Amsterdam, 29 January 2026
EMADOC-1700519818-2833541
Committee for Medicinal Products for Human use (CHMP)

Assessment report

Kerendia

International non-proprietary name: Finerenone

Procedure No. EMA/X/0000248026

Note

Variation 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
MAH	Bayer AG 51368 Leverkusen GERMANY
Active substance:	Finerenone
International Non-proprietary Name/Common Name:	Finerenone
Pharmaco-therapeutic group (ATC Code):	Aldosterone antagonists (C03DA05)
Therapeutic indication(s):	Kerendia is indicated for the treatment of chronic kidney disease (with albuminuria) associated with type 2 diabetes in adults. For study results with respect to renal and cardiovascular events, see section 5.1. Kerendia is indicated for the treatment of symptomatic chronic heart failure with left ventricular ejection fraction (LVEF) $\geqslant$ 40% in adults.
Pharmaceutical form(s):	Film-coated tablet
Strength(s):	10 mg 40 mg 20 mg
Route(s) of administration:	Oral use
Packaging:	Blister Bottle
Package size(s):	98 tablets 100 tablets 100 x 1 tablets (unit dose) 14 tablets 28 tablets

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List of abbreviations

ACEI	Angiotensin-converting enzyme inhibitor
ADR	Adverse drug reaction
AE	Adverse event
AKD	Acute kidney disease
AKI	Acute kidney injury
AQL	Acceptable Quality Attribute
AR	Assessment Report
ARTS	MinerAlocorticoid Receptor antagonist Tolerability Study
ARTS-HF	MinerAlocorticoid Receptor antagonist Tolerability Study - Heart Failure
AUC	Area under curve
AUC_{norm}	AUC divided by dose per body weight
AUC_{tau}	Area under curve in the dosing interval
BA	Bioavailability
BID	Twice daily
BMI	Body mass index
CEC	Clinical Event Committee
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
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
$C_{max,norm}$	C_{max} divided by dose per body weight
COVID-19	Coronavirus disease 2019
CPP	Critical process parameter
CQA	Critical Quality Attribute
CSR	Clinical Study Report
CV	Cardiovascular
CYP3A4	Cytochrome P450 isoenzyme 3A4
DBP	Diastolic blood pressure
DoE	Design of experiments
DDI	Drug-drug-interaction
DKD	Diabetic kidney disease
DMC	Data Monitoring Committee
DSMB	Drug Safety Monitoring Board
EAIR	Exposure-adjusted incidence rate
EC	European Commission
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate

EMA	European Medicines Agency
EU	European Union
EOS	End of study
ERA	Environmental risk assessment
ESC	European Society of Cardiology
F	Bioavailability
FAS	Full analysis set
FIDELIO-DKD	FInerenone in reducing kiDnEy faiLure and dIsease prOgression in Diabetic Kidney Disease
FIDELITY	FInerenone in chronic kiDney disEase and type 2 diabetes: Combined FIDELIO-DKD and FIGARO-DKD Trial programme analYsis pool
FIGARO-DKD	FInerenone in reducinG cArdiovascular moRtality and mOrbidity in Diabetic Kidney Disease
FINEARTS-HF	FInerenone in reduciNg cardiovascular mortality and morbidity in hEART failure Study
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
HF	Heart failure
HHF	Hospitalization for Heart Failure
HLM	Human liver microsomes
HPLC-MS/MS	High performance liquid chromatography linked to tandem mass spectrometry
hs-TnT	High-sensitivity troponin-t
HV	Healthy volunteer
IA	Integrated analysis
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICP-MS	Inductively coupled plasma mass spectrometry
ID	Participant identification number
IR	Immediate Release
i.v.	Intravenous
KCCQ	Kansas City Cardiomyopathy Questionnaire
KDIGO	Kidney Disease Improving Global Outcomes
LLOQ	Lower limit of quantitation
LPLV	Last patient last visit
LVEF	Left ventricular ejection fraction
MAH	Marketing authorization holder
MedDRA	Medical Dictionary for Regulatory Activities
MLG	MedDRA labeling group
MoA	Mechanism of action
MRA	Mineralocorticoid receptor antagonist
NCA	Non-compartmental analysis
NT-proBNP	N-terminal prohormone B-type natriuretic peptide
NYHA	New York Heart Association
OD	Omne in die, once daily

PBPK	Physiologically based pharmacokinetic modelling
PBRER/PSUR	Periodic Benefit-Risk Evaluation Report / Periodic Safety Update Report
PD	Pharmacodynamic
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetics
PT	Preferred term
PVC	Polyvinyl chloride
PVDC	Polyvinylidene chloride
p-yrs	Patient-years
QC	quality control
QbD	Quality by Design
QTPP	Quality target product profile
R_{AC}	Accumulation ratio
RAAS	Renin-angiotensin-aldosterone system
RAS	Renin–angiotensin system
RH	Relative Humidity
RMP	Risk management plan
RR	Rate ratio
SAD	Single ascending dose
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SD	Standard deviation
SGLT2	Sodium-glucose co-transporter 2
SmPC	Summary of Product Characteristics
SMQ	Standard MedDRA queries
SOC	System organ class
$t_{1/2}$	Half-life
T2D	Type 2 diabetes
TAMC	Total Aerobic Microbial Count
TDI	Time dependent inhibition
TEAE	Treatment-emergent adverse event
TID	*ter in die* (three times a day)
t_{max}	Time for C_{max}
TSS	Total symptom score
TTO	Time to onset
TYMC	Total Combined Yeasts/Moulds Count
UACR	Urinary albumin-to-creatinine ratio
UPLC	Ultra Performance Liquid Chromatography
UV	Ultraviolet
V	Volume of distribution
WHO	World Health Organization
WRF	Worsening of renal function

1. Background information on the procedure

1.1. Submission of the dossier

Bayer AG submitted on 27 January 2025 an application for a group of variations and extension application for the following variations:

	Variation(s) requested	**Type**	**Annex affected**
C.1.6.a	C.I.6.a - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II, IIIA and IIIB
C.I.13	C.I.13 - Submission of additional clinical and non-clinical studies, including BE-studies.	Type II	I
C.I.z	C.I.z - Other variation	Type IB	I

Extension application to introduce a new strength (40 mg film-coated tablets) associated with a new indication for the treatment of symptomatic chronic heart failure with left ventricular ejection fraction (LVEF) $\geqslant$ 40% in adults.

C.I.6: Extension of indication to include the treatment of symptomatic chronic heart failure with left ventricular ejection fraction (LVEF) ≥ 40% in adults, based on final results from the phase 3 study FINEARTS-HF (20103). This is a randomized, double-blind, placebo-controlled phase 3 study evaluating the efficacy and safety of finerenone on morbidity and mortality in participants with symptomatic heart failure with left ventricular ejection fraction (LVEF) ≥40%.

C.I.13: Submission of the final report from non-clinical study T105281-7, R-14405 - Juvenile toxicology study in rats.

C.I.z: Minor correction of numbers in the currently approved Annex I due to a previously communicated GCP violation affecting the FIDELIO-DKD and FIGARO-DKD trials.

As a consequence, sections 1, 2, 3, 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2, 5.3, 6.1, 6.6 and 8 of the SmPC are updated. The Labelling and Package Leaflet are updated in accordance. In addition, the MAH took the opportunity to introduce minor editorial and administrative changes to Annex I, II, IIIA and IIIB to bring it in line with the latest QRD template version 10.4.

Version 3.3 of the RMP has also been submitted.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, (2) point (c) - Extensions of marketing authorisations

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

1.3. Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0365/2022 on the agreement of a modification of the paediatric investigation plan (PIP) concerning heart failure. At the time of submission of the application, the PIP P/0365/2022 was not yet completed as some measures were deferred.

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, Bayer AG 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. Steps taken for the assessment of the product

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

Rapporteur: Kristina Dunder

The Rapporteur appointed by the PRAC was:

PRAC Rapporteur: Bianca Mulder

The application was received by the EMA on	27 January 2025
The procedure started on	20 February 2025
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	12 May 2025
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	20 May 2025
The CHMP agreed on the consolidated List of Questions to be sent to Bayer AG during the meeting on	19 June 2025
Bayer AG submitted the responses to the CHMP consolidated List of Questions on	09 September 2025
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	14 October 2025
The CHMP agreed on a list of outstanding issues in writing to be sent to Bayer AG on	13 November 2025
Bayer AG submitted the responses to the CHMP List of Outstanding Issues on	17 December 2025

The CHMP Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	16 January 2026
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	29 January 2026

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The proposed new therapeutic indication for finerenone is:

"Kerendia is indicated for the treatment of symptomatic chronic heart failure with left ventricular ejection fraction (LVEF) ≥ 40% in adults."

Chronic heart failure (CHF) with Left Ventricular Ejection Fraction (LVEF) ≥ 40% encompass the subcategories of heart failure with mildly reduced ejection fraction (HFmrEF; EF 40-49%) and HF with preserved ejection fraction (HFpEF; EF ≥50%).

2.1.2. Epidemiology

Heart Failure (HF) affects approximately 64 million people worldwide, and its prevalence is increasing worldwide due to ageing and lifestyle factors that contribute to comorbidities such as hypertension, diabetes, obesity and renal dysfunction (Desai et al, 2024). Traditionally, it was believed that most HF patients have a reduced LVEF (HFrEF with LVEF ≤40%); however, large inpatient cohort studies have shown that about 50% of the HF population actually have HFpEF (LVEF ≥50%) or HFmrEF (LVEF in the 40-49% range; McDonagh et al, 2021; Ponikowski et al, 2016; Lam & Solomon, 2014).

2.1.3. Clinical presentation and prognosis

HF is associated with an impaired quality of life (Bozkurt et al, 2023) and remains associated with high mortality despite improved treatments (Shahim et al, 2023). In a meta-analysis of 60 studies, survival rates at 1, 5 and 10 years were estimated to be 86.5%, 56.7% and 34.9%, respectively (Jones et al, 2019)

In terms of mortality and HF events, the prognosis for HFmrEF is comparable or worse than for HFpEF patients and often leads to hospitalizations, with elevated rates of both mortality and morbidity post-hospitalization (Rastogi et al, 2017; Soufi et al, 2023).

2.1.4. Management

Current treatment recommendations for HFmrEF/HFpEF include diuretics (class 1), as well as Angiotensin Converting Enzyme (ACE) inhibitors, Angiotensin II Receptor Blockers (ARBs), Angiotensin Receptor–Neprilysin Inhibitors (ARNIs), and beta blockers as class 2b treatment options according to the ESC guidelines. SGLT-2 inhibitors have emerged as a significant advancement and constitute a class 1 recommendation in the ESC guidelines a class 2a recommendation in the AHA guidelines. MRA have a class 2b recommendation for HFmrEF in the ESC guidelines.

2.2. About the product

Finerenone is a mineralocorticoid receptor antagonist that is currently indicated for treatment of chronic kidney disease (with albuminuria) associated with type 2 diabetes in adults. With the present procedure, the applicant proposes to amend the indication to include treatment of symptomatic chronic heart failure with left ventricular ejection fraction (LVEF) ≥ 40% in adults.

The target daily dose of Kerendia for Heart Failure with LVEF ≥ 40% is dependent on renal function (eGFR) at initiation of Kerendia treatment:

- The target daily dose is 40 mg once daily if eGFR at initiation was ≥ 60 mL/min/1.73 m^2
- The target daily dose is 20 mg once daily if eGFR at initiation was ≥ 25 to < 60 mL/min/1.73 m^2

The 40 mg dose is introduced in the current variation. The current posology for treatment of chronic kidney disease associated with type 2 diabetes is 10 mg or 20 mg once daily.

2.3. Type of Application and aspects on development

The development programme/compliance with guidance/scientific advice

There was no Scientific Advice provided for this development program by the CHMP.

General comments on compliance with GMP, GLP, GCP

The MAH states that clinical studies were conducted in accordance with the Declaration of Helsinki ethical principles and the ICH GCP guideline.

2.4. Quality aspects

2.4.1. Introduction

The finished product introduced with this line extension application is presented as film-coated tablets containing 40 mg of finerenone as active substance.

Other ingredients are:

Tablet core: microcrystalline cellulose (E 460), croscarmellose sodium, hypromellose 2910 (E 464), lactose monohydrate, magnesium stearate (E 470b), sodium laurilsulfate (E 487).

Tablet coating: hypromellose 2910 (E 464), titanium dioxide (E 171), talc (E 553b), iron oxide red (E 172), iron oxide yellow (E 172).
The product is available in PVC/PVDC/Aluminium transparent calendarised blisters.

2.4.2. Active Substance

Since the active substance used to manufacture the 40 mg film-coated tablets, is the same as that used for the authorised 10 and 20 mg film-coated tablets no 3.2.S. documents and data have been presented within this line extension application. This is acceptable.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

Kerendia film-coated tablet 40 mg is presented as gray-orange film-coated, oval oblong tablet with a length of 11 mm, a width of 5 mm, a radius of curvature of 3.5 mm, a height of 4.2 mm – 5.0 mm and a weight of 207.00 mg. The tablets are marked with "40" on the top side and "FI" on the bottom side.

The composition of Kerendia 40 mg film-coated tablets has been provided.

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 aqueous media finerenone active substance shows a strongly pH-dependent solubility with a maximum at pH 1 (approx. 46 mg/mL; 0.1 M HCl). The compound is sparingly soluble in aqueous solutions of pH 2 (0.01 M HCl), but due to the decrease in solubility with increasing pH it is only very slightly soluble in buffer solutions of pH 3 and 4 and practically insoluble in buffer solutions of pH 4.5 – pH 6.8 and water. Finerenone active substance is sparingly soluble in ethanol and acetone and soluble in methanol and macrogol 400. Due to the low solubility of finerenone, micronised substance is used in the tablets, as indicated done for the manufacture of the existing strengths.

As for the already authorised 10 mg and 20 mg tablets, the development objective of the 40 mg tablets 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).

Table 1. Summary of Quality Target Product Profile (QTTP) for Kerendia 40 mg film-coated tablets.

QTPP-Element	Target
Dosage form	Immediate release tablet
Route of administration	Oral
Dose strengths	40 mg
Tablet shape and size	Easy to handle by the patient, easy to swallow, tablet dimensions: 11 x 5 roc [a] 4.5 + 1.5 mm (clinical samples) and 11 x 5 roc 3.5 mm (marketed product)
Appearance	Coated tablet, trade dress clinical samples: color- light orange, embossing- "PT" on one side, blank on the other side; trade dress marketed product: color- gray-orange, embossing- "FI" on one side, "40" on the other side
Dissolution	Immediate release dissolution profile
Identity	Positive for Finerenone
Solid state form	Stable modification
Assay	Meets ICH Q6A criteria
Degradation products	Meets ICH Q3B and Q6A criteria
Uniformity of dosage	Meets pharmacopoeial acceptance criteria
Microbial purity	Meets pharmacopoeial acceptance criteria
Stability	36 months in all relevant climate zones
Container closure system	Suitable container closure system to achieve the target shelf-life and in-use stability

a roc = radius of curvature

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 were defined as critical quality attributes (CQAs) for the tablets: identity, appearance, uniformity of dosage units, dissolution, degradation products, assay and microbial purity.

The QTPP and the critical quality attributes (CQAs) are well described and justified in the documentation.

The immediate release (IR) tablet formulations of Kerendia 10 mg and 20 mg film-coated tablets were used as starting point for development. The composition of the tablet core is qualitatively identical to the already approved lower strengths of the 10 and 20 mg strengths but it is not quantitatively dose-proportional. Furthermore, the tablet core composition of the 40 mg dose strength did not change from the clinical formulation to the marketed formulation. There was only one change regarding the colour of the film-coat: tablets used in clinical studies phase III were light orange independent of the dose strength while the colour of the 40 mg dose strength for the market is gray-orange. The basic composition of film-coat, the total amount of colour pigments and the total amount of film-coat has not been changed.

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 were investigated.

The applicant has applied QbD principles in the development of the finished product and its 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 finished product as derived from the QTPP.

Design spaces have been proposed for the manufacture of the finished product and have been adequately verified.

The development of the dissolution method has been well described, and the use of a surfactant has been acceptably justified. The discriminatory ability of the dissolution method has been shown.

The dissolution profiles of three batches used for clinical trials phase III and of three primary stability batches manufactured at final scale have been investigated as well as four process validation batches from the process validation. All batches from process validation show the same dissolution behaviour as the batches used for clinical trials phase III and the primary stability batches manufactured in final scale.

The primary packaging is PVC/PVDC/Aluminium transparent calendarised blisters. The material complies with Ph.Eur. and 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. Acceptable specifications for all packaging materials have been provided. Tests for identification are included in the specifications.

2.4.3.2. Manufacture of the product and process controls

The finished product is manufactured at a site which holds a valid GMP license.

For all sites involved in the manufacture, control and batch release of the finished product sufficient evidence of GMP compliance has been provided.

The manufacturing process is a standard process consisting of fluid-bed granulation followed by post-blending, compression and film-coating. A flow scheme of the manufacturing process including in-process controls has been provided together with a short narrative description of the process. The process description includes relevant information about the equipment used and the process parameters are stated and justified based on results during development.

Critical steps and the CQAs have been identified. The omission of any in-process control has been acceptably justified.

Critical process parameters (CPPs) are stated. For multiple CPPs, it is stated that design spaces will be used. These are based on information from DoE. These DoE were performed at both lab scale, pilot scale and commercial scale. The performed DoE support the claimed design spaces.

Process validation has been performed on multiple commercial scale batches. All results were within the specification parameters. It was verified that the process is robust and capable of consistently producing tablets of the required quality.

Holding times have been included and supported by data.

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".

2.4.3.3. Product specification

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form: description/appearance (visual inspection), identity (UPLC retention time and DAD UV-spectrum), uniformity of dosage units (Ph. Eur.), dissolution (Ph. Eur.), assay (UPLC), degradation products (UPLC), microbial purity (TAMC, TYMC, *E.coli*) (Ph. Eur.). The proposed specification is in line with that approved for the 10 mg and 20 mg strengths.

The proposed tests and corresponding specification limits are adequate for routine control of the finished product at release and shelf life. They are in line with ICH guidelines, Ph. Eur., batch release and stability data.

Acceptable discussions have been provided regarding impurities and residual solvents.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on four commercial scale 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 controls. The information on the control of elemental impurities is satisfactory.

A risk assessment regarding potential presence of nitrosamine impurities 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) has been provided. The conclusion by the Applicant that no risk exists for contamination with any nitrosamine in the finished product and that no routine testing is needed is supported. Therefore, no specific control measures are deemed necessary.

The analytical methods and reference standards used are the same as those used for the authorised strengths.

Batch analysis results are provided for four commercial scale batches and three development batches used for stability testing and/or clinical trials confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

2.4.3.4. Stability of the product

Stability studies according to ICH guidance have been performed on three pilot scale batches of Kerendia 40 mg film-coated tablets stored in the blister as intended for marketing for up to 36 months under long term conditions (25 °C / 60% RH and 30 °C / 75% RH) and for up to 6 months under accelerated conditions (40 °C / 75% RH) according to the ICH guidelines.

Supportive data has also been provided on four production scale batches stored under long term for up to 12 months and accelerated conditions for 6 months.

The stability study samples were tested for appearance, assay, degradation products, dissolution and microbial purity. Microbial purity has been tested at selected time points according to the stability protocol.

All results were within the specification limits and no trends were observed. The tablets are very stable.

Furthermore, bulk stability studies were performed on commercial scale and pilot scale batches manufactured at the proposed commercial manufacturing site stored under long-term conditions. Bulk stability data has shown that the tablets are stable under the tested conditions and time when stored in the proposed bulk packaging.

Stress test studies (thermal and hydrolytic) were performed on 2 pilot scale batches to generate stress stability data for batches of the intended commercial formulation. The tablets complied with the specification also after storage at 80 °C for 3 months, open air storage at 40 °C for 3 months and after light exposure.

In addition, three pilot scale batches were exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. All results of the directly exposed samples met the acceptance criteria and no differences to the unexposed samples were observed. The study confirmed that Kerendia 40 mg film-coated tablets 40 are very stable to light. Therefore, no specific protective packaging, storage requirements or labelling restrictions are required with respect to light exposure.

Based on all the available stability data, the proposed shelf-life of 3 years with no special precautions for storage as stated in the SmPC (sections 6.3 and 6.4) are acceptable.

Adventitious agents

It is confirmed that the lactose 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.

No other excipients derived from animal or human origin have been used. Magnesium stearate is of vegetable origin.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the finished product has been presented in a satisfactory manner. The applicant has applied QbD principles in the development of the finished product and its manufacturing process, defining design spaces for the granulation and film-coating steps. 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 batches used in clinical trials are representative regarding the commercial product to guarantee that the latter will be the same as the clinical batches.

All quality issues have been satisfactorily resolved and the product can be recommended for approval from a quality point of view.

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.

2.4.6. Recommendations for future quality development

n/a.

2.5. Non-clinical aspects

2.5.1. Introduction

New non-clinical studies and amendments have been included to support a new maximum dose of 40 mg/kg/day and the new proposed indication for the treatment of symptomatic chronic heart failure with left ventricular ejection fraction (LVEF) $\geqslant$ 40% in adults.

The applicant submitted an additional non-clinical juvenile toxicity study report R-14405 for the T105281-7 study that is part of the agreed PIP in the condition treatment of heart failure.

In the SmPC section 5.3, the safety margins to human exposure was revised based on the new maximum dose of 40 mg/kg/day.

In addition, the environmental risk assessment (ERA) document was revised based on the requirements specified in the *EMA Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 Rev. 1)*. A new ERA study on the Adsorption/Desorption Behaviour in Soil (OECD test method 106) was submitted, replacing a previous OECD 121 study.

2.5.2. Ecotoxicity/environmental risk assessment

The applicant provided a revised ERA document in line with the most recent requirements specified in the *EMA Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 Rev. 1)*. Updated PEC and PEC/PNEC values, taking the new maximum dose (40mg/kg/day) have been provided.

A new OECD 106 study (Adsorption/Desorption Behaviour in Soil) has been submitted. This study replaces a previous OECD 121 study. The KOC values ranged from 455.75-2,492.79 for the soils and 151.46-162.06 for the sludges. The Freundlich coefficient ranged from 0.85-0.90 for the soils and 0.91-0.93 for the sludges. The results are not considered to trigger additional ERA studies.

Finerenone is not a PBT substance but may pose a risk to surface water and to groundwater. Therefore, finerenone should be used according to the precautions stated in the SmPC in order to

minimize any potential risks to the environment. The applicant has proposed the following SmPC texts to inform on the potential environmental risk and the text was endorsed by the CHMP:

Section 5.3 Preclinical safety data

Environmental risk assessment (ERA)

Environmental risk assessment studies have shown that finerenone may pose a risk for the surface water and groundwater compartment (see section 6.6).

Section 6.6 Special precautions for disposal

This medicinal product may pose a risk to the environment (see section 5.3). Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Table 1. Summary of main study results

Substance (INN/Invented Name): Finerenone			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	2,61 at pH7	Potential PBT N
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	2,61	not B
	BCF	L/kg_{ww}	B/vB/not B
Persistence	DT50		P/ vP/not P
Toxicity	NOEC or CMR		T/not T
PBT-statement :	The compound is considered to be not PBT, nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$	Default: 0,20 Refined: 1.008	μg/L	≥ 0.01 threshold Y
Other concerns (e.g. chemical class)	N/A		
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption Lufa 2.1 (1): Loamy sand Lufa 2.4 (2) : Loam Lufa 6S (3): Clay = A, B, C) and two sludges (R, U),	OECD 106	$K_{oc,\ soil\ 1}$ =455.75 L/kg_{oc} $K_{oc,\ soil\ 2}$ = 790,27 L/kg_{oc} $K_{oc,\ soil\ 3}$ = 2492,79 L/kg_{oc} $K_{oc,\ sludge\ 1}$ =162,06 L/kg_{oc}	

Sludge 1 =Rural Sludge 2 = Urban		$K_{oc,\ sludge\ 2}$ = 151,46 L/kg_{oc}			
Ready Biodegradability Test	OECD 301	N/A			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems Sediment 1 = loamy sand Sediment 2 =Loam Sediment 3= clay	OECD 308	$DT_{50,\ water}$ = 78.9-147.9 days $DT_{50,\ sediment}$ = 44,17 days $DT_{50,\ whole\ system}$ = 80.5-191.7 Days % shifting to sediment at 15d >10% (78.1-79.3%) One main transformation product ("M1)" represented 90% at 100d while finerenone represented ~3% at 100d.			DT50s at 12°C 1 / 2
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/ *Desmodesmus subspicatus*	OECD 201	NOEC / EC_{10}	3.46 µg/L 11,29 mg/L	µg/L	72 h, growth rate
Daphnia sp. Reproduction Test	OECD 211	NOEC LOEC (offspring) EC_{10}	<0.013 0.05 0.005 (0.0002 -0.016)	µg/L	21d
Fish, Early Life Stage Toxicity Test/ (fathead minnow)	OECD 210	NOEC LOEC (survival)	0.00001 0.00007	µg/L	Pimephales promelas 28d
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	≥100	µg/L	3 h
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF: N/A BCF	N/A	L/kg_{ww} L/kg_{ww}	
Aerobic and anaerobic transformation in soil LUFA 6S: clay LUFA 2.1: Lamy sand LUFA 2.3: Sandy loam	OECD 307	DT50 LUFA 6S: 0.6 d DT50 LUFA 2.1: 0.4 d DT50 LUFA 2.3: 0.7 d %CO_2 LUFA 6S: 1.78 %CO_2 LUFA 2.1:0.67 %CO_2 LUFA 2.3:0.66			

Soil Micro organisms: Nitrogen Transformation Test	OECD 216	NOEC / EC_{10}	N/A	mg/kg_{dw}	N transformation
Terrestrial Plants, Growth Test/ Brassica napus Glycine max Avena sativa	OECD 208	NOEC LOEC NOEC LOEC NOEC LOEC	12.3 37.0 <12.3 12.3 12.3 37.0	mg/kg $_{dw}$	
Earthworm, Acute Toxicity Tests /*E. fetida*	OECD 207	NOEC LOEC	500 1000	mg/kg $_{dw}$	
Earthworm, Chronic Toxicity Test/	OECD 222	NOEC / EC_{10}	N/A	mg/kg $_{dw}$	
Collembola, Reproduction Test	OECD 232/ ISO 11267	NOEC	>1000	mg/kg $_{dw}$	
Sediment dwelling organism/ *Chironomus riparius*	OECD 218/219	NOEC / EC_{10}	7 (46.7 in standard sediment)	mg/kg $_{dw}$	

2.5.3. Discussion on non-clinical aspects

The agreed wording of the indication in the current procedure is for adult patients and no dosing in paediatric patients is currently proposed. The data from the submitted juvenile toxicity study (R-14405) that was part of the nonclinical package agreed in the PIP program for condition: treatment of heart failure were assessed within the current procedure.

The safety margins to human exposure were revised based on the new doubled maximum dose of 40 mg/kg/day and this resulted in modifications to Section 5.3 of the SmPC.

Assessment of paediatric data on non-clinical aspects

13 Week Oral (Gavage) Juvenile Toxicity Study in the Rat with 4 Week Recovery period (R-14405)

The previously approved indication (chronic kidney disease associated with type 2 diabetes), or the currently sought heart failure indication only includes administration in adults. Dosing in paediatric patients is currently not proposed, and the submitted juvenile toxicity study (R-14405) was submitted as part of the nonclinical package agreed in the PIP program for condition: treatment of heart failure.

A rat juvenile toxicity study with dosing from PND 14 was performed previously to support the approved chronic kidney disease indication. However, dosing from day 14 would not cover the youngest age (neonates) intended to be treated in a possible future paediatric indication of heart failure. The applicant therefore performed an additional 13-week rat juvenile toxicity study with dosing from PND 10 (R-14405). The new study used the same doses as in the previous juvenile toxicity study and the study design was agreed in the PIP P/0365/2022.

In the new 13-week juvenile toxicity study, finerenone was administered by oral gavage at 1, 3, or 10 mg/kg/day to rats from postnatal day (PND) 10 which could be considered in future applications supporting dosing in a younger neonatal age group.

Finerenone treatment was well-tolerated in juvenile rats, and no deaths or clear clinical signs considered finerenone-related were seen in the study.

Toxicokinetic investigation was carried out on PND 10, PND 29 and in week 13 of the treatment period (PND 94). On PND 29 and PND 94, exposure was higher in females than in males.

In line with the previously performed juvenile rat study (dosing from PND 14), dose-related microscopic findings were noted in the adrenal glands (hypertrophy in zona glomerulosa). Although the adrenal hypertrophy was not noted in recovery animals, a dose related increase in vacuolation in the adrenocorticocytes was present after recovery. The adrenal effects are likely due to the aldosterone inhibitory pharmacological action of finerenone (mineralcorticoid receptor blockade) and are known compensatory effects of aldosterone inhibition. They are therefore not considered to be adverse.

Minor behavioural effects were noted (increase in movements) in connection with finerenone administration and was also present in recovery animals. The applicant considers the increase in activity to be non-adverse since the mean number of movements were comparable to controls at the end of the session. While agreed that they are minor increases in activity, it is noted that similar findings were noted in the previous PPND rat study and could possibly be due to brain exposure to finerenone.

The NOAEL of 10 mg /kg/day is acceptable and collectively, the toxicity profile in the current juvenile toxicity study is similar to the profile seen in adult and adolescent animals.

Assessment of ERA

The revised Environmental Risk Assessment in line with the latest *EMA Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 Rev. 1*) was submitted, replacing previous OECD 121 study with a new OECD 106 study.

