/N (%)	219/2833 (7.7%)	244/2841 (8.6%)	0.895 [95% CI 0.746; 1.075] p=0.2348	
	All-cause hospitalisation	n/N (%)	1263/2833 (44.6%)	1321/2841 (46.5%)	0.946 [95% CI 0.876; 1.022] p=0.1623 explorative	
	Change in UACR, ratio to baseline at month 4	Geom. mean (geom. SD)	0.6550 (2.1043)	0.9524 (2.0659)	0.688 [95% CI 0.662, 0.715] p<.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 (%)	252 /2833 (8.9%)	326/2841 (11.5%)	0.763 [95% CI 0.648; 0.900] p=0.0012 explorative	
Unfavourable Effects						
Any TEAE		n (%)	2468 (87.3%)	2478 (87.5%)		FIDELIO-DKD study
Any TESAE		n (%)	902 (31.9%)	971 (34.2%)		
Hyperkalaemia		n (%)	516 (18.3%)	255 (9.0%)		
Decreased eGFR		n (%)	179 (6.3%)	133 (4.7%)		
AEs from the SOC Renal and urinary disorders (drug-related)		n (%)	84 (3.0%)	64 (2.3)		
Effect of renal function						
Any AE						

Effect	Short Description	Unit	Finerenone	Placebo	Uncertainties/ Strength of evidence	References
eGFR 25 -<45		n (%)	1229 (88.2%)	1333 (88.9%)		FIDELIO-DKD study
eGFR 45 - <60		n (%)	843 (86.8%)	798 (86.2%)		
eGFR ≥60		n (%)	266 (83.9%)	282 (83.7%)		
Any SAE						
eGFR 25 -<45		n (%)	468 (31.8%)	529 (35.3%)		FIDELIO-DKD study
eGFR 45 - <60		n (%)	317 (32.6%)	307 (33.2%)		
eGFR ≥60		n (%)	94 (29.7%)	99 (29.4%)		
Hyperkalaemia						
eGFR 25 -<45		n (%)	325 (22.1%)	159 (10.6%)		FIDELIO-DKD study
eGFR 45 - <60		n (%)	143 (14.7%)	58 (6.3%)		
eGFR ≥60		n (%)	34 (10.7%)	29 (8.6%)		

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 characterised 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. Currently approved MR antagonists (e.g. spironolactone and eplerenone) are not specifically indicated for treatment of patients with CKD. 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.

The FIDELIO-DKD study encompassed 5674 patients with CKD and T2D treated with the maximum tolerated labelled dose of either an ACEi or ARB, or both. Other MR antagonists were not permitted.

The primary endpoint of the study refers to the claimed indication "treatment of chronic kidney disease". Treatment with finerenone resulted in 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 is considered clinically relevant, although relatively modest. However, it should be noted that the effect is obtained on top of current standard of care (ACEi or ARB).

It is noted that initiation of finerenone treatment leads to an initial decrease in eGFR and the values were numerically lower in the finerenone arm until Month 24. When the long term eGFR slope (from Month 4 onwards) was assessed, a slower decline in eGFR over time with finerenone was however observed and the applicant has also presented an analysis suggesting that a more pronounced initial decline is associated with a better long term preservation of renal function which indicates that the

initial decline has no negative long-term consequences on eGFR. The treatment effect is supported by the secondary renal composite endpoint that defined a more pronounced eGFR decrease compared to the primary endpoint (≥57% vs. ≥40%). Treatment with finerenone resulted in a 23.7% relative risk reduction compared with placebo. Further analyses of the primary and relevant secondary endpoints in the subgroup of patients with CKD stage 3 and 4, i.e. the intended population, showed consistent results.

For the key secondary endpoint that is of particular relevance for the initially proposed second part of the indication, *"to reduce the risk of cardiovascular mortality and morbidity"*, the importance of the treatment effect is not convincing. Treatment with finerenone resulted in a 14% relative risk reduction compared with placebo for the CV composite endpoint time to CV death, non-fatal MI, non-fatal stroke, or hospitalisation for heart failure. The confidence interval is wide and the upper limit is approaching unity. Moreover, none of the components of the composite displayed a pronounced positive effect. Thus, further data is considered necessary to support this part of the indication and the FIGARO-DKD trial with a primary cardiovascular objective has recently been finished. The cardiovascular protection claim was removed from the initially proposed indication.

The major safety concern is the increased incidence of 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 could be handled with routine risk minimisation.

3.7.2. Balance of benefits and risks

Overall, the results from the FIDELIO-DKD study show positive effects of finerenone for the treatment of chronic kidney disease (stage 3 and 4 with albuminuria) associated with type 2 diabetes mellitus in adults. Cardiovascular endpoints are in favour of finerenone, but the treatment effect is not convincing enough to support a cardiovascular prevention indication.

3.7.3. Additional considerations on the benefit-risk balance

The initially proposed therapeutic indication was: *"Kerendia is indicated to delay progression of kidney disease and to reduce the risk of cardiovascular mortality and morbidity in adults with chronic kidney disease (stage 3 and 4 with albuminuria) and type 2 diabetes".*

At day 120, the CHMP proposed the following indication*: "Kerendia is indicated for the treatment of diabetic kidney disease stage 3 and 4 in adults."*

At day 180, the applicant removed the cardiovascular prevention indication but preferred a slightly different wording": *"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."*

The applicant proposed to replace the term 'diabetic kidney disease' with the term 'chronic kidney disease associated with type 2 diabetes'. This proposal was endorsed given that the *KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease* suggest not to use the term "diabetic kidney disease" to avoid the connotation that CKD is caused by traditional diabetes pathophysiology in all cases, although this term is entirely appropriate when this limitation is recognised. Given that the study included patients based on specified UACR and eGFR criteria and a diagnosis of type 2 diabetes and excluded patients with known significant nondiabetic renal disease but did not include a requirement of histological evidence of kidney disease caused by diabetes, the

proposal 'chronic kidney disease associated with type 2 diabetes' was considered appropriate. However, the proposed reference to section 5.1 of the SmPC was not considered appropriate and has been removed from the indication.

3.8. Conclusions

The overall B/R balance of Kerendia is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Kerendia is favourable in the following indication(s):

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

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

to be implemented by the Member States

Not applicable.

These conditions fully reflect the advice received from the PRAC.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that finerenone is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

Refer to Appendix on new active substance (NAS).