Finerenone is not a PBT substance but may pose a risk to surface water and groundwater.

Considering the above data, finerenone should be used according to the precautions stated in the SmPC in order to minimize any potential risks to the environment.

The revised ERA was considered acceptable.

2.5.4. Conclusion on the non-clinical aspects

The application is considered acceptable from the non-clinical point of view.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by Bayer AG.

Bayer AG 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**

Table 2: Clinical studies

Study ID	**Enrolment status** **Start date** **Total enrolment/ enrolment goal**	**Design** **Control type**	**Study & control drugs** **Dose, route of administration and duration** **Regimen**	**Population** **Main inclusion/ exclusion criteria**
20103 FINEARTS-HF Phase 3	Complete 7463 participants screened, 6016 participants randomized	Randomized, double-blind, placebo controlled, parallel group, multicenter, event-driven	2 arms; in addition to background therapy: • finerenone tablets 10, 20 or 40 mg OD; Starting dose: 10 or 20 mg OD, Maintenance dose: 20 or 40 mg OD • placebo tablets Planned treatment duration: event-driven, approximately 18 to 42 months	Participants with HF (NYHA II-IV) and LVEF ≥40% eGFR ≥25 mL/min/1.73 m²
14563 ARTS Phase 2 (supportive study)	Part A: Planned total of approx. 70 participants screened to reach 15 valid participants per treatment arm Part B: Planned total of approx. 415 participants screened to reach 60 valid participants per treatment arm	Randomized, double-blind, placebo controlled, parallel group, multicenter design in Parts A and B, with additional open-label active comparator for Part B.	Part A: 4 arms, in addition to standard of care • finerenone tablets: 2.5, 5, and 10 mg OD • placebo tablets Part B: 6 arms, in addition to standard of care • finerenone tablets: 2.5, 5, and 10 mg OD, 5 mg BID • placebo tablets BID • spironolactone tablets 25 mg or	Participants with stable CHF with reduced ejection fraction and mild CKD (Stage 2, Part A) or moderate CKD (Stage 3, Part B)

Study ID	Enrolment status Start date Total enrolment/ enrolment goal	Design Control type	Study & control drugs Dose, route of administration and duration Regimen	Population Main inclusion/ exclusion criteria
			50 mg OD up-titrated (open-label) Planned treatment duration: 4 weeks	
14564 ARTS-HF Phase 2 (supportive study)	Planned total of approx. 845 participants evaluable, approx. 130 participants per finerenone treatment arm and 195 participants for the eplerenone treatment arm.	Randomized, adaptive, double-blind, double dummy, comparator controlled, parallel-group, multicenter	6 arms; in addition to standard of care • finerenone tablets: 2.5 mg OD (possibly up-titrated to 5 mg OD), 5 (to 10), 7.5 (to 15), 10 (to 20), and 15 (to 20) All up-titrations on Day 30 and all possibly (sham) up-titrated on Day 60, if serum potassium ≤5.0 mmol/L. • eplerenone tablets: 25 mg every other day, possibly up-titrated to 25 mg OD on Day 30 if blood potassium ≤5.0 mmol/L, possibly up-titrated on Day 60 to 25 mg OD (if not done on Day 30) or to 50 mg OD if blood potassium ≤5.0 mmol/L Planned treatment duration: 90 days	Participants with worsening CHF and reduced ejection fraction, and either T2D with/without CKD or moderate CKD alone
16815 ARTS-HF Japan	Study design and study population as ARTS-HF but conducted in Japan.			

Study ID	Enrolment status Start date Total enrolment/ enrolment goal	Design Control type	Study & control drugs Dose, route of administration and duration Regimen	Population Main inclusion/ exclusion criteria
Phase 2				

2.6.2. Clinical pharmacology

To support the development of the 40 mg dose, a dedicated study (22292) to compare 2 × 20 mg and 1 × 40 mg finerenone was done to demonstrate bioequivalence between the two formulations. A food effect and dose proportionality study (21081) was also conducted. A new in vivo drug-drug interaction (DDI) Study 22285 was done to investigate finerenone 40 mg as an inhibitor of CYP3A4 and CYP2C8, using midazolam and repaglinide as probes. In contrast to 20 mg, finerenone 40 mg was found to be a weak inhibitor of CYP3A4 and CYP2C8 in vivo. A new popPK study to characterize the PK of finerenone in patients with HF and LVEF $\geqslant$ 40% from the Phase 3 Study 20103 (FINEARTS-HF) has been submitted.

In addition to clinical data, in vitro and in silico analyses were done to address relevant clinical pharmacology aspects at the new dose of 40 mg. Enzyme inhibition and induction was re-assessed at the Cmax estimated for the 40 mg dose level. In vitro study R-14427 addressed inhibitor potential of finerenone and its metabolites towards OAT1, OAT3, OCT1, OCT2, MATE1, or MATE2K. In report B003719, a new in vitro study in Caco-2 cells of the inhibitory potential of finerenone towards P-gp was investigated, that indicated a potential for inhibition by finerenone at the 20 and 40 mg dose levels. This study was supplemented by an in silico PBPK model to support that finerenone at 40 mg does not inhibit P-gp.

2.6.2.1. Pharmacokinetics

Methods

Bioanalytical methods

The bioanalytical methods have been validated and previously assessed in the original MAA for Kerendia (EMEA/H/C/005200/0000).

A new amendment has been submitted to assess finerenone stability in human plasma, focusing on frozen and bench-top stability, matrix effects in the Chinese population, and whole blood stability.

Stability was established for finerenone in human plasma for 97 h at room temperature, up to 232 days at -10 to -30°C, and up to 823 days at -60 to -80°C. Stability in whole blood was established for 4 h in room temperature and on wet ice. LQC (0.300 µg/ml) and HQC (160 µg/ml) were spiked in blank matrix (plasma) from at least 6 Chinese donors and analysed in 6 replicates. Accuracy and precision were acceptable for all experiments.

Population pharmacokinetic analysis

The population PK analysis included data only from Phase 3 study 20103 (FINEARTS-HF). The analysis of the FINEARTS-HF study was executed in a two-step approach: First, data from the formal interim analysis data-cut (when 2/3 of events were reached) were used to develop the PopPK model, including a full covariate analysis, secondly after database lock an update of the model was performed on the final analysis dataset. The aim of this analysis was to characterize the PK of finerenone in patients with HF and LVEF $\geq$ 40% from the Phase 3 Study 20103 (FINEARTS-HF) and identify relevant covariate effects, compare finerenone PK between subgroups of interest, compare finerenone PK to previous finerenone PK analyses, and provide post-hoc estimates for exposure-response analysis.

Finerenone plasma concentrations that were missing or had no recorded sample time and/or date, were excluded from the analysis and documented in the dataset documentation. Identification of outliers was performed, and data point considered outliers according to pre-specified criteria were excluded.

A previously developed model was used as a starting point and the model was optimised prior to a stepwise covariate selection. After the final analysis set became available, further optimisation was done and additional covariates were re-tested.

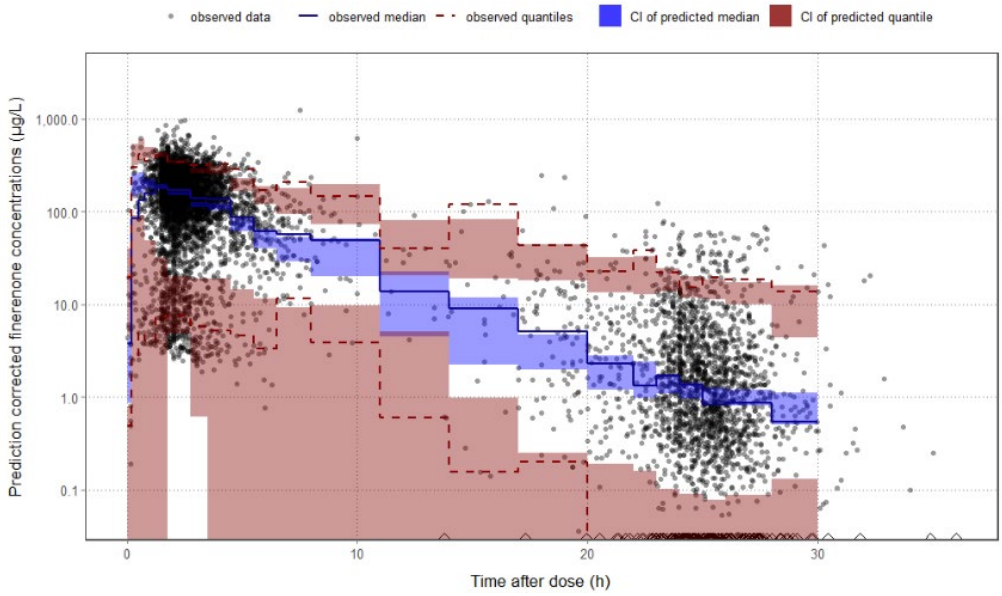
The final model was a two-compartment distribution model with first-order elimination where the delay in absorption was described as first order absorption via three transit compartments with an additional absorption lag time (ALAG). The final model included the following covariates: Body weight on CL/F+F and Vc, time-varying eGFR-EPI on CL/F+F, alanine aminotransferase (ALT0) on CL/F+F, bilirubin (BIL0) on CL/F+F, American Indian or Alaska Native on CL/F+F, and NYHA class III or IV on V/F. For all continuous covariates except WGHT0, $C_{max,md}$ (C_{max}, multiple dose) and $AUC_{\tau,md}$ (AUC_{τ}, multiple dose) at the 5th-95th percentiles of the covariate distribution were within 80-125% of the exposure at the median of the covariate distribution. WGHT0 was associated with 42.6% increase and 28.6% decrease in $C_{max,md}$ at the 5th and 95th percentiles of the WGHT0 distribution, whereas the effect was within the 80-125% range for $AUC_{\tau,md}$. For the categorical covariates, only the effect of race (American Indian or Alaska native versus other) was outside the 80-125% equivalence range, with a 36.3% increase in $AUC_{\tau,md}$, whereas the effect was within the 80-125% range for $C_{max,md}$. All fixed-effect and random-effect parameters of the final PK model were identified with RSE $\leq$31.6% for all parameters. The final PK model assumes dose-proportional PK for finerenone. Shrinkage was 16.3% and 46.5% for the ETA distribution of CL/F and Vc/F, respectively (Table 4). No clear time dependency was observed in the GoF plots, indicating that, apart from the effect of time-varying eGFR-EPI, finerenone PK is constant over time. The final PK model ability to describe data from the final PK dataset is shown in Table 4 and Figure 1.

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

Parameter Name	Estimate	SE	RSE (%)	95% CI
Ka (1/h)	30.8	1.25	4.05	(28.3, 33.2)
CL/F (L/h)	23.3	0.277	1.19	(22.8, 23.9)
Vc/F (L)	96.4	1.52	1.57	(93.4, 99.4)
Q/F (L/h)	0.283	0.00760	2.68	(0.268, 0.298)
Ratio between Vp/F and Vc/F (fixed)	1.00	-	-	-
Absorption lagtime (h)	0.150	0.00145	0.964	(0.147, 0.153)
Relative bioavailability (fixed)	1.00	-	-	-
effect of WGHT0 on V/F	0.745	0.0493	6.61	(0.648, 0.841)
Effect of EGFREPI on CL/F and F1	0.150	0.0148	9.85	(0.121, 0.179)
Effect of ALT0 on CL/F and F1	-0.0254	0.00803	31.6	(-0.0412, -0.00969)
Effect of BILI0 on CL/F and F1	-0.0479	0.00919	19.2	(-0.0659, -0.0299)
Effect of NYHA (CLASS III or IV) on V/F	1.06	0.0261	2.46	(1.01, 1.11)
Effect of race (estimated difference in CL/F and F1 for American indian and Alaska native)	0.857	0.0264	3.08	(0.805, 0.908)
Effect of WGHT0 on CL/F and F1	0.175	0.00494	2.82	(0.165, 0.185)
Variability	**Estimate**	**SE**	**RSE (%)**	**%CV**
CL/F	0.134	0.00681	5.07	37.9
Vc/F and Vp/F	0.0998	0.0126	12.6	32.4
Residual Error	**Estimate**	**SE**	**RSE (%)**	**stDev**
residual error	0.312	0.00658	2.11	0.559

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

Figure 1. pcVPC plot of the final PK model applied to Study FINEARTS-HF data from the final PK dataset



Only data shown between 0-36h after last dose. black/grey dots: prediction-corrected observations; blue line: observed median; red dashed lines: 2.5th and 97.5th percentiles of observations; red area: 95% variability-based prediction interval of the simulated 2.5th and 97.5th percentiles (excluding parameter uncertainty); blue area: 95% prediction interval of the simulated median; diamond symbols: observations below LLOQ.

Physiologically based pharmacokinetic modelling

A Physiologically based pharmacokinetic (PBPK) model of finerenone was developed to evaluate finerenone as an inhibitor of P-gp mediated transport of digoxin. Absence of an effect at 20 mg finerenone was demonstrated in a dedicated Phase 1 study with the sensitive P-gp substrate digoxin (Study 14505). As the FINEARTS-HF study included finerenone in doses up to 40 mg, PBPK modelling was used to further assess the P-gp interaction potential of finerenone at a dose of 40 mg and to further de-risk the interaction potential in addition to the available clinical data.

The digoxin model was tested as a victim of P-gp DDI with various P-gp perpetrators such as itraconazole, clarithromycin, erythromycin, verapamil and rifampicin. In the coupled finerenone-digoxin model, the measured in vitro value for finerenone P-gp Ki of 7.74 µM (competitive inhibition) was employed.

The developed finerenone P-gp interaction model is based on the Ki from in vitro study B003719, as the performed clinical DDI study showed no interaction effects on the PK of digoxin. This means that there is no clinical data informing the model parameters pertaining to the interaction, and it is not clear that the developed PBPK model is capable of simulating the in vivo scenario it is developed for. Therefore, the PBPK model is not considered qualified and should not inform any recommendations in the SmPC.

Absorption and bioavailability

No new data is available for this section.

Bioequivalence

Study 22292 assessed bioequivalence between finerenone 2 x 20 mg tablets and 1 x 40 mg tablet in healthy male adult participants.

The geometric mean $AUC_{0\text{-last}}$ for a single 40 mg finerenone tablet was 944 µg·h/L, while for two 20 mg finerenone tablets it was 916 µg·h/L, resulting in least squares (LS) mean ratio of 103.00% (90% CI: 99.43 to 106.70%). The geometric mean Cmax was 293 µg/L for the 40 mg tablet and 283 µg/L for the two 20 mg tablets, with a LS-mean ratio of 103.54% (90% CI: 94.27 to 113.73%). The median time to reach maximum concentration, Tmax, was 1 hour for both formulations, ranging between 0.5-4h.

Influence of food

In study 21081, the administration of a 40 mg finerenone tablet with a high-fat, high-calorie meal resulted in a delayed peak plasma concentration by 2.25 hours and reduced Cmax by 22.8%, but had a minimal impact on total exposure, with AUC and $AUC_{0\text{-tlast}}$ LS-means of: 101.61% (90% CI: 96.59, 106.90) and 101.70% (90% CI: 96.92.106.83), respectively.

Distribution

No new data were generated for this section.

Elimination

No new data were generated for this section.

Metabolism

No new data is available for this section. Approximately 90% metabolism is mediated by CYP3A4 and 10% by CYP2C8. There are four major metabolites of finerenone, M-1a (38.8%), M-1b (10.1%) and M-

2a (20.3%) and M-3a (~30% of total drug related plasma AUC in renally impaired patients). All major metabolites of finerenone are pharmacologically inactive.
All three major metabolites of finerenone exhibit axial chirality forming the respective pairs of atropisomers, namely M-1a, M-1b, M-2a, M-2b, M-3a, and M-3b. Further detailed analysis has revealed a predominant *in vivo* appearance of a-series of atropisomers while b-series was only present in a higher percentage for M1 metabolite (i.e. a:b for M1 metabolite was about 85:15).

Dose proportionality and time dependencies

Dose proportionality was investigated in study 21081, at a single dose of 20 mg or 40 mg finerenone, in the fasted state. Dose-adjusted AUC/D for 20 mg and 40 mg was 18.4 and 19.3 $h/L \cdot 10^{-3}$, respectively, and Cmax/D for 20 mg and 40 mg was 6.95 and 7.13 $/L \cdot 10^{-3}$, respectively. The point estimates for the ratios of AUC/D and Cmax/D for finerenone when comparing 40 mg to 20 mg in a fasted state were 107.62% and 103.25%. The 90% confidence intervals for these parameters were within the 80.00-125.00% interval.

There is no new dedicated study on time dependency, and no updated information available.

Special populations

The applicant has previously conducted dedicated studies to evaluate impact of gender, age, HI and RI. In addition, available data have been analysed using model-based approaches.

Age was investigated in population PK model analysis and not found have a significant impact on exposure in the target population (FINEARTS-HF, N=2461, age range 40-96 years).

Pharmacokinetic interaction studies

No new drug-drug interaction (DDI) studies have been conducted for the victim potential for finerenone. For finerenone as a perpetrator of DDIs, supplementary studies and analysis have been submitted in this application.

For the purpose of DDI evaluations, the Applicant has reported the maximum plasma concentration (C_{max}) of finerenone at the steady state with the proposed therapeutic dose (i.e. 40 mg given once daily) to be 379 µg/L. This was based on median Cmax,ss derived from popPK analysis of study 20103. This corresponds to finerenone molar concentration of 1.00 µM, when taking into account its molecular weight of 378.42 g/mol. Furthermore, reported plasma protein binding for finerenone was 91.7%, thus fraction unbound is about 8.3%, and a maximum unbound plasma concentration (Cmax,u) of 0.083 µM (31.6 µg/L).

The clinical exposure of the major metabolites following 40 mg OD finerenone were estimated based on popPK and atropisomer ratios to; M-1a: 1.61 µM (604 µg/L), M-2a: 0.775 µM (304 µg/L) and M-3a: 0.343 µM (139 µg/L). The unbound fraction (%), fu in human for M-1a, M-2a and M-3a metabolites were: 5.82%, 17.4% and 67.8%, respectively. Molecular weight for M-1a, M-2a and M-3a are 376.41 g/mol, 392.41 g/mol, and 406.39 g/mol respectively.

See Table 5 for the calculated cut-offs.

Table 4: Cut-offs for the evaluation of interaction potential

	50×Cmax(u)[a] (µM)	10×Cmax(u) (µM)	10×Inlet Cmax(u)[a] (µM)	0.1×dose/250 ml[b] (µM)
Finerenone	4.16	0.83	5.97	42.28
M-1a	4.67	0.93	N/A	N/A
M-1b	0.63	0.13	N/A	N/A
M-2a	6.74	1.35	N/A	N/A

M-3a	11.63	2.33	N/A	N/A

a Multiple dose $Cmax_{ss}$, 40 mg dose (PK modelling-based study 20103)
b Based on a 40 mg dose
NA - Not applicable

Enzyme inhibition/induction

There is no new experimental data generated regarding induction/inhibition of drug metabolizing CYP-enzymes. For both finerenone and metabolites, based on the cut-offs in Table 5, no new signals for either inhibition or induction were detected for the new dose of 40 mg.

Transporter inhibition

In report R-14427, finerenone and its metabolites were tested for their potential to inhibit various transporters, including OCT1, OCT2, OAT1, OAT3, MATE1, and MATE2K. See table 6 below for the resulting IC50 values:

Table 5: Summary of IC50 values for the tested transporters in study R-14427

Transporter	Finerenone	M1a	M2a	M3a
OAT1	**>3.0**	**>5[a]**	**>7[a]**	**>29[a]**
OAT3	**>3.0**	**>50[a]**	**>50[a]**	**>50[a]**
OCT2	**>3.0**	**>50[a]**	**>7[a]**	**>29[a]**
OCT1	**>15.0[a]**	**>8.5**	**>50[a]**	**>50[a]**
MATE1	**>5.0**	**>5**	**>50[a]**	**>50[a]**
MATE2-K	**>5.0**	**>5**	**>7[a]**	**>29[a]**

a) New data in this application

New data was generated for finerenone as an inhibitor of OCT1, which showed a low degree of inhibition (2.37%) at 15 µM, which is above the cut off for liver transporters (5.97 µM).

For the metabolites, new inhibition experiments were conducted of selected transporters with M-1a, M2a and M-3a, at higher concentrations than previously. The results did not indicate that any of the tested metabolites were inhibitors. The b-atropisomer of M1 (also considered a major metabolite) was not tested in the new experiments. However, this is considered acceptable, as the previously tested concentrations were all above the respective M12 cutoff (50 x Cmax, u: 0.63 µM and 10 x Cmax, u; 0.13 µM):

Table 6: IC50 values for the metabolite M-1b

Transporter	M-1b
OAT1	>5.2
OAT3	>5.2
OCT2	>5.2
OCT1	>8.5
MATE1	>5
MATE2-K	>5

To conclude, for finerenone and its major metabolites, there is no new in vitro signal of a clinically relevant risk of DDI through transporter inhibition of OCT1, OCT2, OAT1, OAT3, MATE1, and MATE2K at the 40 mg dose.

P-gp inhibition

An in vitro study was performed in Caco-2 cells to investigate the inhibitory potential of finerenone towards P-glycoprotein (P-gp) transport of digoxin. The measured IC50 from study B003719 indicates a potentially relevant intestinal P-gp inhibition potential for finerenone. The IC50 of 7.74 µM is however higher than the cut-off of $Cmax_u$ x 50 which was 4.16 µM.

PBPK modeling was used to further assess the P-gp interaction potential of finerenone at a dose of 40 mg and to further de-risk the interaction potential in addition to the available clinical data. A digoxin PBPK model that was previously developed by the Open Systems Pharmacology (OSP) community and published by Hanke et al. was used in combination with the previously established model for finerenone.

The PBPK model simulations predict no DDI effect on the pharmacokinetics of digoxin at a finerenone dose of 40 mg OD, and when a worst-case scenario is applied, where the Ki is lowered 50 times, an AUCR of 1.137 is calculated.

In vivo DDI studies

Study 22285 investigated co-administration of finerenone 40 mg with midazolam (a CYP3A4 substrate) and repaglinide (a CYP2C8 substrate). Both treatments resulted in increased exposure of the substrates. Specifically, finerenone increased midazolam's AUC by 31% and Cmax by 15%, and repaglinide's AUC by 59% and Cmax by 30%. These findings indicate that finerenone is a weak inhibitor of CYP3A4 and CYP2C8 at a dose of 40 mg, in contrast to the lower dose of 20 mg.

2.6.2.2. Pharmacodynamics

Relationship between plasma concentration and effect and safety

Concentration-QTc analysis

A dedicated retrospective C-QTc analysis was performed of the previously submitted thorough QT (TQT) study 15113 which investigated a dose of 80 mg. The estimated C-QTcF relationship was not statistically significant (p-value > 0.3417) with a small positive slope of 0.00153 ms/[µg/L]. For finerenone plasma concentrations up to the maximum observed value of 1040 µg/L, the upper limit of the two-sided 90% CI of the estimated placebo adjusted QTcF changes from baseline did not cross the +10 ms threshold. The finerenone concentrations in the dedicated TQT study in HV cover the exposures estimated in this target patient population, including subjects with low body weight. The 40 mg dose in the target population is not expected to affect QT. The average Cmax in the TQT study in subjects given 80 mg was 597 µg/mL (108-1040) µg/L. The median Cmax,md in HF subjects weighing <5th percentile given 40 mg is estimated to 582 µg/mL. The maximum estimated Cmax value was 947 µg/L in the 40 mg dose group.

2.6.3. Discussion on clinical pharmacology

Bioanalytical methods

The bioanalytical methods used to study finerenone, have been validated and performed adequately. The matrix effect was studied in plasma from Chinese donors, and the results were satisfactory.

Bioequivalence and Dose Proportionality

The bioequivalence study 22292 demonstrated that the 2 x 20 mg finerenone tablets are bioequivalent to the 1 x 40 mg finerenone tablet.

Study 21081 was a three-fold cross-over study that investigated the effect of a high-fat meal on 40 mg finerenone. The effects were not considered clinically relevant. Therefore, no change to the current SmPC recommendations regarding food intake and finerenone is required. The dose-adjusted PK-parameters, AUC/D, AUC(0-tlast)/D, and Cmax/D, showed a slight trend towards greater than dose proportional increases between 20 mg and 40 mg, however, it was not considered clinically relevant. This observation is in line with previous data that has shown dose proportionality between 1.25 mg and 80 mg.

Time dependency

There was no new study submitted on time dependency at multiple doses of 40 mg finerenone. Considering previous multiple dose data with the proposed posology (40 mg OD), a slight increase (10%) in AUC was identified after 10 days of dosing in study 13785. This was attributed to time-dependent autoinhibition of CYP3A4, which would result in decreased metabolism of finerenone. This is in line with the in vivo DDI study (22285), where finerenone was found to be a weak inhibitor of CYP3A4 at 40 mg, in contrast to 20 mg.

Population PK analysis

A population PK model was developed on data only from the Phase 3 FINEARTS-HF study (finerenone treatment arm N=2993). As a sparse sampling approach was used in the study for all participating patients, the samples are mainly available at early timepoints or around Ctrough. The aim of the analysis was to characterize PK in the relevant population, compare PK between subgroups and to previous analyses and to derive exposure for graphical dose/exposure and response analysis.

A model with 3 transit compartments and an estimated absorption lag time was selected as the final PK model. The parameters of the final PK model were estimated with an RSE $\leqslant$31.6%. Inter-individual variability of CL/F and Vc/F was estimated to 37.9% and 32.4% percent. Intra-individual variability was not assessed. Shrinkage was 16.0% and 46.1% for the ETA distribution of CL/F and Vc/F, respectively. The covariates in the final population PK model were body weight, time-varying eGFR-EPI, BIL0, ALT0, NYHA and Alaska Indian or Alaska native. Body weight appears to have a relevant impact on exposures, especially with respect to Cmax. A subject weighting 57 kg is estimated to have an average 52% higher Cmax compared to a subject weighing 80 kg subjects.

After correction for covariates, the typical $AUC_{\tau,md}$ in Study FINEARTS-HF was 35% and 42% higher compared to Study FIDELIO-DKD and FIGARO-DKD. None of the investigated covariates could explain the remaining difference in the exposures. Figures of observed dose-normalised exposure with and without outliers to visualize how the exposures differ between the HF population and the FIDELIO-DKD and FIGARO-DKD populations show that the dose-normalised median Ctrough is higher compared to the FIDELIO-DKD and FIGARO-DKD populations, however, the range largely overlaps. The data comparisons reflect findings from the comparative popPK model assessment, i.e. that the HF population has on average a higher exposure compared to the FIDELIO-DKD and FIGARO-DKD populations.

A limitation to the analysis is the quality of the dataset. There are also some limitations of the developed model, however, the overall regulatory impact of the population PK model is considered low.

In this application, the proposed maximum dose (40 mg) dose is higher than the previous application (20 mg). The main aims of this PK analysis were to inform Section 5.2 of the SmPC and to compare if the exposure for the higher maximum dose is covered by the exposures in the previously conducted TQT study. The model is considered sufficient for deriving individual exposures to be used in the comparison of exposures with respect to the TQT and c-QTc analysis.

Physiologically based pharmacokinetic modelling

The applicant has developed a PBPK model to evaluate the risk of precipitant DDIs with the P-gp substrate digoxin. The model has been described in a report titled "Physiologically-based pharmacokinetic (PBPK) modelling of finerenone (BAY 94-8862) as a perpetrator of Permeability-glycoprotein (P-gp) to predict the extent of finerenone-digoxin-interaction".

The developed finerenone P-gp interaction model is based on the Ki from in vitro study B003719, as the performed clinical DDI study showed no interaction effects on the PK of digoxin. This means that there is no clinical data informing the model parameters pertaining to the interaction, and it is not clear that the developed PBPK model is capable of simulating the in vivo scenario it is developed for. Therefore, the PBPK model is not considered qualified and should not inform any recommendations in the SmPC.

The measured in vitro Ki of 7.74 indicates a possible inhibition of intestinal P-gp, but not systemic P-gp, meaning that the risk of a DDI with digoxin is low, as digoxin is primarily affected by P-gp in the kidneys.

The risk for a intestinal inhibition of P-gp from finerenone is considered low however, since the clinical DDI study with 20 mg finerenone indicated no impact on absorption of a P-gp substrate, and the pharmacokinetic properties of finerenone, with rapid and near complete absorption, limits the risk for an effect on the absorption on sensitive P-gp substrates.

Special populations

The impact of impaired renal and hepatic function, age, gender, and ethnic factors has been previously assessed on the PK of finerenone and its major metabolites. Finerenone is dosed based on renal function. According to the population PK simulations, subjects weighing less than 54 kg have approximately 60% higher Cmax and 11-17% higher AUCT after multiple doses, respectively.

Drug-drug interactions (DDI) and transporter inhibition

Data has only been updated for finerenone at 40 mg as a perpetrator. The Applicant reported a median Cmax of 379 µg/L based on popPK modelling (study 20103) for the DDI-evaluation of finerenone 40 mg, as well as for the major metabolites. This is acceptable.

No new experimental data on CYP-enzyme induction/inhibition was generated, and analysis of finerenone and its metabolites at the 40 mg dose revealed no new signals for inhibition or induction. Finerenone and its metabolites were tested in vitro for their potential to inhibit various transporters, including OCT1, OCT2, OAT1, OAT3, MATE1, and MATE2K. In the new experiment, finerenone was evaluated as a potential inhibitor of OCT1, and the findings indicated that finerenone does not inhibit OCT1. For OCT2, OAT1, and OAT3, the ICH M12 guideline recommends a safety margin of 10 x $Cmax_u$, resulting in a cut-off of 0.83 µM for 40 mg finerenone. Finerenone was previously tested at a concentration of 3 µM, therefore, previous data is sufficient to cover the new dose of 40 mg. According to previous data, finerenone IC50 values were >5 µM for MATE and MATE2K, which is also sufficient for the 40 mg dose. Regarding the metabolites, none were shown with new or previous data to be inhibitors of OCT1, OCT2, OAT1, OAT3, MATE1, or MATE2K. Thus, there was no new in vitro signal for finerenone 40 mg or its metabolites as an inhibitor of the tested transporters OCT1, OCT2, OAT1, OAT3, MATE1, or MATE2K.

The clinical study 22285 demonstrated that 40 mg finerenone is a weak inhibitor of CYP3A4 in vivo, resulting in a 31% increase in midazolam AUC and a 15% increase in Cmax. Similarly, finerenone was shown to be a weak inhibitor of CYP2C8 in vivo, with a 59% increase in repaglinide AUC and a 30% increase in Cmax. These findings indicate that finerenone may increase the exposure of sensitive CYP3A4 and CYP2C8 substrates, particularly those with a narrow therapeutic window. The proposed changes to the SmPC section 4.5 are acceptable.

Pharmacokinetics/Pharmacodynamics (PKPD)

Concentration-QTc analysis

The applicant conducted a dedicated retrospective C-QTc analysis to assess this exposure range with regard to its potential impact on cardiac repolarization based on thorough QT Study 15113 (CPMX50241, B003312). The conducted TQT study 15113 has been previously assessed and found to be adequately conducted. It was concluded that administration of a supratherapeutic dose of 80 mg finerenone did not affect QT calculated by any formula. The model development and evaluation of assumptions (heart correction method, linearity etc.) have been adequately conducted. The estimated C-QTcF relationship was not statistically significant (p-value > 0.3417) with a small positive slope of 0.00153 ms/[µg/L]. The finerenone concentrations in the dedicated TQT study in HV cover the exposures estimated in this target patient population, including subjects with low body weight.

In FINEARTS-HF, few events of QT-prolongation were observed in the finerenone treatment (N=2993) arm, and there was no imbalance compared to the placebo treatment (N=2993) arm (3 vs 4 events, respectively; 0.1% vs 0.1%).

Considering the very few events of QT-prolongation observed, the very small positive slope (indicating no QT prolongation) and the derived exposure (exposure for 40 mg in patients is within the range of exposure for 80 mg in the TQT study), the higher dose in this application, is considered acceptable with regards to QT-prolongation.

Exposure-response analyses

The applicant explored the correlation between dose/exposure and response for the safety biomarker serum potassium, the efficacy biomarker NT-proBNP, and the time-to-first occurrence of the cardiovascular composite endpoint. The analyses are mainly descriptive, as there are several limitations impacting the result. Overall, finerenone display exposure-response relationships both for efficacy and safety endpoints, however, due to limitations of the data and analyses, conclusions should be made with caution.

2.6.4. Conclusions on clinical pharmacology

The application for finerenone 40 mg was supported by two clinical pharmacology studies, one demonstrating bioequivalence between 2x20 mg and 1x40 mg, and one showing no food effect and dose proportionality of 20 mg to 40 mg. In addition, new in vitro, in silico and in vivo studies for finerenone 40 mg as a perpetrator were submitted. The in vitro and in vivo studies addressed relevant aspects of DDI for finerenone 40 mg, however, the PBPK model was not considered adequate for its purpose. Overall, the Applicant provided sufficient data to support the application from the clinical pharmacology point of view.

2.6.5. Clinical efficacy

2.6.5.1. Dose response studies

No dedicated clinical dose finding studies in patients with heart failure and left ventricular ejection fraction ≥ 40% were conducted in support for the 40 mg dose that is introduced in the present application, in addition to the currently approved 10 mg and 20 mg doses. The 40 mg dose was supported by data from the previously assessed Phase 2 dose-finding studies (ARTS-HF, with maximum dose 20 mg) and PK/PD-modelling (please see section 2.6.2 Clinical Pharmacology).

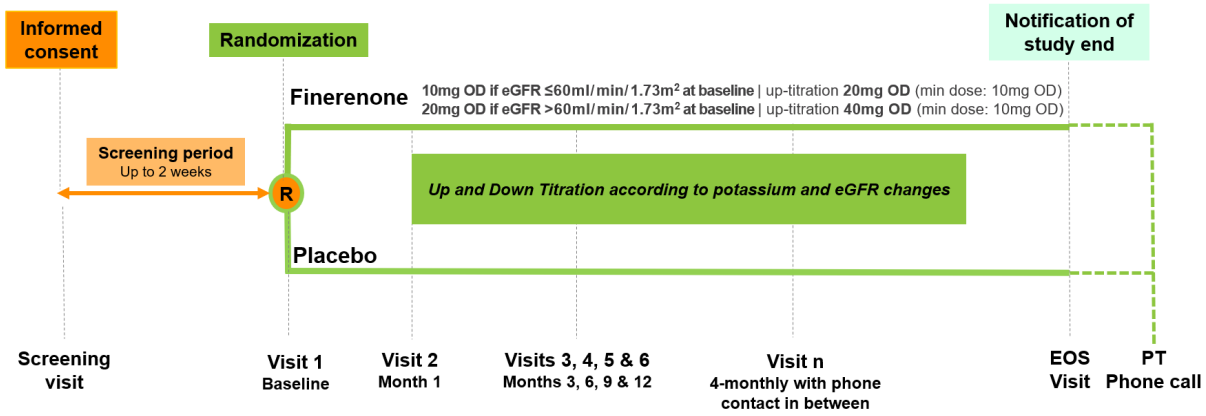
2.6.5.2. Main study

20103 (FINEARTS-HF); EU CT number: 2020-000306-29; NCT number: NCT04435626

Methods

The FINEARTS-HF Study 20103 (Module 5.3.5.1, Report B002803) was a randomized, double-blind, placebo-controlled, parallel-group, multicenter, event-driven Phase 3 study.

Figure 2: Study schema (FINEARTS-HF)



eGFR = estimated glomerular filtration rate, EOS = end of study, OD = once daily, PT = post treatment
Source: adapted from Module 5.3.5.1, Report B002803, Figure 3-1

- **Study Participants**

The study enrolled participants with a diagnosis of HF, NYHA class II – IV, and documented LVEF of ≥40%.

Key inclusion criteria

- Men or women aged 40 years and older, at the time of signing the informed consent.
- Diagnosis of heart failure with NYHA class II–IV, ambulatory or hospitalized primarily for heart failure (if a hospitalized patient could not be randomized as an in patient, randomization as soon as possible after discharge was encouraged)
- On diuretic treatment for at least 30 days prior to randomization
- Structural heart abnormalities based on any local imaging measurement within the last 12 months, latest at screening, defined by at least 1 of the following findings:
  - LAD ⩾3.8 cm, LAA ⩾20 cm^2, LAVI >30 mL/m^2, LVMI ⩾115 g/m^2 (male) / 95 g/m^2 (female), septal thickness or posterior wall thickness ⩾1.1 cm
- Documented LVEF of ⩾40% measured by any modality within the last 12 months, at the latest at screening; if several values were available, the most recent one had to be reported. If LVEF was not measured in the past 12 months, a new measurement could be done at screening
- NT-proBNP ⩾300 pg/mL (BNP ⩾100 pg/mL) in sinus rhythm and patient did not have an ongoing diagnosis of paroxysmal atrial fibrillation or NT-proBNP ⩾900 pg/mL (BNP ⩾300 pg/mL) in atrial fibrillation for participants obtained at the following time:
  - Within 90 days prior to randomization if patient had been hospitalized for HF requiring initiation or change in HF therapy or if patient had an urgent visit for HF requiring intravenous (IV) diuretic therapy, both within 90 days prior to randomization
    or
  - Within 30 days prior to randomization if patient had not been hospitalized for HF nor had an urgent HF visit within the past 90 days.

Key exclusion criteria

- eGFR <25 mL/min/1.73 m^2 at either screening or randomization visit. One reassessment of eGFR was allowed at the screening and randomization visit, respectively

- Serum/plasma potassium >5.0 mmol/L at either screening or randomization visit. One reassessment of potassium was allowed at the screening and randomization visit, respectively
- Myocardial infarction or any event which could have reduced the ejection fraction within 90 days prior to randomization
- SBP ≥160 mmHg if not on treatment with ≥3 blood pressure lowering medications or ≥180 mmHg irrespective of treatments on 2 consecutive measurements at least 2 min apart, at screening or at randomization
- Symptomatic hypotension with mean systolic blood pressure <90 mmHg at screening or at randomization
- Percutaneous coronary intervention in the 30 days prior to randomization
- Continuous (at least 90 days) treatment with an MRA (e.g. spironolactone, eplerenone, canrenone, esaxerenone) within 12 months prior to screening. Last intake at least 30 days before randomization. Treatment with MRA should not be interrupted with the purpose of enrollment into the study

Concomitant systemic therapy with potent cytochrome P450 isoenzyme 3A4 (CYP3A4) inhibitors (e.g. itraconazole, ritonavir, indinavir, cobicistat, clarithromycin) or moderate or potent CYP3A4 inducers, that cannot be discontinued 7 days prior to randomization and for the duration of the treatment period

- **Treatments**

The dosage of the study intervention is summarized in Table 9.

The dose of finerenone depended on the eGFR value at the baseline visit.

For participants with an eGFR≤60 mL/min/1.73 m^2 at baseline, the starting dose was 10 mg OD. From Visit 2 (Month 1) onwards and if potassium ≤5.0 mmol/l and eGFR decrease is <30%, the starting dose could be up-titrated to 20 mg OD.

For participants with an eGFR >60 mL/min/1.73 m^2 at baseline, the starting dose was 20 mg OD. From Visit 2 (Month 1) onwards and if potassium is ≤5.0 mmol/l and eGFR decrease is <30%, the starting dose can be up-titrated to 40 mg OD.

During the study, the dose could be adjusted in relation to serum potassium and a decrease in eGFR.

Table 7. Dosage of study intervention including dose adjustment guidelines and titration procedures

Baseline dosing and administration				
eGFR value at the Baseline Visit	**eGFR 25 to ≤60 mL/min/1.73m²**		**eGFR >60 mL/min/1.73m²**	
Participant randomized to:	**Finerenone**	**Placebo**	**Finerenone**	**Placebo**
Starting dose:	10 mg finerenone OD (**Dose Level 1**)	Placebo OD	20 mg finerenone OD (**Dose Level 2**)	Placebo OD
Maintenance dose:	20 mg finerenone OD (**Dose Level 2**)	Placebo OD	40 mg finerenone OD (**Dose Level 3**)	Placebo OD
Titration:				
Minimum dose after down-titration:	10 mg finerenone OD	Placebo OD	10 mg finerenone OD	Placebo OD
Maximum dose after up-titration:	20 mg finerenone OD	Placebo OD	40 mg finerenone OD	Placebo OD

Administration guidelines	
Intake	• 1 tablet OD, preferably in the morning at approximately the same time each day. • Administered at home, except on the day of first PK visit (taken at study site)
Missed intake	• If discovered within 16 hours: take 1 tablet as soon as possible • If discovered >16 hours after the scheduled time: Skip dose and take next tablet at usual scheduled time

Dose adjustment guidelines - Action to be taken			
Potassium-based (K^+)			
First sample	<5.0 mmol/L		Increase to the next higher dose level (or continue at maximum permitted dose level)
	≥5.0 to <5.5 mmol/L		Continue the current dose level
	≥5.5 to <6.0 mmol/L		Down-titrate to the next lower dose; if on dose level 1, interrupt. Re-check K^+ within 72 h; follow **Option a**
	≥6.0 mmol/L		Interrupt study intervention and re-check K^+ 72 h; follow **Option b**
Follow-up samples	**Option a**	<5.5 mmol/L	Continue current dose
		≥5.5 mmol/L	Down-titrate (dose level 2 to 1, dose level 3 to 2), if possible, or interrupt and recheck K+
	Option b	<5.5 mmol/L	Restart at dose level 1
		≥5.5 mmol/L	Continue withholding; restart at dose level 1 **only** if K+ <5.0
Renal function monitoring			
eGFR decrease ≥25% and <40% from baseline	1. Check for potential reversible causes: a. Concomitant medications (e.g. NSAIDs, antibiotics) b. AE (e.g. urinary infection, urinary retention, dehydration) 2. Address potential reversible causes if considered clinically appropriate		
eGFR decrease ≥40% from baseline	1. Check for potential reversible causes and address, as above. 2. Consider down-titration or interruption: • Monitor eGFR/creatinine • If eGFR/creatinine has reached acceptable levels, re-start at the next lower dose level (or dose level 1 if the participant was already on this dose). 3. Re-test at central laboratory after 4 weeks to confirm eGFR decrease of ≥50% or ≥57%		

Titration procedures (Documentation required in eCRF)		
Uptitration to next higher dose (Sham titration for placebo)	Timing:	From Visit 2 (Month 1) onwards, at any scheduled/ unscheduled visit
	Requirements:	• K+ levels must meet criteria above • eGFR decrease <30% compared to last scheduled visit
	Follow-up:	Safety visit 4 weeks ±7 days after each titration; monitor potassium and renal function
Down-titration	Timing:	At any scheduled/unscheduled visit
	Requirements:	• based on K+ level criteria above: down-titrate in step-wise manner • At dose-level 1: interrupt; re-start at dose-level 1 at the discretion of the investigator • If participant cannot tolerate maximum dose level, dose may be reduced to the next lower dose level
	Follow-up:	Unscheduled safety visit as determined by the investigator for reasons other than hyperkalemia; monitor potassium and renal function

NOTE: Potassium and eGFR according to local laboratory values unless specified otherwise
AE = adverse event, eCRF = electronic case report form; eGFR = estimated glomerular filtration rate; K^+ = potassium; NSAIDS = non-steroidal anti-inflammatory drugs, OD = once daily, PK = pharmacokinetics

- **Objectives**

The primary objective was to demonstrate the superiority of finerenone to placebo in reducing the rate of the primary composite CV endpoint CV death and total (first and recurrent) HF events (HHF or urgent HF visit).

The secondary objectives of this study were to determine the superiority of finerenone to placebo with regard to each of the following:

- Total (first and recurrent) HF events
- Improvement in NYHA class from Baseline to Month 12
- Change from baseline to Month 6, 9 and 12 in TSS of the KCCQ
- Time to first occurrence of composite renal endpoint: sustained decrease in eGFR ⩾50% relative to baseline over at least 4 weeks, or sustained eGFR decline to <15 mL/min/1.73 m2 or initiation of dialysis or renal transplantation
- Time to all-cause mortality (ACM).

- **Outcomes/endpoints**

Primary endpoint:

- CV death and total (first and recurrent) heart failure events (HHF or urgent HF visit).

Secondary endpoints:

- Total (first and recurrent) HF events
- Change from baseline to Month 6, 9 and 12 in TSS of the KCCQ
- Improvement in NYHA class from Baseline to Month 12
- Time to first occurrence of composite renal endpoint: sustained decrease in eGFR ⩾50% relative to baseline over at least 4 weeks, or sustained eGFR decline to <15 mL/min/1.73 m2 or initiation of dialysis or renal transplantation
- Time to all-cause mortality

- **Sample size**

As treatment effects, a hazard ratio for CV death of 0.8 and a rate ratio for heart failure events of 0.75 were assumed. With approximately 5500 randomised participants, it was expected to observe approximately 1310 first events and approximately 2375 total events leading to a power of 90% to show an effect at a two-sided alpha level of 5%. Under these assumptions it was expected to observe a 19% decrease in the rate of the primary endpoint for finerenone. An annual drug discontinuation rate of 5% was assumed, with finerenone participants having the same risk of events as placebo participants after discontinuation and no change in event rate for discontinuing placebo participants.

A total of approximately 2375 total (first and recurrent) primary composite events were targeted. Due to blinded event rates being lower than those assumed in the sample size calculation, the planned number of randomised participants was increased to approximately 6000. The target number of primary composite events was not changed.

- **Randomisation and Blinding (masking)**

Eligible participants were centrally assigned to randomised study intervention at Visit 1 using an IxRS. Participants were randomised in a 1:1 ratio to either finerenone or placebo. The randomisation was stratified by country/region and LVEF (<60%, ⩾60%). Treatment allocation was done according to a

computer-generated randomisation list specified by the sponsor's responsible statistician and provided by the sponsor's randomisation management group.

Tablets containing 10 mg and 20 mg finerenone immediate-release (IR) tablets differ in size from 40 mg finerenone IR tablets, but are identical in appearance (size, shape, color) to matching placebo tablets. The study data remained blinded until database lock and authorization of data release according to standard operating procedures.

A CEC blinded to study treatment assignment adjudicated all events that could potentially fulfil the criteria for the primary and some of the secondary endpoints during the study. The CEC Charter describes the roles and responsibilities of the CEC and defines the events to be adjudicated and the manner in which they were to be adjudicated.

This study was event-driven, and all randomised participants were planned to remain in the study until either (1) an instruction was received from the sponsor after the targeted number of primary efficacy events had occurred, or (2) the study was terminated early at the recommendation of the DMC. Therefore, all participants, including those who stopped taking study intervention, was asked to attend all the protocol-specified study visits in order to perform all assessments as stipulated in the main SoA.

The Interactive Voice/Web Response System was programmed with blind-breaking instructions. In case of an emergency, the investigator had the responsibility for determining if unblinding of a participant's treatment assignment was warranted. If the investigator was unavailable, and a treating physician not associated with the study requested emergency unblinding, the emergency unblinding requests were forwarded to the study-specific emergency medical advice 24 hours/7 day service. If a participant's treatment assignment was unblinded, the sponsor was to be notified within 24 hours after breaking the blind. The date and reason that the blind was broken were to be recorded in the source documentation and eCRF, as applicable.

- **Statistical methods**

Analysis sets

Final decisions regarding the assignment of participants to analysis sets were made during the validity review meetings and documented in the final list of important deviations, validity findings and assignment to analysis sets.

Enrolled participants were all who signed ICF and randomised participants those assigned to study intervention.

- The *Full Analysis Set (FAS)* comprised all randomised participants (except those with critical GCP violations). Participants were analysed according to the intervention they were randomised to.
- The *Safety Analysis Set (SAF)* comprised all participants in the FAS who took at least 1 dose of study intervention. Participants were analysed according to the intervention they actually received.

Main analysis methods for primary endpoint

The primary analysis of this endpoint was performed in the FAS using the planned treatment group, in line with the ITT principle. Participants without an event of the primary composite endpoint at the time of analysis were censored at the date of their last contact or date of non-CV death. A treatment policy

strategy was applied for treatment discontinuation, i.e., all events and follow-up time was included in the analysis.

The number and incidence rate of primary endpoint events and censoring events (i.e. non-CV death) were summarised per treatment group, both overall and per individual event category. 95% CIs of the incidence rates were derived based on a Poisson model with robust variance estimator.

The primary analysis of the primary composite endpoint was based on a stratified Andersen-Gill model (Andersen, 1982) including treatment group as fixed effect and including pooled region for stratified analyses and baseline LVEF (<60%, ≥60%) as stratification factors. Robust standard errors (sandwich estimator) were used to account for correlations of event times within a participant. As shown by Lin et al. 2000, the Andersen-Gill model with robust standard errors can be interpreted as a proportional rates model. After the authors of the paper, the model is also referred to as Lin, Wei, Yang and Ying (LWYY) model. Let θ be the RR for the finerenone versus placebo group. In order to evaluate whether finerenone is superior to placebo in reducing the rate of the composite event of CV death and total HF events the following null hypothesis was tested using the model above.

H_0: $\theta = 1$ versus H_1: $\theta \neq 1$,

where $\theta < 1$ represents a treatment benefit of finerenone over placebo.

A point estimate of the RR together with a 95% CI was presented alongside the point estimate and hazard ratio for the censoring event of non-CV death, calculated using a stratified Cox proportional hazards model.

A small adjustment was planned to the nominal significance level and the critical value at the final analysis to take into account the interim analysis (See *Error probabilities, adjustment for multiplicity and interim analyses* below).

If a participant experienced an HF event and subsequently died for a cardiovascular reason, this was considered as two separate events for the primary analysis unless the participant died on the same calendar day as the HF event (both events would still be considered for the analyses of the separate components). If a participant was hospitalized for HF shortly after an urgent HF visit, this was to be considered as two separate events for the primary analysis unless they occurred on the same calendar day.

Main analysis methods for secondary endpoints

Reducing the rate of total (first and recurrent) HF events

Total HF events was analysed in a similar fashion to the primary endpoint, using an LWYY model including treatment group as fixed effect and including pooled region for stratified analyses and baseline LVEF (<60%, ≥60%) as stratification factors.

Improvement in NYHA class from Baseline to Month 12

The percentage of participants with improvement in NYHA class from Baseline to Month 12 was analysed with a logistic regression model including factors for treatment group and stratification levels. A patient was considered as having improved in NYHA class, if the NYHA class at Month 12 (Visit 6) was at least one category improved compared to the baseline visit.

Participants who were still in the treatment period at Visit 6, but had NYHA assessment missing, were imputed by taking the mean of the last available measurement prior to Visit 6 and the first measurement thereafter. Participants with no further value available after Visit 6 or whose only

available information were from EoS visit were imputed as non-responders. Participants with missing baseline value were excluded from the analysis.

Odds ratio and two-sided 95% confidence intervals was provided for the comparison of finerenone vs. placebo treatment group. In addition, change from baseline in NYHA class was summarised descriptively using shift tables, presented by visit and any time post-baseline. These tables presented the number of participants with the class at a certain visit by their respective baseline class.

Analysis of Change from baseline to Month 6, 9 and 12 in TSS from KCCQ

The absolute change from baseline including measurements up to Month 12 of the KCCQ TSS was analysed by a repeated measures mixed model including the factors treatment group, baseline, visit, baseline-by-visit interaction, and factors for the stratification levels. For each treatment group a separate covariance pattern was planned to be estimated based on an unstructured covariance to adjust for within participant variance.

In case the model did not converge, different covariance patterns were planned to be used, in the following order, until convergence was met: separate unstructured covariance patterns, separate Toeplitz covariance patterns, separate Autoregressive(1) covariance patterns, and finally separate Compound Symmetry covariance patterns.

Differences between the finerenone and the placebo treatment groups were calculated with two-sided 95% CIs. The comparison assumes a common treatment effect across Month 6, 9 and 12.

This analysis investigated the effect on the KCCQ TSS while patients were alive and irrespective of any permanent treatment discontinuation. This means that all observed values were included in the analysis.

Analyses of Time to first occurrence of composite renal endpoint and ACM

The primary analysis of the secondary time-to first event variables (i.e. composite renal endpoint and ACM) was done with a stratified log-rank test for testing and a stratified Cox proportional hazards model for obtaining a point estimate with 95% CIs. The Cox proportional hazards model was stratified according to the stratification factors and included treatment group as fixed effect. For the composite renal endpoint, the cause-specific point estimate with 95% confidence interval for the censoring event of death was also presented.

Cumulative incidence function plots and summaries (calculated using Aalen-Johansen estimates) were produced for the composite renal endpoint and the censoring event of death. In addition, components of the composite renal endpoint were analysed. Furthermore, Aalen-Johansen plots were displayed for the ACM endpoint.

Randomised participants without an event of the composite renal endpoint at the time of analysis were censored at the latest censoring date of their individual components.

Missing data

Dropouts

A participant who has been randomised and discontinues study participation prematurely for any reason, either during study treatment or during post-treatment follow-up, was defined as a 'dropout', even if no study drug had been taken. Dropouts were not replaced. Data from participants who prematurely terminated the study were used to the maximum extent possible.

The number of participants discontinuing the epochs, together with the primary reason for discontinuation, were summarised. The number of participants who prematurely discontinue the study and/or study treatment for any reason, as well as the reasons for premature discontinuation of study and/or study treatment, were to be reported. Kaplan-Meier plots for ”patients still participating in study” and ”patients still on study treatment” were provided.

All dropouts and participants prematurely discontinuing study treatment were evaluated with respect to

- baseline characteristics
- potential differences between the treatment groups in the proportion of participant withdrawals or in the timing of withdrawals
- the reasons for premature discontinuation of study and/or study treatment.

Sensitivity analyses

For primary endpoint

The following sensitivity analyses were performed for the primary endpoint:

- The number of primary composite events were analysed using a negative binomial regression model including stratification factors and treatment group as covariates and log follow-up time as an offset parameter.
- Plots and summaries of the mean cumulative function for the primary endpoint were derived based on a competing-risk approach (Ghosh and Lin, 2000) and cumulative incidence function for the competing event of non-CV death (Aalen and Johansen, 1978) was presented by treatment group.

For secondary endpoints

As a sensitivity analysis for the total HF events endpoint, a joint frailty model (Rogers et al., 2016) with constant baseline hazard for CV death and constant baseline intensity for HF events was planned to be fitted including effects for treatment group, pooled region for stratified analyses and baseline LVEF (<60%, ≥60%). A gamma frailty distribution was to be assumed.

The joint frailty model can sometimes have convergence issues (Toenges & Jahn-Eimermacher, 2020); additionally, estimates obtained from the model have sometimes been observed as unstable (e.g., large differences with changes in starting values and/or ordering of covariates in the model). Should such problems be encountered, a simpler model including only treatment group as a fixed effect was planned to be used instead. The joint frailty model additionally produces an estimate for CV death; however, this will be considered only supportive for the analysis of this component.

Supplementary analyses

For the primary analysis

The following supplementary analysis for the primary analysis were planned and conducted:

- Supportive Analysis of CV death component: As part of the primary analysis, a separate estimate of the treatment effect for CV death as one of the components of the primary endpoint was obtained. The main cause-specific treatment effect estimate for CV death was derived from a stratified Cox proportional hazards model for time to CV death and the main p-value from a stratified log-rank test. A cause-specific treatment effect estimate for the

censoring event of non-CV death was also calculated using a stratified Cox proportional hazards model and presented with associated 95% confidence interval. The cumulative incidence functions for time to CV death and time to non-CV death was calculated using Aalen-Johansen estimates.

- Supportive Analysis of Time-to first event of Composite Endpoint: As supportive analysis, stratified Cox proportional hazard regression analysis was performed for the time to first composite of HF event or CV death and a plot of Aalen-Johansen estimates of the cumulative incidence function was provided.
- A supportive analysis of the primary endpoint excluded urgent HF visits and considered only CV deaths and HHFs as events. The analysis was performed for total (first and recurrent) events and for first events only.
- An additional analysis of the primary endpoint restricted CV deaths to HF-related events and thus considered HF events and CV deaths due to HF. The analysis was performed for total (first and recurrent) events and for first events only.
- A total-time approach considering times from randomisation to the onset of first, second, third composite event using a Wei, Lin, and Weissfeld (WLW, 1989) model will be applied. This model enabled analysis of the cumulative effect on the primary endpoint from randomisation (i.e. the effect on second event includes the effect on the first, and the effect on third event includes the effects on the first and second). The corresponding individual HRs with 95% Cis comparing treatment groups on the first, second, and third event was presented. The model was planned to employ robust standard errors and include the stratification factors and treatment group as fixed effects.
- In addition, a conditional gap-time model according to Prentice, Williams and Peterson (PWP, 1981) was applied to obtain HR estimates with 95% CIs for the time from first to second and from second to third event (note that this gives a non-randomised comparison). The model was planned to employ robust standard errors and include the stratification factors and treatment group as fixed effects. Both WLW and PWP approaches are known to have limitations and hence are strictly only performed as supplemental analyses since they aim at describing different aspects of recurrent events.
- An "on-treatment" analysis was performed, including only events occurring up to 30 days after treatment discontinuation. This analysis was performed in the SAF instead of the FAS.
- In addition, table and figure of risk ratios and respective confidence intervals was to be provided for the primary efficacy endpoint with patients being censored sequentially at each study day similar to figure 3 in Packer et al. (2021). The first day where the upper CI of the RR is below 1 and stays below for the remainder will be marked.
- The primary analysis for the primary endpoint was also repeated for the "Total HF events and ACM" endpoint.
- In addition, the primary analysis was repeated where patients are included with only up to a maximum of 4 composite events, to examine the impact of patients with a large number of events. For this analysis, patients who experienced 4 or more events were censored at the time of their 4th event.
- An additional analysis of the primary endpoint included a time-dependent covariate for SGLT-2 inhibitor use.

For the secondary endpoints

As supportive analysis for the total HF events endpoint, stratified Cox proportional hazard regression analyses were performed for the following endpoints and plots of Aalen-Johansen estimates of the cumulative incidence functions were provided:

- Time to first HF event
- Time to first HHF
- Time to first urgent HF visit

The additional analyses of the secondary time-to-first event endpoints included an "on treatment analysis". For the renal composite endpoint, events were only to be counted if they occurred within 5 months after the last visit with complete information on all components of the composite primary endpoint. A 5-month time window was used as visits are 4-monthly and in order to allow for late attendance by an additional 1 month. The proportional hazards assumption was to be investigated by plotting smoothed Schoenfeld residuals. For the renal endpoint, a time-to-first event analysis was done separately for each of the components.

A supportive analysis of the KCCQ TSS applied a worst-case imputation for death which means that if a patient dies, a worst score of 0 for the TSS was imputed for all subsequent visits after the patient's death (i.e., composite strategy). Treatment effects at Month 6, 9 and 12 was also investigated individually by adding a treatment-by-visit interaction into the model.

A responder analysis for the KCCQ TSS was also performed, defining patients with an increase of ≥5 points from baseline to Month 12 (or, for those with a baseline score of >95, a score of >95 at Month 12 without decline from baseline) as a responder. All observed values were included irrespective of any permanent treatment discontinuation. In case of missing data, a patient's last available post-baseline score prior to Month 12 was used (i.e. while-alive strategy) unless the patient died before Month 12 in which case they were imputed as a non-responder (i.e. composite strategy). Responder status was analysed using a logistic regression model including treatment, baseline TSS and stratification factors as covariates; the odds ratio and associated 95% CI was reported. This analysis was be repeated for cut-offs of ≥10 points increase from baseline to Month 12 (or maintaining a score of >90 from baseline to Month 12 without decrease from baseline) and ≥20 points increase (or maintaining a score of >80 without decrease from baseline). These cut-offs correspond to small (≥5), moderate (≥10) and large (≥ 20) clinically meaningful improvements (Spertus et al, 2005). A further analysis defined those responders who did not experience a ≥5 points decrease from baseline (or, for those with a baseline score of <5, a score of ≥5 at Month 12). This was equivalent to not experiencing a small deterioration. The number and percentage of patients who were responders or non-responders per each of the above criteria was presented at Months 6, 9 and 12. This included a breakdown of the criteria met for response (e.g. increase from baseline of ≥5, >95 at baseline and post-baseline visit) or non-response (e.g. change from baseline of <5, >95 at baseline and ≤95 at post-baseline visit, missing score at post-baseline visit).

A second responder analysis for the KCCQ TSS used the thresholds derived from the anchor-based analyses with the Patient Global Impression of Severity (PGIS) and Patient Global Impression of Change (PGIC) for a clinically meaningful within-patient change in KCCQ TSS at month 6, 9 and 12, respectively, which have been performed separately on blinded data (cf. Section 6.2.3.1). The derived thresholds were

- Minimally important within-patient improvement: 9.09
- Moderate within-patient improvement: 19.85

These thresholds were used for each timepoint. All observed values were included irrespective of any permanent treatment discontinuation. In case of missing data, a patient's last available post-baseline

score prior to Month 6, 9 or 12, respectively, was used unless the patient died before the respective scheduled visit in which case they were imputed as a non-responder. Responder status was analysed using a logistic regression model at each timepoint including treatment, baseline TSS and stratification factors as covariates; the odds ratio and associated 95% CI was reported.

Empirical cumulative density functions were plotted for Months 6, 9 and 12, with change from baseline in KCCQ TSS (+100 to -100, ordered from greatest possible improvement to greatest possible worsening) on the x-axis and proportion of participants achieving this change or greater on the y-axis. Separate curves were presented for each treatment group.

Planned subgroup analyses

Exploratory subgroup analysis was done for the primary and secondary efficacy variables. The subgroup analyses included subgroups based on the stratification factors. The list of key subgroups (in addition to the stratification factors) and other subgroups analysed are specified below. Analysis included descriptive statistics, graphical display of estimated treatment effects with 95% confidence intervals (CIs) in a forest plot and a statistical test for interaction.

Subgroups based on stratification factors

- Pooled region for subgroup analysis (Western Europe, Oceania and Others; Eastern Europe; Asia; North America; Latin America); the subgroup Western Europe, Oceania and Others combines the groups Western Europe and Oceania and Southwestern Europe from the pooled region for stratified analyses. The subgroup Eastern Europe combines the groups Central Europe, Southeastern Europe, and Northeastern Europe from the pooled region for stratified analyses.
- LVEF (<60%, ≥60%)

Key subgroups

- Baseline serum potassium value (≤ 4.5, > 4.5 mmol/L)
- eGFR category at baseline (eGFR <60, ≥60 mL/min/1.73 m²)
- Atrial fibrillation at baseline electrocardiogram (ECG) (present, absent)
- Diabetes Mellitus at baseline (present, absent)
- Index HF event (very recent (≤ 7 days before randomization), recent (> 7 days - ≤ 3 months), > 3 months or no index HF event).

Other subgroups

- Race (white, black, Asian, other)
- Sex (male, female)
- Age (≤ median vs. > median)
- Baseline body mass index (BMI) (< 30 vs. ≥ 30 kg/m2)
- Systolic blood pressure (SBP) at baseline (≤ median vs. > median)
- Angiotensin-converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB) or angiotensin receptor-neprilysin inhibitor (ARNI) use at baseline (yes, no)
- Treatment with sodium-glucose transport proteins-2 inhibitor (SGLT-2i) (yes, no)

- NYHA functional class at baseline (II, III/IV)
- Baseline NT-proBNP (≤ median vs. > median)
- Baseline UACR (<30 vs. ≥30 mg/g)

For subgroups split by median, the FAS was taken as reference population for derivation of median.

Individual country analyses, e.g. for Japan, required for regulatory purposes, were included in a country-specific study SAP.

Adjustment for multiplicity and interim analyses

The study was designed to be able to show an effect on the primary endpoint at a two-sided alpha level of 5%. Two interim analyses were planned and performed, one for futility and one for efficacy. They are summarised below together with the multiple testing procedure.

Interim analysis for futility

One non-binding interim analysis for futility was planned and performed when approximately 30% (~710) of the required total number of primary endpoint events have been observed. If the observed rate ratio (RR) on the primary endpoint was above 0.95, the trial was planned to be stopped for futility. This gives a probability of approximately 69% to stop under the null hypothesis (i.e. no treatment effect on the primary endpoint) and leads to a loss in power of less than 1% under the alternative hypothesis of the treatment effect assumed for the sample size determination. No adjustment for this loss in power were made. On 08 JUL 2022, the DMC communicated the decision to continue the study as planned without changes to the Study Protocol.

Interim analysis for efficacy

Another formal interim analysis for efficacy was planned and performed when approximately 2/3 (~1580) of the required total number of primary efficacy endpoint events had been observed. If the interim analysis showed clear and consistent benefit in the finerenone treatment group (defined as two-sided p-value <0.0027 for the primary efficacy endpoint and two-sided p-value <0.05 for the CV death component at the formal interim analysis for efficacy) the DMC may have recommended early stopping of the study for success. On 23 AUG 2023, the DMC communicated the decision to continue the study as planned without changes to the Study Protocol.

Testing procedure and multiplicity adjustment

The final analysis for the primary endpoint was planned to be performed at an overall two-sided significance level of 0.0027 for the interim analysis. If the study was not stopped early for success, a small adjustment to the alpha level at the final analysis was required to maintain the overall significance level at 0.05. For an information fraction of 2/3, the adjusted alpha level of 0.04967 applies, a p-value of p<0.04967 was therefore required at the final analysis to achieve formal statistical significance.

The following secondary endpoints was included in the testing procedure:

- Total (first and recurrent) HF events
- Improvement in NYHA class from Baseline to Month 12
- Change from baseline to Month 6, 9 and 12 in TSS from KCCQ
- Time to first occurrence of composite renal endpoint was to be formally tested.

If the primary endpoint was significant, the testing strategy of the secondary endpoints was planned as follows:

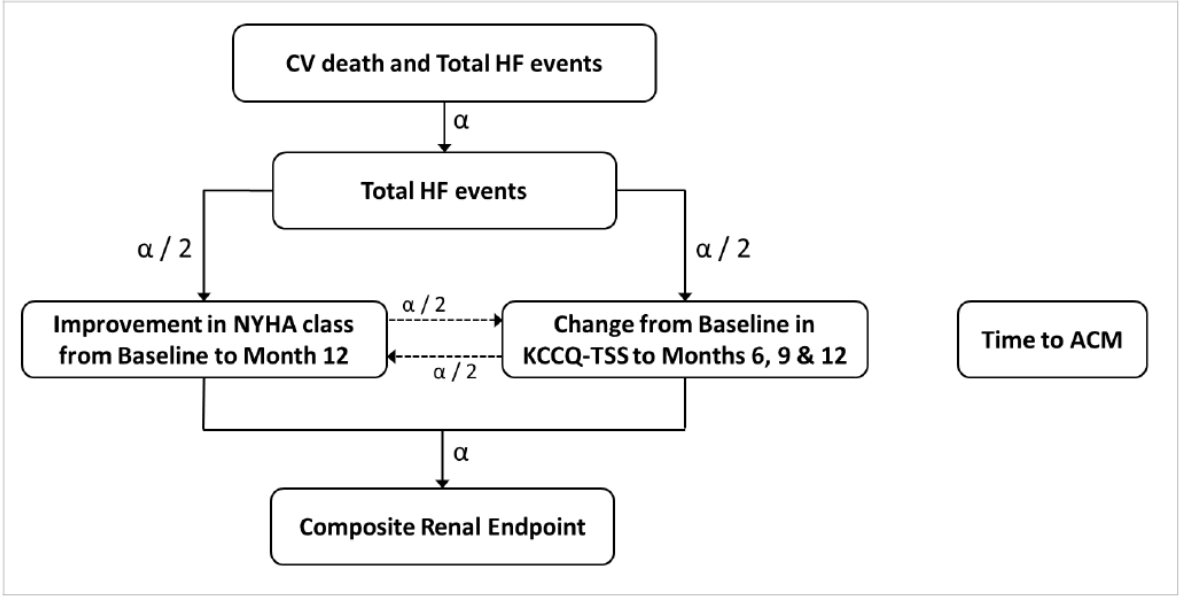
1. Total HF events was to be tested at the predefined (0.0027 or 0.04967, see above) two-sided significance level.
2. If the hypothesis of the secondary endpoint total HF events was rejected, the NYHA class and KCCQ endpoints will be tested using the Bonferroni-Holm procedure, i.e. if at least one of the hypotheses of the two endpoints NYHA class and KCCQ can be rejected at the two-sided (0.0027/2 or 0.04967/2) significance level, the remaining of the two endpoints was to be tested at the predefined (0.0027 or 0.04967) significance level.
3. If the hypotheses for all previous secondary endpoints were rejected, the composite renal endpoint was planned to be tested at the predefined (0.0027 or 0.04967) significance level.

If the test for any endpoint produces a non-significant result, the testing of the remaining endpoints further down in the procedure was to be performed in an explorative manner only.

Furthermore, the second component of the primary endpoint (CV deaths) was to be tested at the predefined (0.0027 or 0.04967) two-sided significance level outside of the alpha-preserving procedure for the primary and other secondary efficacy endpoints (Total HF events, NYHA class, KCCQ, renal composite).

As a hard endpoint and objective indicator of benefit-risk, time to ACM was planned to be tested at a two-sided significance level of 0.05, after the rejection of the primary hypothesis. Testing of time to ACM was thus done outside of the alpha-preserving procedure for the primary and other secondary efficacy variables (total HF events, NYHA class, KCCQ, renal composite).

Figure 3. Testing procedure for primary and secondary endpoints



Changes from protocol-specified analyses

The Statistical Analysis Plan (SAP) version 0.4 dated 16 DEC 2019 was an unsigned draft version for special protocol assessment (SPA) submission. SAP version 1.0 was dated 04 SEP 2020. The following most important changes were made in the two SAP amendments, version 2.0 was dated 24 FEB 2023 and version 3.0 dated 20 JUN 2024.

SAP version 2.0 (24 FEB 2023):

- A figure of the testing procedure is included.
- Total (first and recurrent) HF events was elevated from supportive analysis of the primary endpoint to a new secondary endpoint. Supportive analyses of the primary endpoint concerning only HF events were moved accordingly to become supportive analyses of the new secondary endpoint. This was based on changes made to the secondary endpoints in protocol V3.0
- Improvement in NYHA class from Baseline to Month 12 is elevated from exploratory endpoint to new secondary endpoint. A logistic regression analysis is newly specified for the endpoint accordingly in accordance with protocol V3.0.
- The composite renal secondary endpoint is changed to include sustained decrease in eGFR ⩾ 50% relative to baseline instead of ⩾40% in accordance with protocol V3.0.
- Increase in sample size from 5500 randomised to 6000 randomized was described.
- Handling of death adjudicated as undetermined death is clarified for the analyses.
- The testing procedure and multiplicity adjustment is adjusted to reflect the two new secondary endpoints in accordance with protocol V3.0.
- Analysis strategies for the primary endpoint and secondary endpoints are revised to include the handling of censoring events. This concerns the primary endpoint, the supportive analysis of CV death, as well as secondary and exploratory time-to event endpoints.
- Summary of incidence rate of primary endpoint events has been included.
- The analysis of the secondary endpoint of total HF events is changed from a joint frailty model (as specified in protocol V3.0) to the LWYY model. A joint frailty model with constant baseline hazard for CV death and constant baseline intensity for HF events was instead included as sensitivity analysis. This change in analysis strategy is based on potential convergence issues and unstable estimates of the joint frailty model.
- Additional model specification is included for the repeated measures model of the change in KCCQ TSS.
- A responder analysis based on thresholds of the anchor-based analyses with the PGIS/PGIC are included for KCCQ TSS. Empirical cumulative density functions are included for change from baseline in KCCQ TSS.
- Time to first occurrence of a new composite renal endpoint including sustained decrease in eGFR ⩾57% relative to baseline, mean rate of change in eGFR slope, and change in UACR from baseline are included as new exploratory endpoints and respective analyses of these endpoints are specified.
- Clarification of derivation of incidences per 100 person-years.

SAP version 3.0 (20 JUN 2024):

- Clarification of log-normality assumption for specific parameters added.
- Specification for the derivation of median for subgroup splits included.
- Updated definition of SAF – clarifying exclusion of participants with GCP violation.
- Included total treatment duration in patient-years.
- Removed analyses with continuous covariate of baseline LVEF as well as analysis with time by treatment interaction for primary and secondary endpoints.
- Updated definition of ‘on-treatment’ in general and for renal composite endpoint specifically.
- Included information on handling time after the forth event for analysis of the first 4 composite events.
- Included further imputation rules for secondary endpoint ‘Improvement in NYHA class'.

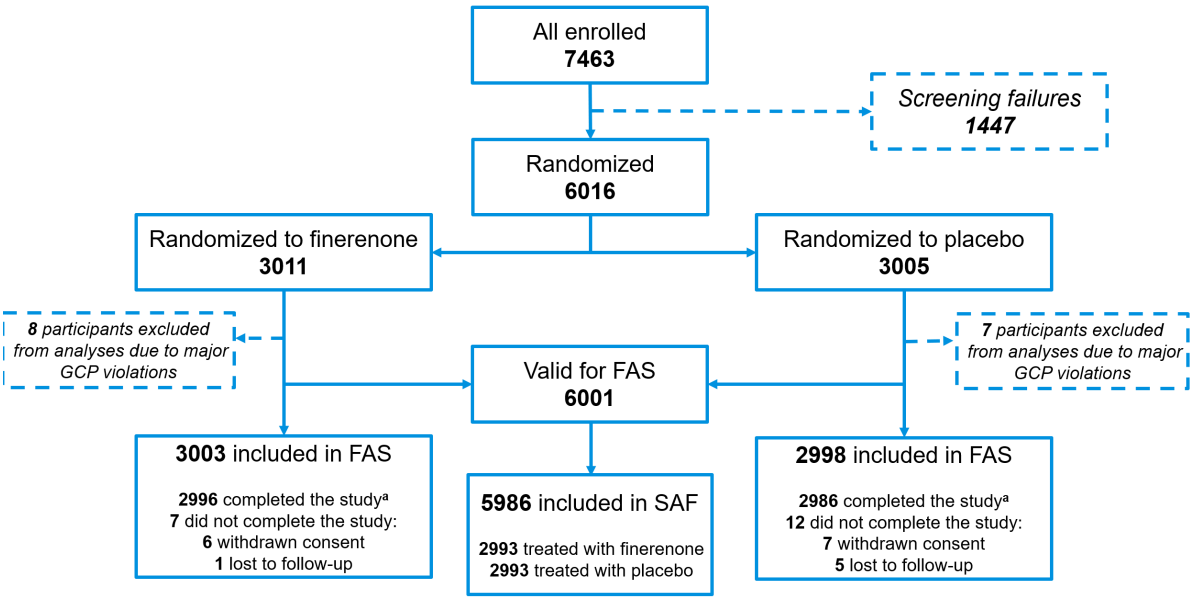
- Rules for usage of covariance patterns in case of non-convergence included for MMRM analysis of KCCQ TSS.
- Updated the information on censoring for the renal endpoint and specifically for the different components.
- Clarified intercurrent event strategies for KCCQ responder analyses.

Included thresholds for clinically meaningful change derived from separate anchor analysis.

Results

- **Participant flow**

Figure 4. Participant flow (FINEARTS-HF)



[a]Participants was considered as having completed the study if there was contact with the participant after the EOS notification or if the participant died. Contact with the participant could be actual visits, phone contacts, or information available from public records, etc.

- **Recruitment**

Study initiation date: 14 SEP 2020 (signed informed consent/first participant first visit)

Study/primary completion date: 14 JUN 2024 (last participant last visit)

The submitted study report is based on a database lock date of 25 JUL 2024

- **Conduct of the study**

There were 2 global amendments:

Amendment 1, dated 21 SEP 2020, addressed requests from health authorities.

Amendment 2, dated 16 MAY 2022, altered certain secondary efficacy endpoints of the study:

- The secondary efficacy variable on sustained eGFR decrease was changed from ≥40% to ≥50% based on data from the FIGARO-DKD and FIDELIO-DKD studies.

- Change in NYHA class from baseline was removed from exploratory endpoints. Total HF events and improvement in NYHA class from baseline to Month 12 were added as secondary endpoints due to their clinical significance.
- Change in UACR from baseline and time to first occurrence of the following composite endpoint: sustained decrease in eGFR ≥57% relative to baseline over at least 4 weeks, or sustained eGFR decline to <15 mL/min/1.73 m^2 or initiation of dialysis or renal transplantation, were added as exploratory endpoints to compare the results with existing data from FIGARO-DKD and FIDELIO-DKD.

In addition, a number of local amendments were made to comply with country-specific regulations.

- **Baseline data**

Baseline demographics are provided in Table 10 and baseline characteristics are provided in Table 11. Relevant medical history is provided in Table 12.

Table 8. Demographics (FAS, FINEARTS-HF)

	Finerenone N=3003 (100%)	Placebo N=2998 (100%)
Sex		
Male	1648 (54.9%)	1621 (54.1%)
Female	1355 (45.1%)	1377 (45.9%)
Race		
White	2366 (78.8%)	2369 (79.0%)
Black or African American	49 (1.6%)	39 (1.3%)
Asian	497 (16.6%)	499 (16.6%)
American Indian or Alaska Native	75 (2.5%)	74 (2.5%)
Native Hawaiian or Other Pacific Islander	1 (<0.1%)	0
Not reported	8 (0.3%)	9 (0.3%)
Multiple	7 (0.2%)	8 (0.3%)
Region (pooled region for stratified analysis)		
Western Europe and Oceania	290 (9.7%)	298 (9.9%)
Southwestern Europe	334 (11.1%)	334 (11.1%)
Central Europe	498 (16.6%)	496 (16.5%)
Southeastern Europe	424 (14.1%)	420 (14.0%)
Northeastern Europe	407 (13.6%)	405 (13.5%)
Asia	493 (16.4%)	490 (16.3%)
North America	235 (7.8%)	236 (7.9%)
Latin America	322 (10.7%)	319 (10.6%)
Region (pooled region for subgroup analysis)		
Western Europe, Oceania and Others	624 (20.8%)	632 (21.1%)
Eastern Europe	1329 (44.3%)	1321 (44.1%)
Asia	493 (16.4%)	490 (16.3%)
North America	235 (7.8%)	236 (7.9%)
Latin America	322 (10.7%)	319 (10.6%)
Age (years)		
Mean (standard deviation)	71.94 (9.60)	72.04 (9.69)
Median	73.00	73.00
Min, Max	40.0, 96.0	40.0, 97.0
Age group (years)		
40 – <65 years	643 (21.4%)	619 (20.6%)
65 – <75 years	1074 (35.8%)	1107 (36.9%)
75 – <85 years	1060 (35.3%)	1030 (34.4%)
≥85 years	226 (7.5%)	242 (8.1%)
Body Mass Index (kg/m^2)		
N	2996	2992
Mean (standard deviation)	29.88 (6.10)	30.00 (6.13)
Median	29.10	29.30
Min, Max	15.2, 65.1	13.5, 50.2
Baseline body mass index (kg/m^2)		
<18.5 kg/m^2	33 (1.1%)	32 (1.1%)
18.5 – <25 kg/m^2	629 (20.9%)	612 (20.4%)
25 – <30 kg/m^2	996 (33.2%)	994 (33.2%)
30 – <35 kg/m^2	767 (25.5%)	779 (26.0%)
≥35 kg/m^2	571 (19.0%)	575 (19.2%)
Smoking History		
Never	1828 (60.9%)	1869 (62.3%)
Former	913 (30.4%)	880 (29.4%)
Current	262 (8.7%)	249 (8.3%)
Alcohol Use		
Abstinent	2102 (70.0%)	2074 (69.2%)
Light	811 (27.0%)	805 (26.9%)
Moderate	89 (3.0%)	116 (3.9%)
Heavy	1 (<0.1%)	3 (0.1%)

Source: Module 5.3.5.1, Report B002803, Table 8.1.1/23

Table 9. Baseline characteristics (FAS, FINEARTS-HF)

	Finerenone N=3003 (100%)	Placebo N=2998 (100%)
Baseline LVEF (%)		
n	2997	2996

	Finerenone N=3003 (100%)	Placebo N=2998 (100%)
Mean (standard deviation)	52.64 (7.82)	52.49 (7.81)
Median	53.00	52.45
Min, Max	34.0, 83.0	40.0, 83.8
Baseline LVEF category		
<60%	2422 (80.7%)	2424 (80.9%)
≥60%	575 (19.1%)	572 (19.1%)
Baseline LVEF category		
<50%	1093 (36.4%)	1079 (36.0%)
≥50% – <60%	1329 (44.3%)	1345 (44.9%)
≥60%	575 (19.1%)	572 (19.1%)
History of LVEF <40%		
Yes	147 (4.9%)	126 (4.2%)
NYHA class		
NYHA class II	2081 (69.3%)	2065 (68.9%)
NYHA class III	903 (30.1%)	910 (30.4%)
NYHA class IV	18 (0.6%)	23 (0.8%)
missing	1 (<0.1%)	0
Index HF event		
≤7 days from randomization	609 (20.3%)	610 (20.3%)
>7 days – ≤3 months	1030 (34.3%)	998 (33.3%)
>3 months or no index HF event	1364 (45.4%)	1390 (46.4%)
Type of (latest) index HF event with respective timing		
Hospitalization for heart failure	1718 (57.2%)	1735 (57.9%)
≤7 days from randomization	501 (16.7%)	504 (16.8%)
>7 days – ≤3 months	813 (27.1%)	794 (26.5%)
>3 months	404 (13.5%)	437 (14.6%)
Urgent HF visit	369 (12.3%)	362 (12.1%)
≤7 days from randomization	108 (3.6%)	106 (3.5%)
>7 days – ≤3 months	217 (7.2%)	204 (6.8%)
>3 months	44 (1.5%)	52 (1.7%)
No index event	916 (30.5%)	901 (30.1%)
Atrial fibrillation at baseline ECG		
present	1165 (38.8%)	1128 (37.6%)
Baseline serum potassium (mmol/L)		
Mean (SD)	4.38 (0.48)	4.37 (0.47)
Median	4.40	4.40
Min, Max	2.6, 7.3	2.9, 7.3
Baseline serum potassium (mmol/L) category		
≤4.5 mmol/L	1969 (65.6%)	1958 (65.3%)
>4.5 mmol/L	1034 (34.4%)	1040 (34.7%)
Baseline serum potassium (mmol/L) category		
≤4.8 mmol/L	2571 (85.6%)	2581 (86.1%)
>4.8 to ≤5.0 mmol/L	223 (7.4%)	215 (7.2%)
>5.0 mmol/L	209 (7.0%)	202 (6.7%)
Baseline SBP (mmHg)		
N	3002	2997
Mean (SD)	129.47 (15.35)	129.30 (15.30)
Median	130.00	129.50
Min, Max	80.5, 180.5	74.0, 181.0
SBP at baseline (mmHg)		
<90 mmHg	2 (<0.1%)	4 (0.1%)
90 – <130 mmHg	1465 (48.8%)	1510 (50.4%)
130 – <160 mmHg	1467 (48.9%)	1421 (47.4%)
≥160 mmHg	68 (2.3%)	62 (2.1%)
Baseline eGFR (mL/min/1.73 m^2)		
Mean (standard deviation)	61.94 (19.42)	62.27 (20.04)
Median	60.90	61.00
Min, Max	19.9, 118.2	4.3, 133.2

	Finerenone N=3003 (100%)	Placebo N=2998 (100%)
Baseline eGFR (mL/min/1.73 m^2) category		
<60 mL/min/1.73 m^2	1451 (48.3%)	1437 (47.9%)
≥60 mL/min/1.73 m^2	1552 (51.7%)	1561 (52.1%)
Baseline eGFR (mL/min/1.73 m^2) category		
<45 mL/min/1.73 m^2	649 (21.6%)	683 (22.8%)
45 – <60 mL/min/1.73 m^2	802 (26.7%)	754 (25.2%)
60 – <90 mL/min/1.73 m^2	1278 (42.6%)	1274 (42.5%)
≥90 mL/min/1.73 m^2	274 (9.1%)	287 (9.6%)
Diabetes Mellitus at baseline		
present	1217 (40.5%)	1222 (40.8%)
ACEI, ARB or ARNI use at baseline		
Yes	2379 (79.2%)	2380 (79.4%)
SGLT-2 inhibitors use at baseline		
Yes	393 (13.1%)	424 (14.1%)
Baseline NT-proBNP (pg/mL)		
N	2930	2913
Geom mean (standard deviation)	932.93 (3.10)	921.94 (3.10)
Median	1052.50	1028.00
Min, Max	10.2, 39357.9	10.2, 61579.4
Baseline UACR (mg/g)		
N	2901	2896
Geom mean (standard deviation)	24.66 (5.53)	24.89 (5.54)
Median	18.00	19.00
Min, Max	0.8, 10135.0	1.0, 11451.0
Baseline albuminuria (mg/g) category		
<30 mg/g	1765 (58.8%)	1746 (58.2%)
30 – <300 mg/g	844 (28.1%)	868 (29.0%)
≥300 mg/g	292 (9.7%)	282 (9.4%)
missing	102 (3.4%)	102 (3.4%)

ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker, ARNI = angiotensin receptor neprilysin inhibitor, ECG = electrocardiogram, eGFR = estimated glomerular filtration rate, HF = heart failure, LVEF = left ventricular ejection fraction, NT-proBNP = n-terminal prohormone B-type natriuretic peptide, NYHA = New York Heart Association, SBP = systolic blood pressure, SGLT-2 = sodium-glucose co-transporter-2, UACR = urinary albumin-to-creatinine ratio
Source: Module 5.3.5.1, Report B002803, Table 8.1.1/27

Table 10. Medical history of interest (FAS, FINEARTS-HF)

	Finerenone N=3003 (100%)		Placebo N=2998 (100%)	
	Medical history	**Ongoing at baseline**	**Medical history**	**Ongoing at baseline**
	n (%)	**n (%)**	**n (%)**	**n (%)**
Cardiac Failure (MLG)	3003 (100.0%)	2993 (99.7%)	2998 (100.0%)	2986 (99.6%)
Atrial fibrillation/flutter (PBMQ)	1669 (55.6%)	1501 (50.0%)	1650 (55.0%)	1494 (49.8%)
Pattern				
Paroxysmal	571 (19.0%)		552 (18.4%)	
Persistent	360 (12.0%)		367 (12.2%)	
Permanent	705 (23.5%)		699 (23.3%)	
Hypertension (MLG)	2640 (87.9%)	2634 (87.7%)	2685 (89.6%)	2678 (89.3%)
Myocardial Infarction (MLG)	784 (26.1%)	43 (1.4%)	757 (25.3%)	39 (1.3%)
Coronary Artery Bypass Graft (PBMQ)	460 (15.3%)	132 (4.4%)	456 (15.2%)	132 (4.4%)
Percutaneous coronary intervention (PBMQ)	746 (24.8%)	11 (0.4%)	725 (24.2%)	14 (0.5%)
Peripheral Arterial Occlusive Disease (PBMQ)	284 (9.5%)	253 (8.4%)	273 (9.1%)	248 (8.3%)
Type 2 diabetes mellitus (PT)	1217 (40.5%)	1217 (40.5%)	1223 (40.8%)	1222 (40.8%)
COVID-19 (SMQ narrow)	265 (8.8%)	4 (0.1%)	257 (8.6%)	5 (0.2%)
Hepatic cirrhosis (PT)	12 (0.4%)	10 (0.3%)	15 (0.5%)	15 (0.5%)
Chronic Obstructive Pulmonary Disease (PT)	380 (12.7%)	379 (12.6%)	393 (13.1%)	387 (12.9%)
Sleep Apnoea Syndrome (PT)	191 (6.4%)	189 (6.3%)	210 (7.0%)	207 (6.9%)
Hyperlipidemia (MLG)	765 (25.5%)	758 (25.2%)	767 (25.6%)	763 (25.5%)
Coronary Artery Disease (PBMQ)	1143 (38.1%)	1108 (36.9%)	1157 (38.6%)	1124 (37.5%)
Ischemic Stroke/Transitory Ischemic Attack (PBMQ)	427 (14.2%)	63 (2.1%)	404 (13.5%)	69 (2.3%)
Chronic Kidney Disease (PT)	564 (18.8%)	562 (18.7%)	549 (18.3%)	548 (18.3%)

MLG = MedDRA Labeling Group, PBMQ = project-specific Bayer MedDRA queries, PT = preferred term, SMQ = standard MedDRA queries
Source: Table 8.1.2/1

Prior and concomitant use was similar across both treatment groups and is summarized below for the standard drug groups of interest for prior medication (Table 13) and concomitant medication that started after the start of study intervention (Table 14).

Table 11. Prior medication of interest (FINEARTS-HF, FAS)

	Finerenone N=3003 (100%)	Placebo N=2998 (100%)
Number (%) of participants who took at least 1 drug of an SDG of interest before start of study intervention	**2987 (99.5%)**	**2989 (99.7%)**
ACEIs or ARBs	2379 (79.2%)	2388 (79.7%)
ARNIs	262 (8.7%)	261 (8.7%)
Beta-blocker	2540 (84.6%)	2539 (84.7%)
Loop diuretics	2665 (88.7%)	2667 (89.0%)
Thiazide diuretics	493 (16.4%)	462 (15.4%)
Digoxin	273 (9.1%)	266 (8.9%)
Nitrates	348 (11.6%)	301 (10.0%)
Potassium supplements	395 (13.2%)	440 (14.7%)
Potassium lowering agents (including binders)	9 (0.3%)	8 (0.3%)
Alpha blocking agents	730 (24.3%)	768 (25.6%)
Calcium channel blockers	998 (33.2%)	1051 (35.1%)
Centrally acting antihypertensives	103 (3.4%)	115 (3.8%)
Strong, unclassified, moderate, weak CYP3A4 inhibitors	1906 (63.5%)	1930 (64.4%)
Strong, unclassified, moderate, weak CYP3A4 inducers	71 (2.4%)	85 (2.8%)
Aspirin	1003 (33.4%)	1017 (33.9%)
Statins	2017 (67.2%)	2008 (67.0%)
MRAs	152 (5.1%)	161 (5.4%)
OATP substrates	2275 (75.8%)	2289 (76.4%)
Insulins and analogues	341 (11.4%)	357 (11.9%)
SGLT-2 inhibitors	380 (12.7%)	407 (13.6%)
Other anti-diabetic drugs	822 (27.4%)	842 (28.1%)

Medications taken before the start of study intervention (regardless of when they ended) are included in this table.
A participant is counted only once within each SDG. Other anti-diabetic drugs includes dipeptidyl peptidase 4 inhibitors, glucagon-like peptide-1 agonists, biguanides, sulfonylureas, alpha glucosidase inhibitors, metiglinides or thiazolidinediones.
ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker, ARNI = angiotensin receptor neprilysin inhibitor, CYP3A4 = cytochrome P450 isoenzyme 3A4, MRA= mineralcorticoid receptor antagonist, OATP = organic anion transporting polypeptides, SDG = Standard Drug Group, SGLT-2 = sodium-glucose co-transporter-2
Source: Table 8.1.3/3

Table 12. Concomitant medication of interest that started after start of study intervention (FAS, FINEARTS-HF)

	Finerenone N=3003 (100%)	Placebo N=2998 (100%)
Number (%) of participants who took at least 1 drug of an SDG of interest	**2283 (76.0%)**	**2309 (77.0%)**
ACEIs or ARBs	995 (33.1%)	1022 (34.1%)
ARNIs	217 (7.2%)	250 (8.3%)
Beta-blocker	999 (33.3%)	1014 (33.8%)
Loop diuretics	1441 (48.0%)	1441 (48.1%)
Thiazide diuretics	208 (6.9%)	213 (7.1%)
Digoxin	199 (6.6%)	189 (6.3%)
Nitrates	266 (8.9%)	282 (9.4%)
Potassium supplements	385 (12.8%)	557 (18.6%)
Potassium lowering agents (including binders)	102 (3.4%)	41 (1.4%)
Alpha blocking agents	400 (13.3%)	456 (15.2%)
Calcium channel blockers	523 (17.4%)	591 (19.7%)
Centrally acting antihypertensives	67 (2.2%)	70 (2.3%)
CYP3A4 inhibitors	1252 (41.7%)	1269 (42.3%)
CYP3A4 inducers	385 (12.8%)	380 (12.7%)
Aspirin	276 (9.2%)	265 (8.8%)
Statins	530 (17.6%)	519 (17.3%)
MRAs	410 (13.7%)	418 (13.9%)
OATP substrates	846 (28.2%)	876 (29.2%)
Insulins and analogues	305 (10.2%)	289 (9.6%)
SGLT-2 inhibitors	596 (19.8%)	656 (21.9%)
Other anti-diabetic drugs	395 (13.2%)	401 (13.4%)

Medications taken within the treatment period are included in this table, if started **after** start of study intervention.
A participant is counted only once within each Standard Drug Group.
Other anti-diabetic drugs includes dipeptidyl peptidase 4 inhibitors, glucagon-like peptide-1 agonists, biguanides, sulfonylureas, alpha glucosidase inhibitors, metiglinides or thiazolidinediones
ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker, ARNI = angiotensin receptor neprilysin inhibitor, CYP3A4 = cytochrome P450 isoenzyme 3A4, MRA= mineralcorticoid receptor antagonist, OATP = organic anion transporting polypeptides, SDG = Standard Drug Group, SGLT-2 = sodium-glucose co-transporter-2
Source: Module 5.3.5.1, Report B002803, Table 8.1.3/6

Baseline characteristics were similar in the two treatment arms and reflect the intended indication. Mean LVEF was 52.56% and most patients had NYHA class II (69.1%) and class III (30.2%).

Regarding index events, 57.5% of participants had been previously hospitalised for heart failure and 12.2% had a previous urgent HF event.

20.3% of participants had an index HF event <7 days prior to randomisation, and 33.8% of participants had an event >7 days to ⩽3 months prior to randomisation.

The mean eGFR value was 62.11 mL/min/1.73 m^2. 42.5% of participants had eGFR 60 - < 90, 25.9% 45 - <60 and 22.2% <45 mL/min/1.73m^2.

79.3% of participants were treated with an ACEI/ARB at baseline. Nearly all patients were treated with diuretics (87.3% loop diuretics, 13.8% thiazides). 13.6% were treated with a SGLT-2 inhibitor.

Concomitant medications initiated during the study were in general balanced between study arms apart from potassium supplements that were more frequently administered in the placebo group (18.6% vs. 12.8%) and potassium lowering agents that were more frequent in the finerenone group (3.4% vs. 1.4%). Frequencies were also slightly lower for alpha blockers (13.3% vs. 15.2%), calcium channel inhibitors (17.4% vs. 19.7%) and SGLT-2 inhibitors (19.8% vs. 21.9%) in the finerenone group compared to placebo.

A summary of prohibited medication is presented in Table 15.

Table 13. Summary of prohibited medication use (FAS and SAF)

	Full analysis set [1]		**Safety analysis set [2]**	
	Finerenone N=3003 (100%) n (%)	**Placebo** N=2998 (100%) n (%)	**Finerenone** N=2993 (100%) n (%)	**Placebo** N=2993 (100%) n (%)
Any prohibited medication	**555 (18.5%)**	**578 (19.3%)**	**379 (12.7%)**	**417 (13.9%)**
MRA	258 (8.6%)	285 (9.5%)	108 (3.6%)	144 (4.8%)
Moderate CYP3A4 inducer	195 (6.5%)	189 (6.3%)	160 (5.3%)	150 (5.0%)
Strong CYP3A4 inducer	14 (0.5%)	9 (0.3%)	7 (0.2%)	7 (0.2%)
Strong CYP3A4 inhibitor	129 (4.3%)	132 (4.4%)	109 (3.6%)	111 (3.7%)
>1 ACEI, ARB or ARNI	61 (2.0%)	70 (2.3%)	41 (1.4%)	57 (1.9%)

[1] Includes medication taken on or after randomization date and up to date of censoring for primary efficacy endpoint.
[2] Includes medication taken on or after start of study drug and before end of study drug
Source: Module 5.3.5.1, EMA_Day120_finearts, Table 1.4.1/1, Table 1.4.1/2

- **Numbers analysed**

Table 14. Analysis sets (FINEARTS-HF)

	Finerenone N=3011 (100%)	Placebo N=3005 (100%)
Participants valid for full analysis set	3003 (99.7%)	2998 (99.8%)
Participants valid for safety analysis set	2993 (99.4%)	2993 (99.6%)
Participants valid for pharmacokinetic analysis set	2670 (88.7%)	0
Excluded from full analysis set	8 (0.3%)	7 (0.2%)
Exclude participant from all analysis datasets on account of critical GCP violations, causing unreliable data.	8 (0.3%)	7 (0.2%)
Excluded from safety analysis set	18 (0.6%)	12 (0.4%)
Exclude participant from all analysis datasets on account of critical GCP violations, causing unreliable data.	8 (0.3%)	7 (0.2%)
Participant was randomized but never received any study intervention.	10 (0.3%)	5 (0.2%)
Excluded from pharmacokinetic analysis set	341 (11.3%)	3005 (100.0%)
Exclude participant from all analysis datasets on account of critical GCP violations, causing unreliable data.	8 (0.3%)	7 (0.2%)
None of the PK samples available for a participant assigned to Finerenone is valid.	333 (11.1%)	0
Participants was not treated with Finerenone	0	2998 (99.8%)

If a participant has more than one validity finding that excludes him/her from an analysis set, all of the findings are displayed.

Source: Table 8.1.1/13

Table 15. Reasons for discontinuation of treatment (FAS, FINEARTS-HF)

	Finerenone N=3003 (100%)	Placebo N=2998 (100%)
Completed treatment period	**2051 (68.3%)**	**2021 (67.4%)**
Not completed	952 (31.7%)	977 (32.6%)
Primary reason		
Adverse event	143 (4.8%)	127 (4.2%)
Death	332 (11.1%)	356 (11.9%)
Withdrawal by participant	37 (1.2%)	34 (1.1%)
Non-compliance with study intervention	16 (0.5%)	21 (0.7%)
Physician decision	66 (2.2%)	59 (2.0%)
Technical problems	13 (0.4%)	14 (0.5%)
Protocol deviation	63 (2.1%)	72 (2.4%)
Outcome event	40 (1.3%)	46 (1.5%)
Participant decision	212 (7.1%)	217 (7.2%)
Participant decision: COVID-19 pandemic-related	8 (0.3%)	10 (0.3%)
Logistical reason: COVID-19 pandemic-related	1 (<0.1%)	2 (<0.1%)
Participant decision: regional crisis	0	1 (<0.1%)
Logistical reason: regional crisis	2 (<0.1%)	3 (0.1%)
Other	19 (0.6%)	15 (0.5%)

Source: Module 5.3.5.1, Report B002803, Table 8.1.1/18

Table 16. Treatment duration (FAS, FINEARTS-HF)

	Finerenone N=3003 (100%)	Placebo N=2998 (100%)
Treatment duration (months)		
Mean (SD)	25.07 (12.48)	25.29 (12.38)
Median	28.03	28.07
Min, Max	0.0, 43.9	0.0, 43.9
Treatment duration in patient-years	6183.85	6226.92
Cumulative treatment duration		
At least one dose	2993 (99.7%)	2993 (99.8%)
At least 1 months	2906 (96.8%)	2910 (97.1%)
At least 3 months	2775 (92.4%)	2778 (92.7%)
At least 6 months	2648 (88.2%)	2657 (88.6%)
At least 9 months	2527 (84.1%)	2540 (84.7%)
At least 12 months	2424 (80.7%)	2442 (81.5%)
At least 15 months	2334 (77.7%)	2352 (78.5%)
At least 18 months	2129 (70.9%)	2150 (71.7%)
At least 21 months	1946 (64.8%)	1968 (65.6%)
At least 24 months	1759 (58.6%)	1802 (60.1%)
At least 27 months	1572 (52.3%)	1574 (52.5%)
At least 30 months	1359 (45.3%)	1354 (45.2%)
At least 33 months	1098 (36.6%)	1115 (37.2%)
At least 36 months	733 (24.4%)	755 (25.2%)
At least 39 months	300 (10.0%)	298 (9.9%)
At least 42 months	51 (1.7%)	45 (1.5%)

Treatment duration is defined as time from start of study intervention to permanent stop of study intervention (in months)
Source: Module 5.3.5.1, Report B002803, Table 8.1.4/2

Of the 7463 participants enrolled in FINEARTS-HF, a total of 1447 (19.4%) were screening failures of which most (1320 participants; 91.2%) concerned violation of inclusion and exclusion criteria. The following inclusion/exclusion criteria were driving the screen failures:

- Inclusion criterion 6 (elevated NT-proBNP levels): 780 participants (53.9%)
- Exclusion criterion 2 (Serum/plasma potassium >5.0 mmol/L): 189 participants (13.1%)
- Exclusion criterion 1 (eGFR <25 mL/min/1.73m2): 83 participants (5.7%)
- Inclusion criterion 4 (documented LVEF ⩾40%): 60 participants (4.1%)

Out of the randomized patients (n=6016) almost all were included in the FAS (n=6001). A relatively large proportion of patients did not complete the treatment period (31.7% in finerenone vs. 32.6% in placebo). The main reasons were death (11.1% vs. 11.9%), patient decision (7.1% vs. 7.2%) and adverse events (4.8% vs. 4.2% in finerenone vs. placebo) and there were no major differences between the study arms.

The mean treatment duration was approximately 25 months in both study arms. Approximately 80% of participants took the study drug for at least 12 months and 60% for at least 24 months.

The number of patients having an intercurrent event is presented according to each particular intercurrent event in the table below.

Table 17. Incidence of intercurrent events and resulting proportion of follow-up time not observed (FAS)

	Finerenone		Placebo	
	N=3003 (100%)		N=2998 (100%)	
Intercurrent event	n (%)	% f-up	n (%)	% f-up
Permanent discontinuation of study treatment	952 (31.7%)	0.0	977 (32.6%)	0.0
CV death	242 (8.1%)	4.4	260 (8.7%)	4.7
Non-CV death (including undetermined death)	249 (8.3%)	4.6	262 (8.7%)	4.5

% f-up = percentage of total potential follow-up time not observed due to the intercurrent event.
Source: Module 5.3.5.1, Report B002803, Table 8.1.1/18, Table 8.2.1.1/1, Table 8.2.3/4

- **Outcomes and estimation**

Primary endpoint

Finerenone was superior to placebo in reducing the risk of the composite of CV death and total (first and recurrent) HF events (HHF or urgent HF visit) with on average 16% (RR=0.84; 95% CI 0.74; 0.95), see Table 20. The effect was mainly driven by an effect on HF events (RR=0.82 95% CI 0.71; 0.94). The difference in CV death between the groups was small (242 vs. 260 events in finerenone vs. placebo; HR 0.93, 95% CI 0.78; 1.11).

Of those who experienced a CV composite endpoint event, most participants had 1 (13.1% finerenone, 14.2% placebo) or 2 events (3.8% finerenone, 5.4% placebo), with only a few who had 5 or more events (0.9% finerenone, 1.1% placebo; Module 5.3.5.1, Report B002803, Table 8.2.1.1/2).

The Nelson-Aalen estimates show an early curve separation and indicate a sustained effect (Figure 5). The mean number of events per participant compared with placebo was reduced by 0.066 at 24 months. The pre-specified sensitivity analyses had minimal impact on the estimate of the endpoint.

Figure 5. Nelson-Aalen estimates (mean cumulative functions) for CV composite endpoint of CV death and total (first and recurrent) HF events (HHF and urgent HF visit; FAS, FINEARTS-HF)

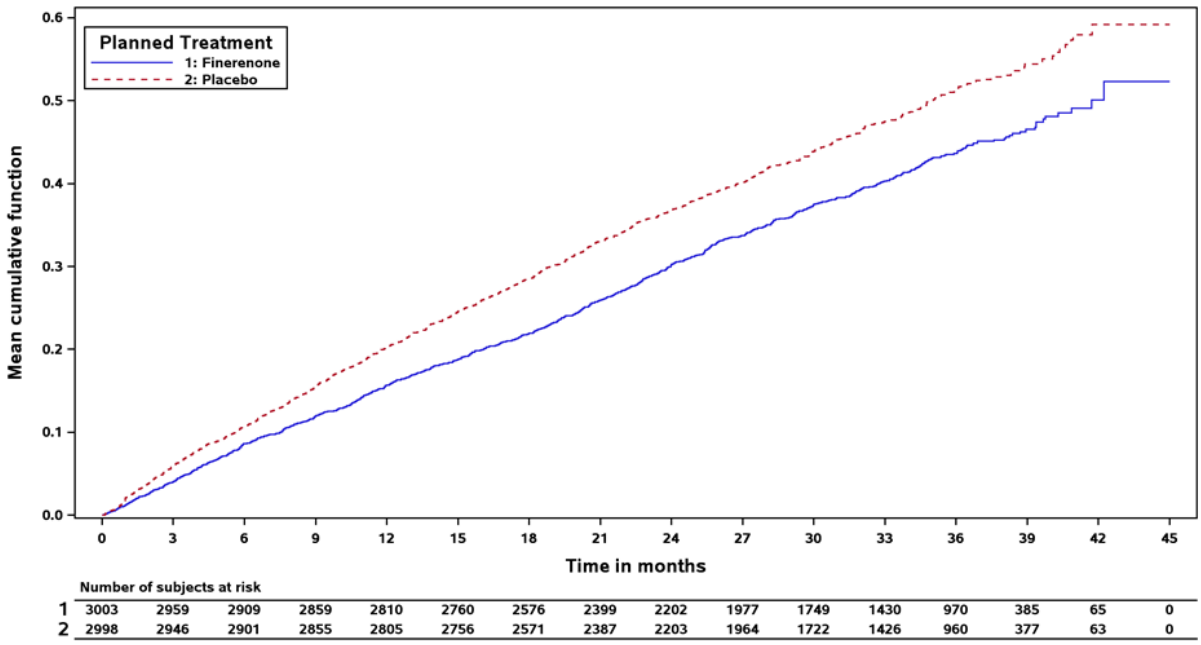


Table 18. Summary of results for the adjudicated CV composite endpoint and its components (recurrent event analyses, FAS, FINEARTS-HF)

	Finerenone N=3003 (100%)		Placebo N=2998 (100%)		Ratio
	E (n, %)	E/100 p-yrs	E (n, %)	E/100 p-yrs	(95% CI)
Event of interest: CV composite endpoint	**1083 (624; 20.8%)**	**14.88**	**1283 (719; 24.0%)**	**17.70**	**RR 0.84 [0.74; 0.95]**
CV death	242 (242; 8.1%)	3.33	260 (260; 8.7%)	3.59	csHR 0.93 [0.78; 1.11]
HF events	842 (479; 16.0%)	11.57	1024 (573; 19.1%)	14.12	RR 0.82 [0.71; 0.94]
HHF	744 (450; 15.0%)	10.22	877 (514; 17.1%)	12.10	-
Urgent HF visit	98 (73; 2.4%)	1.35	147 (113; 3.8%)	2.03	-
Censoring events: Non-CV death and undetermined death	**249 (249; 8.3%)**	**3.42**	**262 (262; 8.7%)**	**3.61**	**csHR 0.94 [0.79; 1.12]**
Non-CV death	185 (185; 6.2%)	2.54	183 (183; 6.1%)	2.52	-
Undetermined death	64 (64; 2.1%)	0.88	79 (79; 2.6%)	1.09	-

csHR = cause-specific hazard ratio, CV = cardiovascular, CV composite endpoint = CV death and total (first and recurrent) HF events (HHF and urgent HF visit), E = number of events, E/100 p-yrs = incidence rate, HF = heart failure, HHF = hospitalization for heart failure, n = number of participants with at least one event, N = total number of participants, p-yrs = patient-years, RR = rate ratio
Source: Module 5.3.5.1, Report B002803, Table 8.2.1.1/1, Table 8.2.1.1/3, Table 8.2.1.3/2, Table 8.2.2.1/3, Table 8.2.3/3

Secondary endpoints

The first secondary endpoint in the testing hierarchy was total (first and recurrent) HF events (HHF or urgent HF visit), which was also one of the components of the primary composite endpoint. The rate ratio was 0.82 (95% CI 0.71; 0.94) and the endpoint was statistically significant. As previously discussed, the HF events were the main driver for the effect on the primary endpoint. A plot of the Nelson-Aalen estimates is provided in Figure 6.

For the secondary endpoint change from baseline to month 6, 9 and 12 in TSS of KCCQ, the mean change from baseline was 7.99 in the finerenone group and 6.43 in the placebo group (Table 21). The difference in LS mean was 1.56 (95% CI 0.79; 2.34) which was formally statistically significant. Thus, both groups displayed an increase in this score but indicating a slightly better increase in the finerenone group however the clinical relevance is questionable. Baseline values were 67.6 and 66.5 in finerenone and placebo, respectively.

The testing hierarchy was broken with the secondary endpoint improvement in NYHA class from Baseline to Month 12 where no significant difference was found between the study groups (Table 22). The odds ratio finerenone/placebo was 1.01 (95% CI 0.88; 1.15).

The secondary renal composite endpoint time to first occurrence of the renal composite endpoint of sustained decrease in eGFR $\geqslant$50% relative to baseline over at least 4 weeks, or sustained eGFR decline to <15 ml/min/1.73m^2 or initiation of dialysis or renal transplantation was tested exploratively and no significant difference was found between the groups (RR 1.33; 95% CI 0.94; 1.89). The point estimate was higher than unity and the early and sustained separated curves in the Aalen-Johansen estimates indicates an effect favouring placebo, however the events were relatively few (Table 233, Figure 8). The effect was mainly caused by the components sustained eGFR decline $\geqslant$50% and sustained decline to <15 mL/min/1.73m^2, respectively.

All-cause mortality was tested separately from the testing hierarchy. The point estimate was slightly lower in the finerenone group but the differences were small (HR=0.93 95% CI 0.83; 1.06). CV death (8.1% vs. 8.7%) and undetermined death (2.1% vs. 2.6%) was lower in the finerenone group whereas non-CV death (6.2% vs. 6.1%) was similar in both treatment arms (Table 24).

Figure 6. Nelson-Aalen estimates (mean cumulative functions) for the secondary efficacy endpoint of total (first and recurrent) HF events (HHF and urgent HF visit; FAS, FINEARTS-HF)

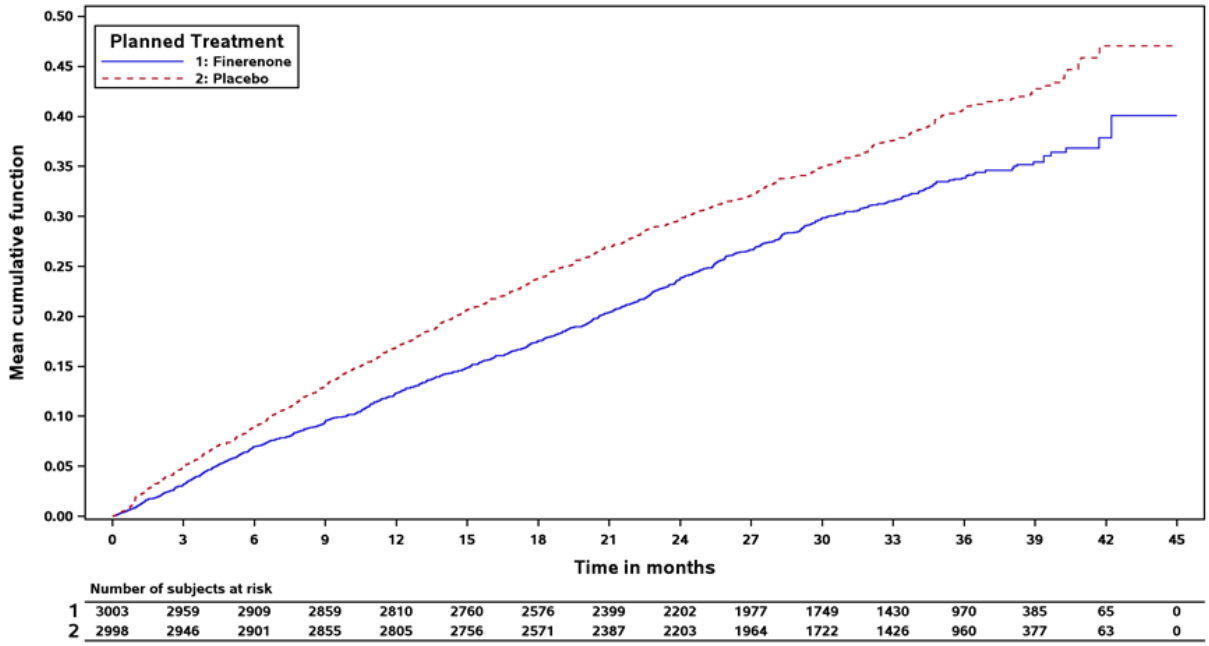


Table 19. Mixed model analysis of change from baseline to Month 6, 9, and 12 in KCCQ-TSS (FAS, FINEARTS-HF)

Finerenone (N = 3003)		Placebo (N = 2998)		Treatment comparison	
n	LS Mean change from baseline (95% CI)	n	LS Mean change from baseline (95% CI)	Difference in LS Mean	p-value
2731	7.99 [7.37, 8.62]	2710	6.43 [5.79, 7.07]	1.56 [0.79, 2.34]	<.0001

KCCQ-TSS = Kansas City Cardiomyopathy Questionnaire – total symptom score, LS = least squares
Source: Module 5.3.5.1, Report B002803, Table 8.2.2.1/9

Table 20. Logistic regression analysis of improvement in NYHA class from baseline to Month 12 (FAS, FINEARTS-HF)

Planned treatment	Estimated proportion	95% CI of estimated proportion	Odds ratio (finerenone / placebo)	95% CI of Odds ratio	p-value for treatment group	p-value for additional main factors [a]
Finerenone	0.179	[0.163, 0.195]	1.01	[0.88, 1.15]	0.9295	<.0001, 0.3760
Placebo	0.178	[0.162, 0.194]				

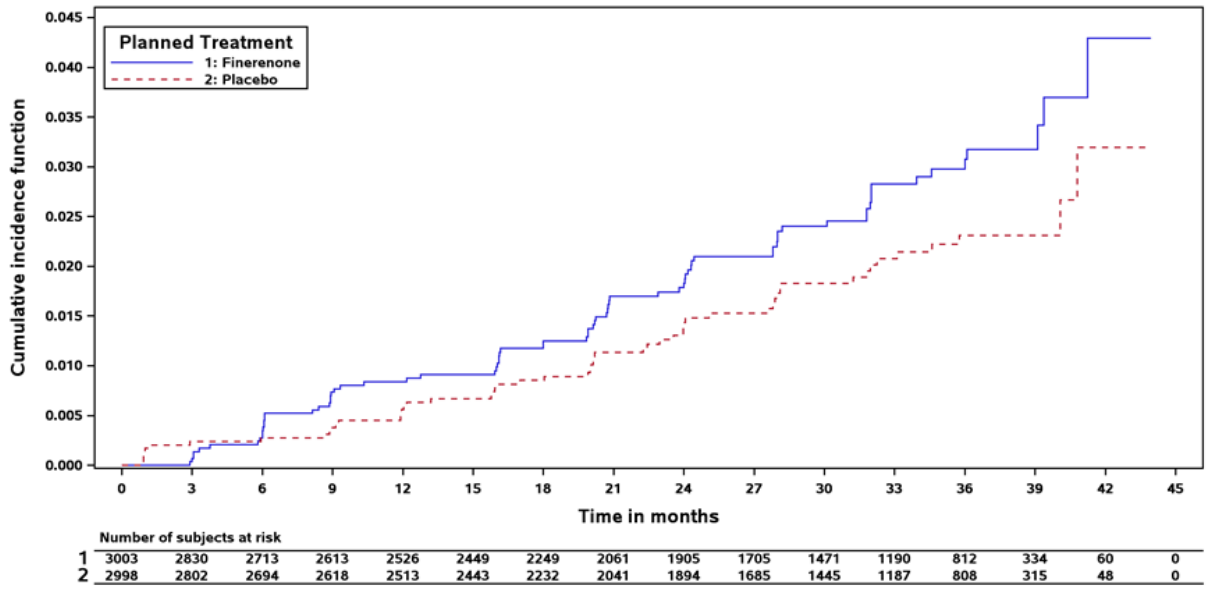
a Test of equal proportions between the additional factor levels: region and LVEF category.
NYHA = New York Health Association
Source: Module 5.3.5.1, Report B002803, Table 8.2.2.1/7

Table 21. Summary of results for the renal composite endpoint and its components (FAS, FINEARTS-HF)

	Finerenone N=3003 (100%)		Placebo N=2998 (100%)		csHR (95% CI)
	n (%)	n/100 p-yrs	n (%)	n/100 p-yrs	
Event of interest: Renal composite endpoint	**75 (2.5%)**	**1.16**	**55 (1.8%)**	**0.85**	**1.33 [0.94; 1.89]**
Sustained decrease of eGFR ≥50% relative to baseline	73 (2.4%)	1.13	52 (1.7%)	0.81	1.37 [0.96; 1.95]
Sustained eGFR decline to <15mL/min/1.73 m²	25 (0.8%)	0.38	12 (0.4%)	0.19	2.09 [1.05; 4.15]
Initiation of dialysis	7 (0.2%)	0.11	6 (0.2%)	0.09	1.14 [0.38; 3.40]
Renal transplantation	0	0	0	0	Not calculated

csHR = cause-specific hazard ratio, eGFR = estimated glomerular filtration rate, n = number of participants with event, n/100 p-yrs = incidence rate, renal composite endpoint = sustained decrease of eGFR ≥50% relative to baseline, sustained eGFR decline to <15mL/min/1.73 m², initiation of dialysis or renal transplantation
Source: Module 5.3.5.1, Report B002803, Table 8.2.2.1/10, Table 8.2.2.1/12, Table 8.2.2.3/14 to Table 8.2.2.3/17

Figure 7. Aalen-Johansen estimates (cumulative incidence functions) for the 50% renal composite endpoint (FAS, FINEARTS-HF)



Source: Module 5.3.5.1, Report B002803, Figure 8.2.2.1/2

Table 22. Summary of results for all-cause mortality and its components (FAS, FINEARTS-HF)

	Finerenone N=3003 (100%)		Placebo N=2998 (100%)	
	n (%)	n/100 p-yrs	n (%)	n/100 p-yrs
Event of interest: all-cause mortality[a]	**491 (16.4%)**	**6.71**	**522 (17.4%)**	**7.17**
CV death	**242 (8.1%)**	**3.33**	**260 (8.7%)**	**3.59**
Acute MI	9 (0.3%)		16 (0.5%)	

CV Procedure	5 (0.2%)		2 (<0.1%)	
HF	77 (2.6%)		86 (2.9%)	
Other CV	12 (0.4%)		6 (0.2%)	
Presumed CV death	15 (0.5%)		8 (0.3%)	
Pulmonary Embolism	2 (<0.1%)		1 (<0.1%)	
Stroke	22 (0.7%)		26 (0.9%)	
Sudden cardiac death	100 (3.3%)		115 (3.8%)	
Non-CV death	**185 (6.2%)**	**2.54**	**183 (6.1%)**	**2.52**
Gastrointestinal	12 (0.4%)		13 (0.4%)	
Infection (including sepsis)	95 (3.2%)		95 (3.2%)	
Malignancy	40 (1.3%)		46 (1.5%)	
Non-intracranial hemorrhage (not CV-related)	4 (0.1%)		0	
Other non-CV	9 (0.3%)		7 (0.2%)	
Pulmonary	8 (0.3%)		8 (0.3%)	
Renal	2 (<0.1%)		2 (<0.1%)	
Suicide	0		1 (<0.1%)	
Trauma/accident	15 (0.5%)		11 (0.4%)	
Undetermined death	**64 (2.1%)**	**0.88**	**79 (2.6%)**	**1.09**

a HR from stratified Cox-proportional hazards model (finerenone/placebo) of 0.93 (95% CI 0.83; 1.06),
two-sided p-value= 0.2794 for the comparison of finerenone with placebo from stratified logrank test.
All-cause mortality was tested outside of the testing hierarchy (Table 8.2.2.1/15).
Events were adjudicated by an independent adjudication committee and considered from randomization up until the cut-off date.
CV = cardiovascular, eGFR = estimated glomerular filtration rate, HF = heart failure, HR = hazard ratio, MI = myocardial infarction, n = number of participants with event, n/100 p-yrs = incidence rate
Source: Module 5.3.5.1, Report B002803, Table 8.2.2.1/14

- **Ancillary analyses**

Subgroup analyses

Subgroup analyses of the primary CV composite endpoint of CV death and total (first and recurrent) HF events (HHF or urgent HF visit) are provided in Figure 8. The number of events for the subgroups is provided in Table 25. All point estimates for the rate ratio were <1.0 and no treatment interaction p-values <0.05 were observed. Post-hoc analysis by LVEF categories were conducted. The RR for the categories <50%, ≥50% to <60% and ≥60% were 0.84 [0.68; 1.03], 0.80 [0.66; 0.97] and 0.94 [0.70; 1.25], respectively. No significant interaction was found (0.7026).

Primary endpoint data according to the prespecified subgroups were in general consistent with the overall analysis and no point estimates were above unity. RR was higher for Asian (0.96) that encompassed more patients. For race, the RR was higher for black (0.98) however it is a very small subgroup and the estimate lacks precision (29/49 vs. 22/39 E/N for finerenone vs. placebo). For region, RRs were higher for Asia (RR=0.95) and North America (RR=0.98).

The effect was similar regardless of BMI, diabetes, NYHA Class and LVEF. The RR was higher in the subgroup of patients without index HF event (or that had one earlier than 3 months prior to randomisation) than patients with an index HF event less than 7 days or between 7 days and 3 months before randomisation. Patients with eGFR ≥60 mL/min/1.73m^2 tended to have a more pronounced effect of the treatment than those with eGFR ≤60 mL/min/1.73m^2 (RR 0.72 vs. 0.91).

The subgroup analysis indicates a similar treatment effect in the subgroups with or without concomitant treatment with ACEi, ARB or ARNi and SGLT2i, respectively.

Figure 8. Forest plot for the primary CV composite endpoint of CV death and total (first and recurrent) HF events by subgroups (FAS, FINEARTS-HF)

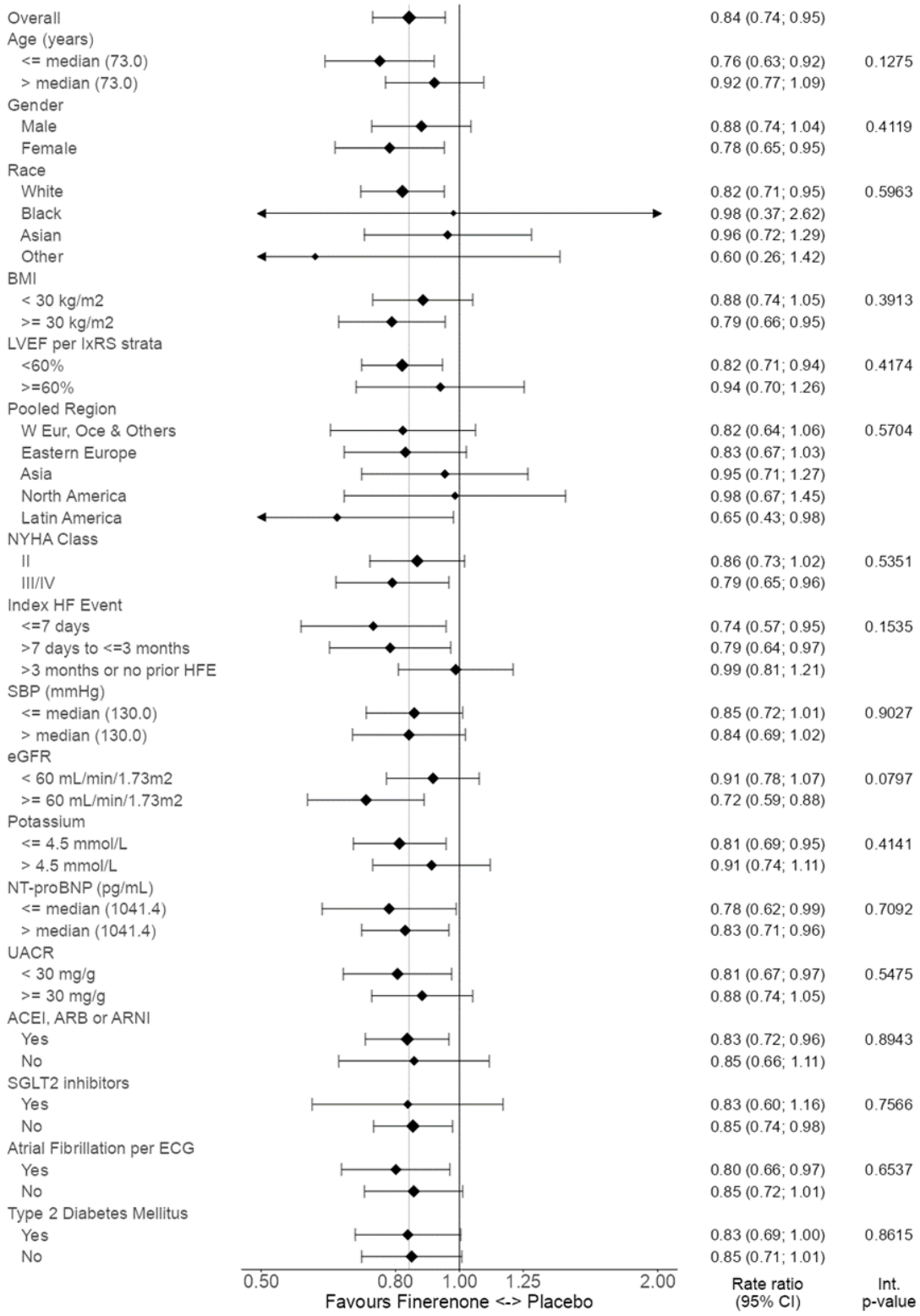


Table 23. Number of events for the primary CV composite endpoint of CV death and total (first and recurrent) HF events by subgroups (FAS, FINEARTS-HF)

	Finerenone E; n/N (E/100 p-yrs)	Placebo E; n/N (E/100 p-yrs)
Overall	1083; 624/3003 (14.88)	1283; 719/2998 (17.70)
Pooled Region [1]		
Western Europe, Oceania and Others	322; 171/624 (21.92)	395; 195/632 (26.66)
Eastern Europe	322; 213/1329 (9.53)	389; 244/1321 (11.51)
Asia	211; 117/493 (17.43)	218; 123/490 (18.25)
North America	122; 63/235 (23.18)	118; 69/236 (23.58)
Latin America	106; 60/322 (15.32)	163; 88/319 (23.51)
LVEF category per stratification [1]		
LVEF <60%	877; 512/2427 (15.17)	1061; 594/2425 (18.47)
LVEF >=60%	206; 112/576 (13.76)	222; 125/573 (14.73)
Baseline potassium		
<= 4.5 mmol/L	714; 397/1969 (14.96)	875; 480/1958 (18.55)
> 4.5 mmol/L	369; 227/1034 (14.73)	408; 239/1040 (16.10)
Baseline eGFR		
< 60 mL/min/1.73m2	727; 394/1451 (21.45)	796; 426/1437 (23.70)
>= 60 mL/min/1.73m2	356; 230/1552 (9.16)	487; 293/1561 (12.51)
Atrial fibrillation at baseline		
present	521; 287/1165 (18.83)	621; 330/1128 (23.11)
absent	562; 337/1838 (12.46)	662; 389/1870 (14.51)
Diabetes Mellitus at baseline		
present	524; 291/1217 (18.28)	638; 344/1222 (22.09)
absent	559; 333/1786 (12.67)	645; 375/1776 (14.79)
Index HF event		
<= 7 days from randomization	270; 158/609 (20.47)	372; 183/610 (28.25)
>7 days - <= 3 months	404; 219/1030 (17.53)	492; 268/998 (22.10)
>3 months or no index HF event	409; 247/1364 (11.20)	419; 268/1390 (11.30)
Race		
White	809; 478/2366 (14.10)	986; 560/2369 (17.16)
Black	29; 13/49 (24.97)	22; 12/39 (24.07)
Asian	211; 117/497 (17.26)	218; 122/499 (17.95)
Other	34; 16/91 (16.94)	57; 25/91 (28.91)
Sex		
Male	632; 358/1648 (15.77)	691; 392/1621 (17.80)
Female	451; 266/1355 (13.80)	592; 327/1377 (17.57)
Age group		
<= median in FAS	468; 278/1589 (11.87)	623; 338/1579 (15.84)
> median in FAS	615; 346/1414 (18.45)	660; 381/1419 (19.89)
Baseline BMI		
< 30 kg/m2	586; 338/1658 (14.76)	648; 379/1638 (16.61)
>= 30 kg/m2	486; 282/1338 (14.77)	632; 338/1354 (18.93)
Baseline systolic blood pressure		
<= median in FAS	608; 348/1549 (16.44)	740; 403/1597 (19.38)
> median in FAS	475; 276/1453 (13.28)	543; 316/1400 (15.83)
ACEI or ARB or ARNI at baseline		
No	288; 154/624 (19.57)	332; 171/618 (23.49)
Yes	795; 470/2379 (13.70)	951; 548/2380 (16.29)
SGLT-2 inhibitors at baseline		
No	907; 529/2610 (14.02)	1049; 597/2574 (16.48)
Yes	176; 95/393 (21.77)	234; 122/424 (26.50)
NYHA class at baseline		
NYHA CLASS II	646; 375/2081 (12.58)	741; 437/2065 (14.57)
NYHA CLASS III/IV	437; 249/921 (20.46)	542; 282/933 (25.02)
Baseline NT-proBNP		
<= median in FAS	266; 182/1458 (7.22)	342; 215/1475 (9.14)
> median in FAS	782; 422/1472 (22.84)	918; 488/1438 (27.62)
Baseline UACR		
< 30 mg/g	429; 268/1765 (9.74)	518; 318/1746 (12.02)
>= 30 mg/g	601; 324/1136 (22.75)	705; 370/1150 (26.11)

Supportive analyses

The primary endpoint included recurrent events. The applicant has performed a supportive time to first event of the primary endpoint (HR=0.84 95% CI 0.76; 0.94, p = 0.0020) which yielded a similar outcome as the analysis of the primary endpoint (Table 26, Figure 9).

The applicant has provided an on-treatment analysis of the primary endpoint only including events occurring up to 30 days after treatment discontinuation. The analysis yielded a slightly more pronounced effect on the primary composite endpoint (RR 0.71 95% CI 0.62; 0.81).

The applicant has also performed a statistical analysis of CV death (HR 0.93 95% CI 0.78; 1.11) that was a component of the primary endpoint. The effect of CV death was not statistically significant in the exploratory analysis.

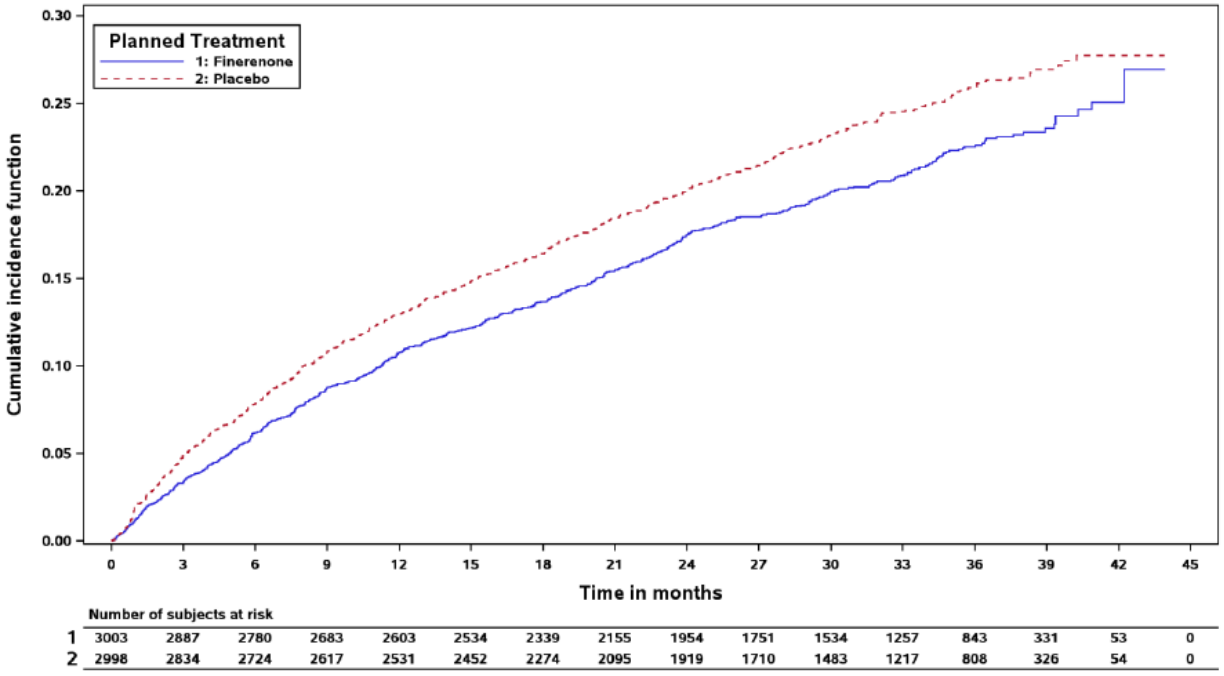
For the KCCQ-TSS, the applicant conducted a responder analysis using thresholds determined in an anchor-based analysis for minimal and moderate improvements (Table 27). The differences in the proportion of responders between the groups were in general small but the proportion of responders were numerically increased in the finerenone group and was nominally significant at 9 months for the minimally improved (OR 1.14 95% CI 1.01; 1.29) and the moderately improved (OR 1.18 95% CI 1.02; 1.37) thresholds.

Table 24. Number and incidence rate of subjects with CV death or first HF event (HHF or urgent HF visit) and censoring event (full analysis set)

	Finerenone n (%) N=3003 (100%)	Finerenone n/100 p-yrs (95% CI)	Placebo n (%) N=2998 (100%)	Placebo n/100 p-yrs (95% CI)
Event-of-interest: Cardiovascular Death or First Heart Failure Event	624 (20.8%)	9.31 (8.60; 10.08)	719 (24.0%)	11.01 (10.21; 11.86)
Cardiovascular Death	145 (4.8%)	2.16 (1.84; 2.55)	146 (4.9%)	2.24 (1.90; 2.63)
Acute myocardial infarction	8 (0.3%)		14 (0.5%)	
CV Procedure	4 (0.1%)		0	
Heart failure	14 (0.5%)		9 (0.3%)	
Other cardiovascular	9 (0.3%)		4 (0.1%)	
Presumed Cardiovascular Death	13 (0.4%)		4 (0.1%)	
Pulmonary Embolism	1 (<0.1%)		1 (<0.1%)	
Stroke	21 (0.7%)		21 (0.7%)	
Sudden cardiac death	75 (2.5%)		93 (3.1%)	
Heart Failure Events	479 (16.0%)	7.15 (6.53; 7.83)	573 (19.1%)	8.77 (8.07; 9.54)
Heart Failure Events - Hospitalizations for Heart Failure	428 (14.3%)	6.39 (5.80; 7.03)	493 (16.4%)	7.55 (6.90; 8.26)
Heart Failure Events - Urgent Heart Failure Visits	51 (1.7%)	0.76 (0.58; 1.00)	80 (2.7%)	1.22 (0.98; 1.53)
Censoring events: Non-cardiovascular Death and Undetermined Death	182 (6.1%)	2.72 (2.35; 3.14)	177 (5.9%)	2.71 (2.34; 3.14)
Non-cardiovascular Death	131 (4.4%)	1.96 (1.65; 2.32)	124 (4.1%)	1.90 (1.59; 2.26)
Undetermined Death	51 (1.7%)	0.76 (0.58; 1.00)	53 (1.8%)	0.81 (0.62; 1.06)

n = Number of subjects with event; N=Total number of subjects; CV=cardiovascular; HF=heart failure; HHF = hospitalization for heart failure.

Figure 9. Cumulative incidence functions for CV death or first HF event (HHF or urgent HF visit) and censoring event (full analysis set)



Plots display Aalen-Johansen estimates.
Events were adjudicated by an independent adjudication committee and considered from randomization up until the cut-off date.
Bayer: /var/swan/root/bhc/948862/20103/stat/main01/prod/analysis/pgms/tf_8_2_1_3_adtte_hfcv_aj.sas 18SEP2024 18:29

Table 25. Logistic regression analyses of anchor-based analyses of KCCQ-TSS responders from baseline to Months 6, 9 and 12 (FAS)

Visit	Planned treatment	Estimated proportion of responders	95% CI of estimated proportion	Odds ratio (finerenone / placebo)	95% CI of Odds ratio	p-value for treatment group
Considered responder if ≥9.09 points increase in KCCQ-TSS (minimally improved)						
Visit 4 (Month 6)	Finerenone	0.374	[0.351, 0.398]	1.13	[1.00, 1.28]	0.0559
	Placebo	0.346	[0.323, 0.370]			
Visit 5 (Month 9)	Finerenone	0.393	[0.369, 0.416]	1.14	[1.01, 1.29]	0.0367
	Placebo	0.362	[0.339, 0.386]			
Visit 6 (Month 12)	Finerenone	0.372	[0.349, 0.395]	1.04	[0.92, 1.17]	0.5659
	Placebo	0.364	[0.341, 0.387]			
if ≥19.85 points increase in KCCQ-TSS (moderately improved)						
Visit 4 (Month 6)	Finerenone	0.148	[0.133, 0.166]	1.16	[1.00, 1.35]	0.0539
	Placebo	0.131	[0.116, 0.147]			
Visit 5 (Month 9)	Finerenone	0.160	[0.143, 0.178]	1.18	[1.02, 1.37]	0.0307
	Placebo	0.139	[0.124, 0.156]			
Visit 6 (Month 12)	Finerenone	0.154	[0.138, 0.171]	1.07	[0.92, 1.24]	0.3737
	Placebo	0.145	[0.130, 0.162]			

Logistic regression analysis with factors treatment group, baseline KCCQ-TSS and stratification levels (pooled region and baseline LVEF). Participants with missing data at respective visit were imputed with last available post-baseline score unless a participant died; in which case they were imputed as non-responder. Participants with missing baseline value were excluded from the analysis.
KCCQ-TSS = Kansas City Cardiomyopathy Questionnaire – total symptom score
Source: Table 8.2.2.3/32 to Table 8.2.2.3/37

Explorative analyses

The applicant has included a number of exploratory analyses.

The time to first event analysis of CV hospitalisations (HR 0.89 95% CI 0.81; 0.98) yielded a result that was significant in the explorative analysis, indicating an effect also on other causes of CV hospitalisations than HF which was included as a component of the primary endpoint (Table 28). A recurrent event analysis showed a similar trend however it was not significant (RR 0.90 95% CI 0.80; 1.00)

For time to first event of all-cause hospitalisation (HR 0.94 95% CI 0.88; 1.02) the point estimate was below unity but was not significant (Table 28). The composite was mainly influenced by the large number of hospitalisations for non-heart failure reasons (37.7% vs. 36.5% in finerenone vs. placebo). A recurrent event analysis indicates no difference between the groups (RR 0.99 95% CI 0.92; 1.07).

For the time to first event analysis of the composite CV death or non-fatal CV event (HR 0.95 95% CI 0.86; 1.05) the point estimate was below unity (Table 28). The estimate seems to be mainly influenced by hospitalisations for heart failure (14.2% vs. 16.5% in finerenone vs. placebo) whereas there was no difference in CV death (4.5% vs. 4.7% in finerenone vs. placebo). The incidences of non-fatal MI (2.3% [69 events] vs. 1.5% [44 events] in finerenone vs. placebo) and non-fatal stroke (2.7% [82 events] vs. 2.1% [64 events]) were however slightly higher in the finerenone group compared to placebo. Cases of non-fatal MI and stroke in this study were investigator reported and non-adjudicated.

The applicant has also provided an explorative analysis of 3-point MACE using all-cause mortality and cardiovascular mortality, respectively (Table 29) indicating a neutral effect on MACE from the treatment.

The change in eGFR from baseline was assessed. Finerenone was associated with an acute reduction in eGFR vs. placebo. The maximum difference occurred at Month 6 (-3.53 mL/min/1.73m^2). The applicant has also conducted a slope analysis where a negative slope represents a worsening in eGFR. The chronic eGFR slope (assessed from 3 months) was within the same range in both treatment groups but numerically lower in the finerenone group (-0.96 vs. -1.15 mL/min/1.73m^2/year). The total eGFR slopes were instead numerically higher in the finerenone group vs. placebo, -3.80 vs. -0.95 mL/min/1.73m^2/year for the first year, the differences narrowing in during the two consecutive years). The data thus indicate that patient on average display a more pronounced decline in eGFR at the start of treatment in the finerenone group followed by a similar yearly decline in the two treatment arms.

Urine albumin creatinine ratios measured up to month 24 show a sustained ~25-30% reduction by finerenone compared to placebo from 3 month onwards, which is in line with findings from the previous FIDELIO-DKD and FIGARO-DKD studies.

Similar to the 50% secondary renal endpoint, analysis of the composite endpoint of time to first occurrence of sustained decrease in eGFR ≥57% relative to baseline over at least 4 weeks, or sustained eGFR decline to <15 mL/min/1.73 m^2 over at least 4 weeks or initiation of chronic dialysis or renal transplantation displayed a slightly increased HR in favour of placebo, but the events were few (41 [1.4%] vs 31 [1.0%] events in finerenone vs. placebo).

Table 26. Analysis of time to first event exploratory efficacy endpoints (full analysis set; adapted from Table 8.2.3 / 1)

	Finerenone n (%) N=3003 (100%)	Finerenone n/100 p-yrs (95% CI)	Placebo n (%) N=2998 (100%)	Placebo n/100 p-yrs (95% CI)	Treatment comparison HR (95% CI) [1]	p-value [2]
CV hospitalization	793 (26.4%)	12.64 (11.77; 13.57)	870 (29.0%)	14.25 (13.30; 15.26)	0.89 [0.81; 0.98]	0.0154
All-cause hospitalization	1433 (47.7%)	26.90 (25.46; 28.41)	1481 (49.4%)	28.61 (27.10; 30.21)	0.94 [0.88; 1.02]	0.1264
Hospitalization for heart failure	300 (10.0%)	4.45 (3.97; 4.99)	387 (12.9%)	5.88 (5.31; 6.51)		
Hospitalization for non-heart failure reasons	1133 (37.7%)	20.30 (19.10; 21.57)	1094 (36.5%)	19.68 (18.50; 20.93)		
CV death or non-fatal CV event	712 (23.7%)	10.84 (10.06; 11.68)	746 (24.9%)	11.44 (10.63; 12.31)	0.95 [0.86; 1.05]	0.3079
CV Death	135 (4.5%)	1.86 (1.57; 2.20)	142 (4.7%)	1.96 (1.66; 2.31)		
Non-fatal MI	69 (2.3%)	0.96 (0.76; 1.22)	44 (1.5%)	0.61 (0.46; 0.82)		
Non-fatal stroke	82 (2.7%)	1.15 (0.92; 1.42)	64 (2.1%)	0.89 (0.70; 1.14)		
Hospitalization for heart failure	426 (14.2%)	6.31 (5.73; 6.95)	496 (16.5%)	7.48 (6.84; 8.18)		
New onset of atrial fibrillation	76 (5.6%)	2.34 (1.87; 2.93)	99 (7.2%)	3.01 (2.47; 3.66)	0.78 [0.58; 1.05]	0.0968

n = Number of subjects with an event; N = Total number of subjects.
CV = cardiovascular, MI = myocardial infarction, eGFR = estimated Glomerular Filtration Rate.
[1] Hazard ratio (Finerenone over Placebo) and confidence interval from stratified Cox proportional hazard model.
[2] p-value based on stratified log-rank test.
Pooled region and baseline LVEF (<60%, >=60%) are the stratification factors.
Subsequent event of the same or another type are not shown. For components of the composite, the subject is counted with the event contributing to the composite, effectively decomposing the composite outcome.
For all-cause hospitalizations (and breakdown by HF and non-HF reasons) investigator-reported events are considered from randomization up until the cut-off date.
For the endpoint New onset of atrial fibrillation only patients without medical history of atrial fibrillation are included for the denominator.

Table 27. Summary of results for the exploratory MACE endpoints and their components (FAS)

	Finerenone N=3003 (100%)		**Placebo** N=2998 (100%)		**csHR** (95% CI)
	n (%)	n/100 p-yrs	n (%)	n/100 p-yrs	
CV death, non-fatal MI or non-fatal stroke	**388 (12.9%)**	**5.49**	**373 (12.4%)**	**5.25**	**1.05 (0.91; 1.21)**
CV death	216 (7.2%)	3.06	242 (8.1%)	3.41	-
Non-fatal MI	81 (2.7%)	1.15	54 (1.8%)	0.76	-
Non-fatal stroke	91 (3.0%)	1.29	77 (2.6%)	1.08	-
ACM, non-fatal MI or non-fatal stroke	**612 (20.4%)**	**8.67**	**617 (20.6%)**	**8.68**	**1.00 (0.89; 1.12)**
ACM	440 (14.7%)	6.23	487 (16.2%)	6.85	-
Non-fatal MI	81 (2.7%)	1.15	53 (1.8%)	0.75	-
Non-fatal stroke	91 (3.0%)	1.29	77 (2.6%)	1.08	-

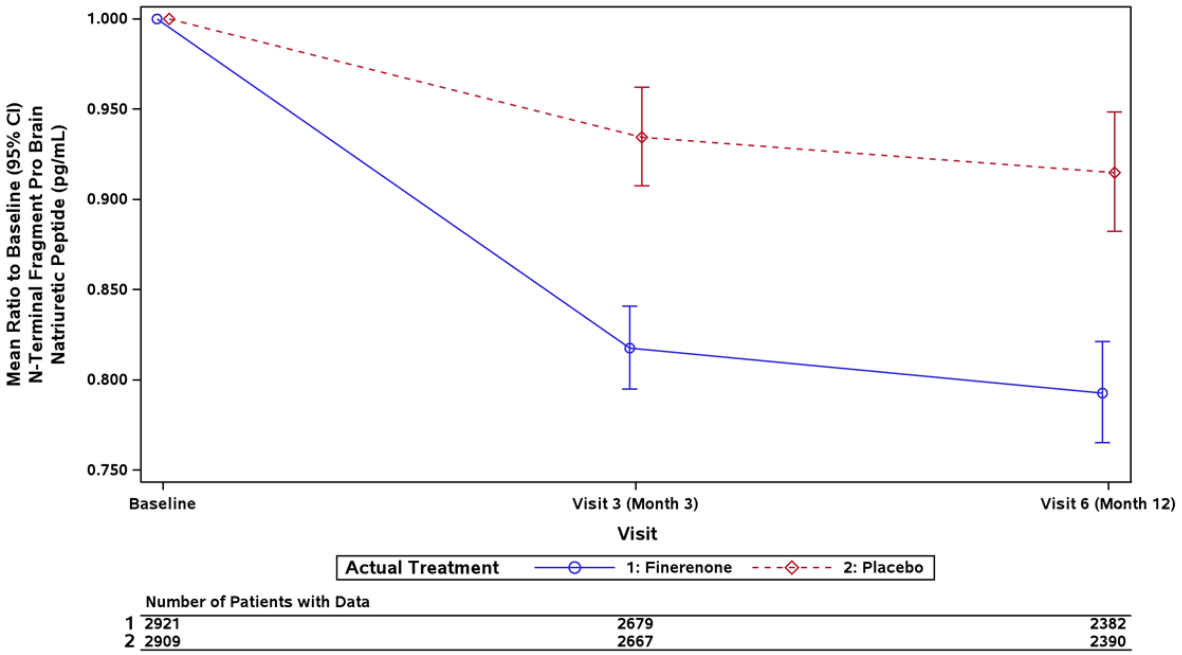
n = number of participants with event, N =total number of participants, MACE = major adverse cardiac events; MI = myocardial infarction
Only fatal events were adjudicated by an independent adjudication committee; non-fatal events were investigator-reported.
Events are considered from randomization up until the cut-off date.
n/100 p-yrs: incidence rate estimated as number of subjects with the respective event divided by the cumulative at-risk time in the reference population, where a subject is no longer at risk once the event-of-interest occurred.
A subject is counted with the time and type of their first event observed after randomization. Subsequent events of the same or another type are not shown. For components of the composite, the subject is counted with the event contributing to the composite, effectively decomposing the composite outcome.
Source: Module 5.3.5.1, EMA_Day120_finearts, Table 1.8.1/1, Table 1.8.1/2, Table 1.8.1/4 and Table 1.8.1/5

Clinical biomarkers analyses

NT proBNP was measured as an important clinical marker in HF with scheduled visits at baseline, Month 3, and Month 12. Finerenone led to a larger NT-proBNP reduction compared to placebo up to Month 12. The (geometric) mean (SD) ratio to baseline was 0.793 (2.384) in the finerenone group and 0.915 (2.437) in the placebo group at Month 12 (Figure 10).

Hs-TnT was measured at the same timepoints and was numerically lower in the finerenone group at month 12 but given the large standard deviations, no conclusions can be drawn.

Figure 10. NT-proBNP (pg/mL): mean ratio to baseline by visit with 95% CIs (SAF, FINEARTS-HF)

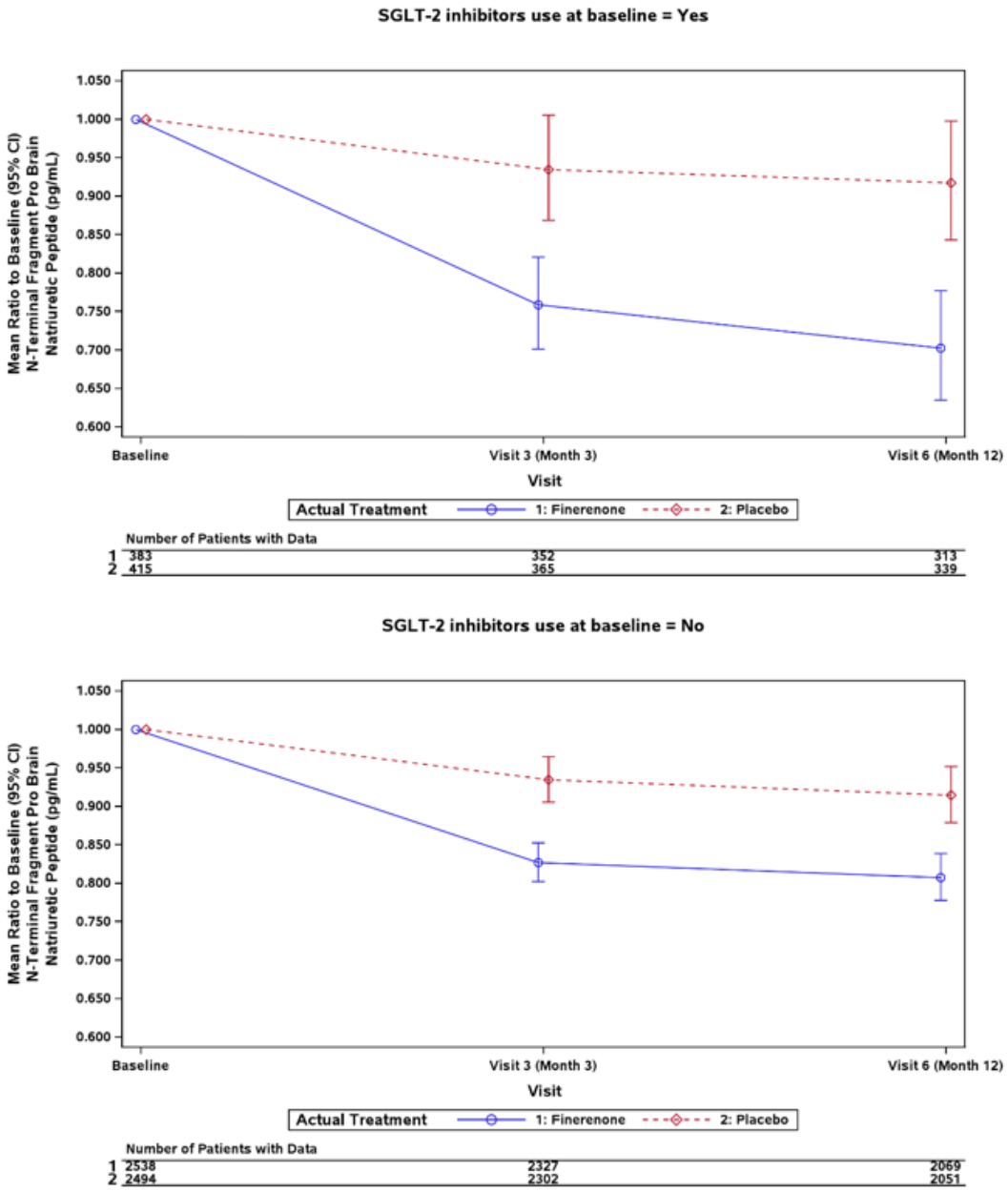


Visits are no longer displayed, if only 5% of participants or fewer remain in the study and have data available.
Mean of ratio to baseline and corresponding CIs were calculated on log-transformed ration to baseline values and then back-transformed to the original scale by exponentiating them.
NT-proBNP = N-terminal prohormone B-type natriuretic peptide
Source: Module 5.3.5.1, Report B002803, Figure 8.3.3/1

SGLT2i is expected as a common co-medication for finerenone and a subgroup analysis of NT-proBNP values for patients with concomitant use of SGLT2 inhibitors was provided by the applicant upon request. At baseline, participants with SGLT2-inhibitor use generally had higher NT-proBNP levels (median 1217.3 and 1139.9 pg/mL for finerenone and placebo, respectively) compared to those without SGLT2-inhibitor use (median 1019.1 and 1002.9 pg/mL). However, regardless of SGLT2

inhibitor use at baseline, finerenone led to a larger NT-proBNP reduction compared to placebo up to Month 12 (Figure 5).

Figure 5. NT-proBNP (pg/mL): mean ratio to baseline by SGLT2 inhibitor use at baseline and visit (SAF)



Mean of ratio to baseline and corresponding CIs were calculated on log-transformed ratio to baseline values and then back-transformed to the original scale by exponentiating them. CIs were based on a Normal approximation.
CI = confidence interval, NT-proBNP = N-terminal prohormone B-type natriuretic peptide
Source: Module 5.3.5.1, EMA_Day120_finearts, Figure 1.5.1/1

- **Summary of main efficacy results**

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

Table 30. Summary of Efficacy for trial FINEARTS-HF

<table>
<tr><td colspan="3">Title: A multicenter, randomized, double-blind, parallel-group, placebo-controlled study to evaluate the efficacy and safety of finerenone on morbidity and mortality in participants with heart failure (NYHA II-IV) and left ventricular ejection fraction ≥40% (LVEF ≥40%)</td></tr>
<tr><td>Study identifier</td><td colspan="2">Protocol number 20103, EudraCT: 2020-000306-29, Report number B002803</td></tr>
<tr><td>Design</td><td colspan="2">Randomized, double-blind, placebo-controlled, parallel-group, multicenter, event-driven Phase 3 study.

This was a study to evaluate the efficacy and safety of finerenone compared to placebo (1:1 ratio) in patients with HF (NYHA II-IV) and LVEF ≥40%. The starting dose of finerenone was based on the eGFR value at the screening visit: 10 mg once daily if eGFR was ≤60 mL/min/1.73m² with a maximum maintenance dose of 20 mg once daily; 20 mg once daily if eGFR was >60 mL/min/1.73m² with a maximum maintenance dose of 40 mg once daily. Investigators were encouraged to reach the maximum (target) dose based on the level of serum/plasma potassium and eGFR without compromising safety. Down-titration or interruption of study intervention was allowed at any time during the study for safety reasons.</td></tr>
<tr><td></td><td>Duration of main phase:

Duration of Run-in phase:
Duration of Extension phase:</td><td>Event driven, expected approx. 3.5 years,
First patient first visit 14 SEP 2020
Last patient last visit 14 JUN 2024
not applicable
not applicable</td></tr>
<tr><td>Hypothesis</td><td colspan="2">Finerenone is superior to placebo in reducing the rate of the composite CV endpoint of CV death and total (first and recurrent) HF events (HHF or urgent HF visit).</td></tr>
<tr><td>Treatments groups</td><td>Finerenone, 10, 20 or 40 mg tablets once daily</td><td>Median treatment duration: 28.03 months,

Median study duration (defined as time from randomization to end-of-study visit or last contact date): 32.23 months,

Number randomized: 3011 participants,

FAS: 3003 participants</td></tr>
<tr><td></td><td>Placebo</td><td>Median treatment duration: 28.07 months,

Median study duration: 32.08 months,

Number randomized: 3005 participants,

FAS: 2998 participants</td></tr>
</table>

Endpoints and definitions	Primary efficacy	CV composite	Composite of CV death and total (first and recurrent) HF events (HHF or urgent HF visit).
	Secondary efficacy	Total HF events	Total (first and recurrent) HF events
		Change in TSS of KCCQ	Change from baseline to Month 6, 9 and 12 in TSS of the KCCQ
		NYHA improvement	Improvement in NYHA class from baseline to Month 12
	Secondary efficacy (continued)	Renal composite	Composite of sustained decrease in eGFR ≥50% relative to baseline over at least 4 weeks, or sustained eGFR decline to <15 mL/min/1.73 m^2 or initiation of dialysis or renal transplantation
		All-cause mortality	Mortality by any cause
Database lock	25 JUL 2024		

Results and Analysis

Analysis description	Primary Analysis
Analysis population and time point description	Of the 6016 randomized participants, 15 participants were prospectively excluded from the analyses because of GCP violations, resulting in a FAS population of 6001 participants (3003 participants in the finerenone arm and 2998 participants in the placebo arm). Vital status was ascertained after EOS notification for all but 19 participants (0.3%, 7 participants in the finerenone group and 12 participants in the placebo group). Thus 2996 participants (99.5%) in the finerenone arm and 2986 participants (99.4%) in the placebo arm completed the study. The primary analysis was performed on the FAS based on the endpoint events (total and recurrent events) from randomization up until the end-of-study visit that were positively adjudicated by an independent Clinical Events Committee. To account for multiple testing, primary and secondary efficacy endpoints were tested using a combination of hierarchical testing and the Bonferroni-Holm method.

Descriptive statistics and estimate variability	Treatment group	**Finerenone** (3003 participants)	**Placebo** (2998 participants)
	Primary composite endpoint		
	CV composite		
	Event number (number of participants with at least one event, %)	1083 (624; 20.8%)	1283 (719; 24.0%)

	Events/100 patient-years (95% CI)	14.88 (13.52;16.38)	17.70 (16.22;19.31)
	Secondary endpoints		
	Total HF events		
	Event number (number of participants with at least one event, %)	842 (479; 16.0%)	1024 (573; 19.1%)
	Events/100 patient-years (95% CI)	11.57 (10.37; 12.91)	14.12 (12.79; 15.60)
	Change in TSS of KCCQ		
	Least squares mean change from baseline (95% CI)	7.99 (7.37, 8.62)	6.43 (5.79, 7.07)
	NYHA improvement		
	Estimated proportion of responders (95% CI)	0.179 (0.163, 0.195)	0.178 (0.162, 0.194)
	Renal composite		
	Number of participants with first event (%)	75 (2.5%)	55 (1.8%)
	n/100 patient-years (95% CI)	1.16 (0.92; 1.45)	0.85 (0.66; 1.11)
	All-cause mortality		
	Number of participants (%)	491 (16.4%)	522 (17.4%)
	n/100 patient-years (95% CI)	6.71 (6.15; 7.33)	7.17 (6.59; 7.81)
Effect estimate per comparison	**Primary composite endpoint**	**Comparison group**	**Finerenone vs Placebo**
	CV composite	Rate ratio	**0.84**
		[95% CI]	**[0.74; 0.95]**
		p-value	0.0072
	Secondary endpoints	**Comparison group**	**Finerenone vs Placebo**
	Total HF events	Rate ratio	0.82
		[95% CI]	[0.71; 0.94]
		p-value	0.0062
	Change in TSS of KCCQ	Difference in LS means	1.56

		[95% CI]	[0.79, 2.34]
		p-value	<0.0001
	NYHA improvement	Odds ratio (finerenone/ placebo)	1.01
		[95% CI]	[0.88, 1.15]
		p-value	0.9295
	Renal composite	Cause-specific hazard ratio	1.33
		[95% CI]	[0.94; 1.89]
		p-value	0.1071
	All-cause mortality	Hazard ratio	0.93
		[95% CI]	0.83; 1.06
		p-value	0.2794
Notes	For the comparison of finerenone versus placebo, the reduction in the primary CV composite endpoint and the secondary efficacy endpoints of total HF events and change in TSS of the KCCQ was significantly superior for finerenone. For NYHA no advantage for finerenone was indicated; therefore, the remaining secondary renal composite was not tested formally, but in an exploratory manner. Time to all-cause mortality was tested outside of the testing hierarchy at a two-sided significance level of 0.05, after the rejection of the primary hypothesis.		
CI = confidence interval, CV = cardiovascular, eGFR = estimated glomerular filtration rate, FAS = full analysis set, GCP = Good Clinical Practice, HF = heart failure, HHF = hospitalization for heart failure, KCCQ = Kansas City Cardiomyopathy Questionnaire, LS means= least squares means, n = number of subjects with event, NYHA = New York Health Association, TSS = total symptom score			

2.6.5.3. Clinical studies in special populations

The previous FIDELIO-DKD and FIGARO-DKD studies were conducted on patients with chronic kidney disease. In the FINEARTS-HF study, 48% of participants had eGFR < 60mL/min/1.73m^2. No other dedicated studies were performed in special populations.

Table 28. Number of participants by age group (SAF)

Study phase and indication Study intervention received	Number of participants in age subgroup			
Age subgroup:	**<65 years**	**65–74 years**	**75–84 years**	**85+ years**
Controlled trials				
Phase 3, HF and LVEF ≥40% (FINEARTS-HF)				
Finerenone (N=2993, 100%)	641 (21.4%)	1072 (35.8%)	1054 (35.2%)	226 (7.6%)
Placebo (N=2993, 100%)	619 (20.7%)	1103 (36.9%)	1029 (34.4%)	242 (8.1%)
Phase 3, CKD in T2D (FIGARO-DKD)				
Finerenone (N=3671, 100%)	1744 (47.5%)	1432 (39.0%)	466 (12.7%)	29 (0.8%)
Placebo (N=3646, 100%)	1745 (47.9%)	1378 (37.8%)	493 (13.5%)	30 (0.8%)
Phase 3, CKD in T2D (FIDELIO-DKD)				
Finerenone (N=2818, 100%)	1198 (42.5%)	1191 (42.3%)	411 (14.6%)	18 (0.6%)
Placebo (N=2828, 100%)	1169 (41.3%)	1199 (42.4%)	435 (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. In vitro biomarker test for patient selection for efficacy

Not applicable.

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

The applicant has conducted an integrated efficacy analysis of the present FINEARTS-HF study and the previous FIDELIO and FIGARO studies that were conducted for the initial MAA. The purpose of the analysis was to increase the precision to assess the efficacy of the non-steroidal MRA finerenone on CV death in a population with a high burden of cardio-kidney-metabolic multimorbidity. The efficacy outcome of the analysis is CV death which was a component of the respective CV composite endpoints in these studies. The incidence of CV death was numerically lower in the pool (HR=0.89; 95% CI 0.78;

1.01; p=0.078). Aalen-Johansen curves are provided in Figure 6. The subcomponents for CV are provided in Table 32 with no clear pattern among the components.

Figure 6. Display of Aalen-Johansen curves for CV death (FAS, pool and individual studies FINEARTS-HF, FIDELIO-DKD, FIGARO-DKD)

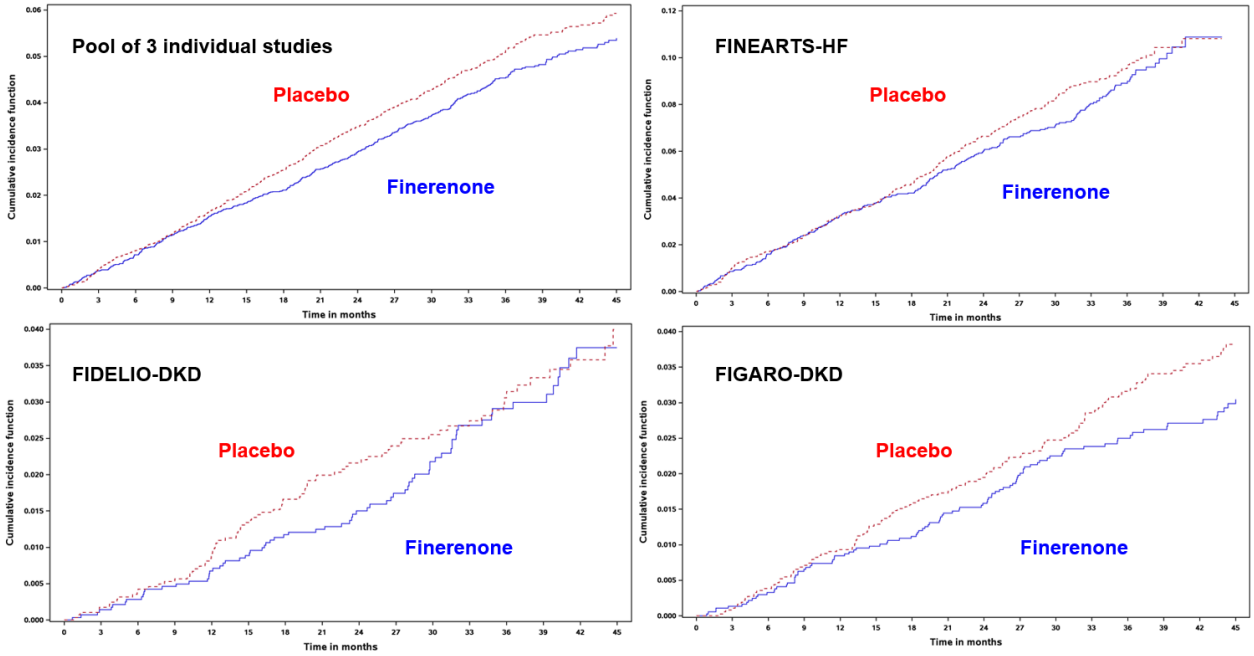


Table 29. CV death components (pool of FINEARTS-HF, FIDELIO-DKD and FIGARO-DKD)

	Finerenone N = 9501 (100 %)			Placebo N = 9490 (100 %)		
	n	%	n/100 p-yrs	n	%	n/100 p-yrs
CV death	421	4.43	1.55	471	4.96	1.75
Sudden	188	1.98	0.69	230	2.42	0.85
Heart failure	92	0.97	0.34	113	1.19	0.42
Stroke	47	0.49	0.17	59	0.62	0.22
Myocardial infarction	35	0.37	0.13	37	0.39	0.14
Cardiovascular procedural	12	0.13	0.04	7	0.07	0.03
Other cardiovascular related	47	0.49	0.17	25	0.26	0.09

Source: Module 5.3.5.3, EMA_Day120_ia_finearts, Table 1.2/1

2.6.5.6. Supportive studies

The 30-day part B of the ARTS study (14563) encompassed patients with moderate CKD (eGFR 30-60 mL/min) and CHF (NYHA II-III; LVEF ≤40%). Administration of finerenone was associated with a dose dependent decrease in the UACR. The measurements of BNP and NT-proBNP displayed a high variability but data indicate a slight reduction from baseline in BNP for 5 mg BID and 10 mg finerenone OD, respectively, after 29 days of treatment. A reduction within the same range was observed for the comparator spironolactone.

The 90-day ARTS-HF study (14564) enrolled CHF patients (NYHA II-IV; LVEF ≤40%) with T2D (eGFR ⩾30 mL/min) or without T2D (eGFR 30-60 mL/min). Patients were required to have a clinical diagnosis of worsening chronic heart failure (WCHF) requiring emergency presentation to hospital and treatment with intravenous diuretics. Following a screening visit, eligible subjects were randomized within ≤7

days after emergency hospital presentation to receive a 90-day study drug treatment with one of 5 doses of finerenone, or eplerenone, in addition to their standard therapy for HF.

The finerenone groups started with 2.5 mg, 5 mg, 7.5 mg, 10 mg or 15 mg OD. The dose was increased (to 5 mg, 10 mg, 15 mg, 20 mg or 20 mg OD, respectively) on Day 30, and all treatment arms were possibly (sham) up titrated on Day 60. The finerenone arms were designated as 2.5-5 mg, 5-10 mg, 7.5-15 mg, 10-20 mg, and 15-20 mg OD dose groups. The eplerenone group started with 25 mg every other day, was increased to 25 mg OD on Day 30 and up titrated to 50 mg OD on Day 60 (or 25 mg OD if not up titrated on Day 30). Up titration occurred in all arms provided that blood potassium was ⩽5.0 mmol/L.

For the primary efficacy endpoint, the percentage of subjects with a relative decrease in NT-proBNP of more than 30% from baseline to day 90, there was no difference between the different finerenone doses evaluated compared with the comparator eplerenone (Table 33).

Table 30. Treatment comparison for percentage of subjects with a relative decrease in NT-proBNP of >30% from baseline to Visit 9 (Day 90±2) (full analysis set)

		Responders at Visit 9 (Day 90±2)			Treatment difference (finerenone – eplerenone)			
Actual treatment	N	n	%	90% CI[a]	Mean	SE	90% CI[b]	p-value[c]
Eplerenone	207	77	37.2	[31.6; 43.1]				
2.5-5 mg OD	162	50	30.9	[24.9; 37.4]	-6.3	0.049	[-14.9; 2.3]	0.8771
5-10 mg OD	157	51	32.5	[26.3; 39.2]	-4.7	0.050	[-13.4; 4.0]	0.7945
7.5-15 mg OD	158	59	37.3	[30.9; 44.1]	0.1	0.051	[-8.5; 8.8]	0.5000
10-20 mg OD	160	62	38.8	[32.3; 45.5]	1.6	0.051	[-7.1; 10.2]	0.4225
15-20 mg OD	158	54	34.2	[27.9; 40.9]	-3.0	0.051	[-11.7; 5.7]	0.6865

For missing Visit 9 (Day 90±2) data, a LOCF approach was used for subjects not considered as non-responders, where the higher NT-proBNP value from the premature discontinuation measurement and the follow-up measurement was used for subjects who prematurely terminated the study (worst-case imputation on subject level).
Relative decrease = 100 * [(baseline value – post-baseline value) / baseline value].
Subjects who died prior to Visit 9 (Day 90±2) or experienced permanent (≥5 consecutive days) withdrawal of study drug after a CV hospitalization or emergency presentation due to WCHF were considered as "non-responders" and counted for "No".
[a] Clopper-Pearson confidence intervals are presented for the treatment groups.
[b] Exact unconditional confidence intervals are presented for the treatment group differences.
[c] p-value is based on a one-sided Chi-square test with continuity correction.
Source: Table 14.2 / 30

Results concerning the exploratory endpoint death from any cause, CV hospitalizations, or emergency presentations for worsening CHF until Day 90 is provided in Table 34.

Table 31. Hazard ratios and logrank test results for the composite clinical endpoint - ARTS-HF Study 14564 (Full analysis set)

	Subjects with event			Comparison Finerenone vs Eplerenone	
Treatment	N	n	(%)	Hazard ratio [95% CI]	p-value[a]
Composite endpoint: first event of all-cause death, CV hospitalization or emergency presentation for worsening CHF					
Eplerenone	207	52	(25.1)		
2.5-5 mg OD	162	48	(29.6)	1.21 [0.82; 1.79]	0.3470
5-10 mg OD	157	29	(18.5)	0.70 [0.44; 1.10]	0.1233
7.5-15 mg OD	158	33	(20.9)	0.77 [0.50; 1.19]	0.2315
10-20 mg OD	160	25	(15.6)	0.56 [0.35; 0.90]	0.0157
15-20 mg OD	158	37	(23.4)	0.89 [0.58; 1.36]	0.5886

a 2-sided p-value from logrank test unstratified
Hospitalizations and deaths were adjudicated by an independent adjudication committee and classified as CV or non-CV. Analyses include events occurring up to end of treatment, defined as the last study drug intake +3 days. Further details are available in Module 5.3.5.1, Report PH-38020.
ARTS = minerAlocorticoid-Receptor antagonist Tolerability Study, CHF = chronic heart failure, CI = confidence interval, CV = cardiovascular, FAS = full analysis set, HF = heart failure, OD = once daily
Source: Module 5.3.5.1, PH-38020, Table 14.2/217, Table 14.2/218

eGFR was assessed throughout the study and a follow-up assessment 30±5 days after last intake of study drug was also included (Table 35).

Table 32. Summary statistics for general chemistry values and relative changes from baseline by visit for estimated glomerular filtration rate (mL/min/1.73 m^2) in blood (calculated by MDRD) (safety analysis set)

Actual treatment	Visit	Value at visit						Relative change from baseline					
		n	Mean	SD	Min	Median	Max	n	Mean	SD	Min	Median	Max
Eplerenone	Baseline	221	52.015	17.949	18.30	48.600	106.70						
	Visit 5 (Day 30±2)	178	53.375	17.730	16.90	51.550	106.70	178	2.170	20.155	-63.81	0.000	86.40
	Visit 7 (Day 60±2)	149	53.203	21.400	17.80	48.400	132.90	149	1.801	37.813	-48.84	0.000	201.36
	Visit 9 (Day 90±2)	143	51.849	20.894	16.70	46.300	122.30	143	-0.318	26.496	-48.84	-0.282	136.76
	Last on-treatment	208	50.984	19.650	16.70	46.500	122.30	208	-0.493	27.686	-48.84	-0.348	148.52
	Follow-up	162	51.802	18.499	12.00	49.750	105.20	162	-0.204	22.871	-53.56	-0.204	109.56
2.5-5 mg OD	Baseline	172	52.206	16.048	22.60	49.350	116.90						
	Visit 5 (Day 30±2)	137	53.786	17.624	23.90	51.800	118.80	137	3.181	28.597	-57.81	0.000	136.76
	Visit 7 (Day 60±2)	127	54.214	19.079	8.80	50.800	112.90	127	3.439	26.362	-78.05	0.000	136.76
	Visit 9 (Day 90±2)	119	54.886	19.929	21.60	52.200	139.40	119	4.147	30.480	-48.65	0.000	171.21
	Last on-treatment	165	51.796	20.266	7.70	47.400	139.40	165	0.407	29.965	-87.97	-0.161	171.21
	Follow-up	131	54.440	21.094	24.70	49.000	175.20	131	4.538	29.313	-41.32	0.000	148.51
5-10 mg OD	Baseline	163	51.567	16.401	21.00	50.300	119.60						
	Visit 5 (Day 30±2)	139	53.814	17.176	22.50	51.600	119.60	139	3.360	26.099	-57.10	0.000	139.09
	Visit 7 (Day 60±2)	125	53.446	16.284	26.30	51.700	103.10	125	3.339	26.150	-53.04	0.000	139.09
	Visit 9 (Day 90±2)	118	53.631	16.557	23.40	52.000	94.20	118	2.876	25.353	-51.35	0.000	108.47
	Last on-treatment	156	51.901	16.917	21.50	49.900	102.50	156	2.284	25.911	-59.96	0.000	108.47
	Follow-up	136	52.721	17.003	13.50	50.750	107.90	136	5.255	29.554	-77.23	0.000	139.09
7.5-15 mg OD	Baseline	167	54.778	20.011	25.00	48.500	124.00						
	Visit 5 (Day 30±2)	141	57.576	21.169	21.70	52.000	120.70	141	5.114	20.790	-37.28	0.000	99.42
	Visit 7 (Day 60±2)	128	55.191	20.214	23.10	50.550	139.20	128	1.457	20.844	-48.09	0.000	68.67
	Visit 9 (Day 90±2)	119	55.808	21.239	22.80	51.800	144.20	119	0.580	21.922	-41.30	0.000	90.67
	Last on-treatment	162	54.112	21.249	20.80	50.500	144.20	162	0.138	24.878	-41.44	0.000	122.54
	Follow-up	134	54.387	20.380	18.70	53.100	139.20	134	2.275	26.682	-55.05	0.000	89.95
10-20 mg OD	Baseline	168	52.917	17.415	21.90	51.050	141.20						
	Visit 5 (Day 30±2)	144	53.844	17.901	24.50	51.300	141.20	143	4.135	24.566	-58.09	0.000	133.45
	Visit 7 (Day 60±2)	136	53.245	19.847	20.90	51.350	141.20	135	1.150	23.007	-55.05	0.000	110.77
	Visit 9 (Day 90±2)	130	52.627	17.754	20.80	51.650	141.20	130	0.223	22.915	-55.11	0.000	92.24
	Last on-treatment	165	51.927	17.707	20.80	51.200	141.20	164	0.148	22.619	-55.11	0.000	92.24
	Follow-up	147	53.960	18.967	22.90	52.000	143.30	146	4.575	25.940	-60.79	0.000	106.49
15-20 mg OD	Baseline	163	54.941	18.618	19.00	50.100	127.40						
	Visit 5 (Day 30±2)	135	55.714	19.075	17.00	53.900	130.60	135	-0.486	22.767	-47.54	0.000	71.98
	Visit 7 (Day 60±2)	127	54.060	19.738	24.40	51.300	130.60	127	-2.262	24.300	-51.58	-6.053	109.49
	Visit 9 (Day 90±2)	120	53.938	18.859	22.70	53.700	121.50	120	-2.687	24.201	-60.86	-8.237	94.07
	Last on-treatment	156	52.067	19.640	10.60	51.150	121.50	156	-4.987	24.468	-60.86	-8.591	94.07
	Follow-up	137	54.383	21.834	13.90	52.400	136.80	137	-1.006	23.653	-55.15	-0.327	94.07
Total	Baseline	1054	53.011	17.798	18.30	49.600	141.20						
	Visit 5 (Day 30±2)	874	54.626	18.471	16.90	52.000	141.20	873	2.905	23.835	-63.81	0.000	139.09
	Visit 7 (Day 60±2)	792	53.869	19.510	8.80	50.650	141.20	791	1.488	24.907	-78.05	0.000	201.36
	Visit 9 (Day 90±2)	749	53.711	19.295	16.70	51.100	144.20	749	0.751	25.390	-60.86	0.000	171.21
	Last on-treatment	1012	52.079	19.298	7.70	49.350	144.20	1011	-0.406	26.146	-87.97	-0.231	171.21
	Follow-up	847	53.558	19.614	12.00	51.300	175.20	846	2.495	26.362	-77.23	0.000	148.51

Relative change = 100*[(post-baseline value – baseline value)/baseline value].
Source: Table 14.3.4 / 70

The ARTS-HF Japan study (16815) was a comparator-controlled, double-blind, phase II dose finding study to evaluate 5 dosing regimens of finerenone against eplerenone in patients with worsening chronic heart failure with reduced EF. The design was similar as ARTS-HF but in a Japanese population. The patients either had T2D and eGFR ≥30 mL/min/1.73 m^2 or without T2D and eGFR 30 to ≤60 mL/min/1.73 m^2.

2.6.6. Discussion on clinical efficacy

Finerenone is a mineralocorticoid receptor antagonist, previously approved for the treatment of chronic kidney disease (with albuminuria) associated with type 2 diabetes in adults. In the current variation,

the following new indication was granted: treatment of symptomatic chronic heart failure with left ventricular ejection fraction (LVEF) ⩾ 40% in adults, based in the results of one pivotal phase III study FINEARTS-HF (20103).

Design and conduct of clinical studies

No clinical studies concerning the mechanism of action have been submitted with this variation. Non-clinical data from various heart failure (HF) models suggest a beneficial effect of finerenone which may be mediated by reducing cardiac fibrosis and hypertrophy. Within this pharmacological class, eplerenone is currently approved for treatment of heart failure with reduced ejection fraction (HFrEF) whereas the pivotal study in the current application concerned heart failure with preserved ejection fraction (HFpEF)/heart failure with mildly reduced ejection fraction (HFmrEF). Both conditions encompass LVEF ≥40%.

No CHMP scientific advice was obtained prior to the conduct of the FINEARTS-HF study.

Dose-response studies

No dedicated clinical dose finding studies in patients with heart failure and left ventricular ejection fraction ≥ 40% were conducted in support for the 40 mg dose that is introduced in the present procedure in addition to the currently approved 10 mg and 20 mg doses. In the supportive 90-day ARTS-HF study, 5 different finerenone dose groups (5-20 mg) and eplerenone were studied in a HFrEF population with T2D (eGFR ≥30 mL/min) or without T2D (eGFR 30-60 mL/min). The ARTS-HF Japan study (16815) had a similar design as the ARTS-HF study but in a Japanese population. The study was a comparator-controlled, double-blind, phase II dose finding study to evaluate 5 dosing regimens of finerenone against eplerenone in patients with worsening chronic heart failure (CHF) with reduced EF.

The FINEARTS-HF study

The FINEARTS-HF study was a randomized, double-blind, placebo-controlled, parallel-group, event-driven Phase 3 study conducted at 654 centers across 37 countries and included 6016 randomised patients. The study was designed to evaluate the effect of finerenone compared to placebo, when added to standard of care, in patients with a diagnosis of HF, NYHA II-IV and LVEF ≥40%.

For patients with eGFR 25-60 mL/min/1.73m², the starting dose was 10 mg, and the maintenance dose was 20 mg. For patients with eGFR >60 mL/min/1.73m², the starting dose was 20 mg, and the maintenance dose was 40 mg. Doses were further adjusted according to serum potassium levels during the study. The 40 mg strength is new and is introduced with the current procedure.

The primary endpoint was a composite endpoint defined as CV death and total (first and recurrent) HF events (HHF or urgent HF visit).

Secondary endpoints were total (first and recurrent) HF events, improvement in NYHA class from Baseline to Month 12, change from baseline to Month 6, 9 and 12 in TSS of the KCCQ, time to first occurrence of composite renal endpoint: sustained decrease in eGFR ≥50% relative to baseline over at least 4 weeks, or sustained eGFR decline to <15 mL/min/1.73 m^2 or initiation of dialysis or renal transplantation and time to all-cause mortality.

The primary endpoint is considered clinically relevant and in line with EMA Guideline on clinical investigation of medicinal products for the treatment of chronic heart failure (CPMP/EWP/235/95, Rev.2). Similar endpoints have been used in other recent studies for medicinal products for treatment of HF. All-cause mortality could have been considered instead of CV death but is included as a secondary endpoint. The primary endpoint includes recurrent HF events which may have potential to better characterise the effect of treatment but interpretation may be complicated by the terminal events (CV and non-CV deaths) which limits the total numbers of HF events per subject.

For the secondary endpoints, the endpoint improvement of NYHA class is expected in HF trials. The KCCQ is a well-defined PRO instrument in HF patients. The secondary renal endpoint is considered relevant to characterise the renal outcome in the new HF population.

The FINEARTS-HF study encompassed 3011 patients randomized to finerenone and 3005 patients randomised to placebo. Out of the randomized patients (n=6016) almost all were included in the FAS (n=6001). A relatively large proportion of patients did not complete the treatment period (31.7% in finerenone vs. 32.6% in placebo). The main reasons were death (11.1% vs. 11.9%), patient decision (7.1% vs. 7.2%) and adverse events (4.8% vs. 4.2% in finerenone vs. placebo) and there were no major differences between the study arms. Approximately 80% of participants took the study drug for at least 12 months.

Baseline characteristics were similar in the two treatment arms. The mean age of the study population was 72 years. 46% of participants were female. The mean eGFR was 62 mL/min/1.73m^2 and 22% of participants had eGFR below 45 mL/min/1.73m^2. 57.5% of participants had been previously hospitalised for heart failure. 20% of participants had an index HF event <7 days prior to randomisation, and 34% of participants had an event >7 days to ≤3 months prior to randomisation. The majority (69%) was in NYHA class II with few patients in class IV (0.7%). The mean LVEF was 53%, 89% had hypertension, 25% previous myocardial infarction and 50% ongoing atrial fibrillation. The incidence of T2D was 41%. Also baseline medications were similar in both treatment arms and the patients appeared appropriately treated according to the standard of care in clinical practice guidance at the time when the study was conducted. 79% of participants were treated with an ACEI/ARB at baseline. Nearly all patients were treated with diuretics (87% loop diuretics, 14% thiazides). 14% were treated with a SGLT-2 inhibitors and 9% with angiotensin receptor neprilysin inhibitors. Treatment with other mineralocorticoid-receptor antagonists (MRAs) was prohibited according to the protocol.

Estimands and statistical considerations

The clinical question of interest was to demonstrate the superiority of finerenone over placebo in reducing the rate of the composite CV endpoint (CV death and total [first and recurrent] HF events [HHF or urgent HF visit]) in patients with heart failure (NYHA II-IV) and left ventricular ejection fraction ≥40% (LVEF ≥40%), regardless of discontinuation of assigned treatment, while the patient was alive.

For the estimand of the primary objective three intercurrent events were defined – Treatment discontinuation, CV death and non-CV death. For treatment discontinuation a treatment policy strategy was applied. CV death was counted as both an outcome event as well as a censoring event, i.e. a combination of a composite and a while-alive strategy was used. Non-CV death was handled with a while-alive strategy, resulting in a censoring event.

Censoring of non-CV death is considered a competing event. To account for the possible competing event of death, the Applicant was asked during the procedure to provide an analysis of time to first composite of HF event or all-cause mortality. From this analysis, the stratified Cox proportional hazards model generated a HR of 0.87 (95% CI 0.79, 0.96), which is line with the result of the primary endpoint (RR 0.84; 95% CI 0.74; 0.95). Hence, the primary analysis is considered robust for the competing event of non-CV death.

The defined intercurrent events (ICEs) together with the chosen strategies seem accurate. However, use of prohibited medication was not defined as a potential ICE and there was no strategy defined for the occurrence of prohibited medication use. The Applicant was asked to provide information on the occurrence of usage of prohibited medication and specify how this was handled in the analysis. The applicant stated that for the intercurrent event of prohibited medication use a treatment policy

approach was applied, meaning that all events and follow-up time were included in the primary analysis regardless of the use of prohibited medication. This is endorsed.

For the primary analysis of the secondary endpoints, a treatment policy strategy was mostly followed for intercurrent events. In the analysis of the key secondary endpoint of *Total HF events*, all-cause death, including CV death, was a censoring event, introducing the same issues as for the primary estimand.

A while-alive strategy was followed for *Change from baseline to Month 6, 9 and 12 in TSS from KCCQ* meaning all observed values up to death for any cause were included in the analysis. This strategy might introduce bias in the point estimate of the endpoint. For the *Time to first occurrence of renal composite endpoint*, the point estimate of the endpoint might also be biased, due to censoring for all-cause death.

The sample size calculations appear adequate. A total of approximately 2375 total (first and recurrent) primary composite events were targeted, leading to a power of 90% to show an effect at a two-sided alpha level of 5%. Due to blinded event rates being lower than those assumed in the sample size calculation, the planned number of randomised participants was increased from the planned 5500 to approximately 6000. However, since the target number of primary composite events was not changed this is accepted.

Participants were randomised using an IxRS in a 1:1 ratio to either finerenone or placebo. The randomisation was stratified by country/region and LVEF (<60%, ≥60%). Blinding and randomisation appear to have been accurately conducted.

All primary analyses of efficacy variables were performed in *Full Analysis Set (FAS)*, which comprised of all randomised participants except those with critical GCP violations. Totally, 15 randomised participants were removed from FAS. Of those were 13 participants, all from the same site, excluded due to critical GCP violations by the investigator. Additionally, during study conduct it was detected that one participant was randomised in 2 different study sites. This was also considered a critical GCP violation and hence the participant was excluded. The Applicant was asked to provide information regarding the GCP violations, both for the site where all participants were excluded due to critical GCP violations by the investigator and for the participant which was randomised twice. The applicant has explained how these GCP violations was detected, handled in the study and furthermore, dealt with in the analyses. Since it is not deemed to affect the conclusion of the result of the primary endpoint, this is accepted.

Primary analysis of the *primary endpoint* was performed in the FAS using the planned treatment group, in line with the ITT principle. Participants without an event of the primary composite endpoint at the time of analysis were censored at the date of their last contact or date of non-CV death. The primary analysis was based on an Andersen-Gill model with robust standard errors (sandwich estimator), referred to as the Lin, Wei, Yang and Ying (LWYY) model. The model included treatment group as fixed effect and pooled region and baseline LVEF (<60%, ≥60%) as stratification factors. Choice of primary analysis model for the primary endpoint is considered appropriate.

The primary analysis of the primary endpoint was based on a LWYY model, which is an extension of the Cox proportional hazards model. The model is expected to generate Hazard Ratios (HR). However, for analyses using this model, Rate Ratios (RR) are presented. The applicant confirms that the Rate Ratio (RR) presented for the primary analysis is estimated using the LWYY model pre-specified for the primary analysis. Further, the applicant argues that the treatment effect estimated from the LWYY model identified as a Hazard Ratio (HR) should preferably be interpreted as a Rate Ratio (RR). This is endorsed.

The *secondary endpoint* of Total HF events was analysed using an LWYY model adjusting for stratification variables, as for the primary analysis of the primary endpoint. Improvement in NYHA class from Baseline to Month 12 was estimated with logistic regression and Change from baseline to Month 6, 9 and 12 in TSS of the KCCQ was analysed by a repeated measures mixed model including treatment group, baseline, visit, baseline-by-visit interaction, and factors for the stratification levels. The secondary time-to first event variables (i.e. composite renal endpoint and all-cause mortality [ACM]) was done with a stratified log-rank test for testing and a stratified Cox proportional hazards model. Choice of methods for the primary analyses of the secondary endpoints appears eligible. Four of the five secondary endpoints were defined within the multiple testing procedure (MTP), which will be discussed further below.

Sensitivity analyses for the primary endpoint and key secondary endpoint of total HF events were planned and conduced according to specifications. Sensitivity analyses for the primary analysis included a negative binomial regression model including stratification factors and treatment group as covariates and log follow-up time as an offset parameter.

Several *supplementary analyses* were planned and carried out for the primary endpoint. To estimate the treatment effect for CV death as one of the components of the primary endpoint, a stratified Cox proportional hazards model for time to CV death was performed. A stratified Cox PH regression analysis was also used to estimate time to first composite of HF event or CV death. The primary analysis for the primary endpoint was also repeated for the composite endpoint of Total HF events and ACM. These analyses are considered relevant for the interpretation of the primary endpoint.

If the primary hypothesis was rejected, the secondary endpoint was planned to be tested according to a pre-defined *Multiple Testing Procedure*. First, the endpoint Total HF events was to be tested. If the hypothesis of total HF events was rejected the NYHA class and KCCQ endpoints was to be tested using the Bonferroni-Holm procedure, i.e. if at least one of the hypotheses of the two endpoints NYHA class and KCCQ could be rejected at the two-sided ($\alpha/2$) significance level, the remaining of the two endpoints was to be tested at the α significance level. If the hypotheses for all previous secondary endpoints were rejected, the composite renal endpoint was planned to be tested at the α significance level. The multiple testing procedure as described in the final version of the SAP is considered accurate.

Two interim analyses were planned and performed, one for futility when approximately 30% of expected number of events had occurred and a second for efficacy when 2/3 of expected number of events had occurred. The second interim analysis was performed using a two-sided p-value <0.00270. Since the study was not stopped early for success, a small adjustment to the alpha level at the final analysis to maintain the overall significance level at 0.05 was required. A p-value of p<0.04967 was therefore required at the final analysis to achieve formal statistical significance.

Since the secondary endpoint of Time to ACM was tested outside the multiple testing procedure, the p-value is considered nominal and hence no claim in the SmPC was accepted.

In the first SAP amendment, two endpoints were elevated to secondary endpoints – Total (first and recurrent) HF events (initially a supportive analysis of the primary endpoint) and Improvement in NYHA class from Baseline to Month 12 (initially an exploratory endpoint). Due to the changes in secondary endpoints, the multiple testing procedure was re-specified. Further, analysis strategies for the primary endpoint and secondary endpoints were revised to include the handling of censoring events. The analysis of the secondary endpoint of total HF events was changed from a joint frailty model to the LWYY model, which is used for the primary analysis of the primary endpoint. This change was motivated due to a potential convergence issue and is endorsed. However, the Applicant was asked to provide previous versions of the SAP and a table listing the changes performed, and detailed

explanations and reasons for these changes. A detailed list of changes together with the previous SAP versions has been provided by the Applicant in response to the LoQ. The changes raise no concern.

Efficacy data and additional analyses

Dose-response studies

The ARTS-HF study did not provide conclusive evidence of a dose-response relationship for finerenone in the context of heart failure. There was no difference between the finerenone doses evaluated for the primary efficacy endpoint, the percentage of subjects with a relative decrease in NT-proBNP of more than 30% from baseline to day 90.

For the exploratory endpoint death from any cause, CV hospitalizations, or emergency presentations for worsening CHF until Day 90, there was a trend for reduced hazard ratios (HRs) across the different dose groups of finerenone of 10 mg or higher. There was however no clear dose-response-relationship between increasing doses of finerenone and this endpoint.

Due to the small sample size of the ARTS-HF Japan study (11-13 patients/dosing regimen in the FAS) no clear conclusions can be drawn on the efficacy.

These studies were included and assessed in the initial market authorisation application. Given limited study duration, scattered data and lack of placebo, the supportive phase 2 studies have a limited value in addition to the FINEARTS-HF study for the current application.

The FINEARTS-HF study

Finerenone was superior to placebo in reducing the risk of the composite of CV death and total (first and recurrent) HF events (HHF or urgent HF visit) with on average 16% (RR=0.84; 95% CI 0.74; 0.95). The effect was mainly driven by an effect on HF events (RR=0.82 95% CI 0.71; 0.94). The difference in CV death between the groups was small (242 vs. 260 events in finerenone vs. placebo; HR 0.93, 95% CI 0.78; 1.11). The mean number of events per participant compared with placebo was reduced by 0.066 at 24 months. The pre-specified sensitivity analyses were in line with the primary estimate of the endpoint.

The primary endpoint included recurrent events and censored death, which is further discussed in the statistics section below. The applicant has performed a supportive time to first event of the primary endpoint (HR=0.84 95% CI 0.76; 0.94, p = 0.0020) which yielded a similar outcome as the analysis of the primary endpoint.

Secondary endpoints

The first secondary endpoint in the testing hierarchy was total (first and recurrent) HF events (HHF or urgent HF visit), which was also one of the components of the primary composite endpoint. The rate ratio was 0.82 (95% CI 0.71; 0.94) and the endpoint was statistically significant. As previously discussed, the HF events were the main driver for the effect on the primary endpoint.

For the secondary endpoint change from baseline to month 6, 9 and 12 in TSS of the patient report outcome KCCQ, the mean change from baseline was 7.99 in the finerenone group and 6.43 in the placebo group. The difference in LS mean was 1.56 (95% CI 0.79; 2.34) which was formally statistically significant. Thus, both groups displayed an increase in this score with a slightly larger increase in the finerenone group. For the KCCQ-TSS, the applicant conducted a responder analysis using thresholds determined in an anchor-based analysis for minimal and moderate improvement, respectively. The differences in the proportion of responders between the groups were on overall small but the proportion of responders were numerically increased in the finerenone group but was only nominally significant at 9 months for the minimally improved (OR 1.14 95% CI 1.01; 1.29) and the moderately improved (OR 1.18 95% CI 1.02; 1.37) thresholds. On a group level, the clinical relevance

of the improvements is thus questionable. Nevertheless, the findings confirms that the treatment is not related to a worsening in the patients' self-assessed health status.

For the secondary endpoint improvement in NYHA class from Baseline to Month 12 no significant difference was found between the study groups and the testing hierarchy was thus broken. The odds ratio finerenone/placebo was 1.01 (95% CI 0.88; 1.15).

The secondary renal composite endpoint time to first occurrence of the renal composite endpoint of sustained decrease in eGFR ≥50% relative to baseline over at least 4 weeks, or sustained eGFR decline to <15 ml/min/1.73m^2 or initiation of dialysis or renal transplantation was tested exploratively, and no significant difference was found between the groups (RR 1.33; 95% CI 0.94; 1.89). The point estimate was higher than unity and the early and sustained separated Aalen-Johansen estimate curves indicates an effect favouring placebo, however the events were relatively few. The effect was mainly caused by the components sustained eGFR decline ≥50% and sustained decline to <15 mL/min/1.73m^2, respectively. Given the established renoprotective effect in the currently approved population of T2D and CKD, this is an unexpected result. The study protocol was amended during the study, increasing the eGFR threshold from 40% to 50% for this secondary renal endpoint. The applicant has provided an exploratory analysis of the renal endpoint using the ≥40% threshold to provide data comparable to the FIDELIO/FIGARO studies; HR = 1.55 [95% CI 1.23; 1.94] yielding a nominally significant outcome in favour of placebo. The composite was almost exclusively driven by sustained eGFR decreases of at least 40%. The effects on GFR may be related to hemodynamic instability in this population and effects on GFR has been reported in earlier studies with MRAs. In order to understand the clinical relevance for this decline, the applicant was requested to provide additional data on reversibility. The FINEARTS-HF study did however not include an assessment of eGFR after study drug discontinuation limiting any conclusions on reversibility of drug induced reductions in eGFR. The applicant has furthermore discussed data from the phase 2 ARTS study showing a larger eGFR rebound upon treatment discontinuation in the finerenone vs. the placebo group (3.168 mL vs. -0.462 mL). However, it is difficult to translate small changes measured on a group level to the situation in patients initially experiencing a more substantial eGFR decline (i.e. 40% or 50%). Also, the phase 2 studies were conducted in a different patient population making conclusions on HFpEF uncertain. The ARTS study had a short treatment duration (4 weeks), and the longer ARTS-HF study (90 days) did not include a placebo group. Renal safety is further discussed in the Clinical Safety section of this report.

All-cause mortality was not part of the testing hierarchy. The point estimate was below unity but the differences between treatment groups were small (HR=0.93 95% CI 0.83; 1.06). CV death (8.1% vs. 8.7%) and undetermined death (2.1% vs. 2.6%) was lower in the finerenone group whereas non-CV death (6.2% vs. 6.1%) was similar in both treatment arms.

Subgroups

In the pre-specified subgroup (age, gender, race, region, BMI, LVEF, NYHA class, NT-proBNP, time of index HF event, SBP, eGFR, serum potassium, UACR, ACEi/ARB/ARNi, SGLT2 inhibitors, AF and T2D) the effect was in general consistent with the effect in the overall population. The relative risk (RR) was higher in the subgroup of patients without index HF event (or that had one earlier than 3 months prior to randomisation) than patients with an index HF event less than 7 days or between 7 days and 3 months before randomisation (RR 0.99 vs. RR 0.74 and 0.79). The general event rate/100 years was substantially lower in this group but it should be considered that the post-acute period of a HF event conventionally identifies a progression/worsening phase, implying important difference in haemodynamic aspects and therapeutic management compared to a more stable disease. Therefore, it cannot be excluded that the inconsistent performance of the finerenone arm by time from prior HF events implies a differential efficacy of the medicinal product when administrated either during the so-called vulnerability phase (conventionally covering up to 3 months post-event) or at later stages. The

inconsistency could however not be confirmed in an explorative time to first event of the primary endpoint. Furthermore, an exploratory analysis showed a similar reduction in NT-proBNP regardless of timing of the index event. Patients with eGFR ≥60 mL/min/1.73m^2 tended to have a more pronounced effect of the treatment than those with eGFR ≤60 mL/min/1.73m^2 (RR 0.72 vs. 0.91). In the subgroup analysis, RRs were higher for Asia (0.95) and North America (0.98) compared to the overall response (RR=0.84).

Exploratory analyses

For the time to first event analysis of the composite CV death or non-fatal CV event (HR 0.95 95% CI 0.86; 1.05) the point estimate was below unity. The estimate appears mainly influenced by hospitalisations for heart failure (14.2% vs. 16.5% in finerenone vs. placebo) whereas there was no difference in CV death (4.5% vs. 4.7% in finerenone vs. placebo). The incidences of non-fatal MI (2.3% [69 events] vs. 1.5% [44 events] in finerenone vs. placebo) and non-fatal stroke (2.7% [82 events] vs. 2.1% [64 events]) were however slightly higher in the finerenone group compared to placebo. The applicant has also provided an explorative time to first event analysis of 3-point MACE using all-cause mortality and cardiovascular mortality, respectively. The provided data indicate a neutral effect on MACE from the treatment.

The change in eGFR from baseline was assessed. Finerenone was associated with an acute reduction in eGFR vs. placebo. The maximum difference occurred at Month 6 (-3.53 mL/min/1.73m^2). The applicant has also conducted a slope analysis where a negative slope represents a worsening in eGFR. The chronic eGFR slope (assessed from 3 months) was within the same range in both treatment groups but numerically lower in the finerenone group (-0.96 vs. -1.15 mL/min/1.73m^2/year). The total eGFR slopes were instead numerically higher in the finerenone group vs. placebo, -3.80 vs. -0.95 mL/min/1.73m^2/year for the first year, the differences narrowing in during the two consecutive years). The data thus indicate that patient on average display a more pronounced decline in eGFR at the start of treatment in the finerenone group followed by a similar yearly decline in the two treatment arms.

Urine albumin creatinine ratios measured up to month 24 show a sustained ~25-30% reduction by finerenone compared to placebo from 3 month onwards, which is in line with findings from the previous FIDELIO-DKD and FIGARO-DKD studies.

The phase 2 dose finding studies did not include the 40 mg dose and the dose was selected based on PK/PD modelling. Given that the dose was titrated according to serum potassium and declines in eGFR during the study, data on efficacy strictly related to the different dose levels (10, 20 and 40 mg) is not available from the FINEARTS-HF study.

2.6.7. Conclusions on the clinical efficacy

The current application is based on efficacy data from the FINEARTS-HF study encompassing 6016 patients with a diagnosis of CHF, NYHA II-IV and LVEF ≥40% else treated with standard of care. Nearly all patients were treated with diuretics (87% loop diuretics, 14% thiazides), 79% with ACEI/ARBs, 14% with a SGLT-2 inhibitors and 9% with angiotensin receptor neprilysin inhibitor. Finerenone was superior to placebo in reducing the risk of the composite of CV death and total (first and recurrent) HF events (HHF or urgent HF visit) with on average 16% (RR=0.84; 95% CI 0.74; 0.95) which is considered a clinically relevant effect. The effect on the primary endpoint was mainly driven by an effect on HF events while the effect on CV death was more limited. The effect was in general consistently shown in important pre-defined subgroups.

2.6.8. Clinical safety

Finerenone is indicated for the treatment of chronic kidney disease (with albuminuria) associated with type 2 diabetes in adults. The main evidence to support the indication were the studies FIDELIO-DKD and FIGARO-DKD. FIDELITY is the pooled analysis of FIDELIO-DKD and FIGARO-DKD.

With this application, one pivotal phase 3 study, FINEARTS-HF, has been conducted in patients with HF (NYHA class II-IV) and LVEF ⩾40% treated with background therapy.

2.6.8.1. Patient exposure

In FINEARTS-HF, 5,986 patients were included, of which were 2,993 exposed to finerenone. The median duration of treatment was similar between finerenone (28 months; 6184 patient-years) and placebo (28 months; 6227 patient years). The mean duration of treatment was approximately 25 months. Approximately 80% of the study population were exposed for at least 12 months and 60% for at least 24 months.

2.6.8.2. Adverse events

The incidence of TEAEs was similar for finerenone (84.0%) and placebo (82.3%); however, the incidence of drug-related AEs was increased for finerenone (19.2%) compared with placebo (10.8%) (**Table 36**).

Table 33 Overview of TEAEs (SAF) – FINEARTS-HF and FIDELITY

	FINEARTS-HF				FIDELITY			
	Finerenone N=2993 n(%)	Finerenone N=2993 EAIR per 100 p-yr	Placebo N=2993 n(%)	Placebo N=2993 EAIR per 100 p-yr	Finerenone N=6489 n(%)	Finerenone N=6489 EAIR per 100 p-yr	Placebo N=6474 n(%)	Placebo N=6474 EAIR per 100 p-yr
Number (%) of subjects with adverse events								
Any AE	2515 (84.0%)	114.77	2464 (82.3%)	110.90	5582 (86.0%)	103.46	5592 (86.4%)	102.83
Maximum intensity for any AE								
MILD	821 (27.4%)	16.70	716 (23.9%)	14.07	1881 (29.0%)	14.37	1824 (28.2%)	13.58
MODERATE	1081 (36.1%)	22.85	1089 (36.4%)	22.89	2563 (39.5%)	20.29	2508 (38.7%)	19.57
SEVERE	613 (20.5%)	10.67	659 (22.0%)	11.47	1138 (17.5%)	7.40	1260 (19.5%)	8.13
Any study drug-related AE	576 (19.2%)	10.65	324 (10.8%)	5.59	1204 (18.6%)	8.16	859 (13.3%)	5.53
Maximum intensity for study drug-related AE								
MILD	321 (10.7%)	6.53	191 (6.4%)	3.75	680 (10.5%)	5.20	516 (8.0%)	3.84
MODERATE	217 (7.3%)	4.59	116 (3.9%)	2.44	439 (6.8%)	3.48	293 (4.5%)	2.29
SEVERE	38 (1.3%)	0.66	17 (0.6%)	0.30	85 (1.3%)	0.55	50 (0.8%)	0.32
Any AE related to procedures required by the protocol	34 (1.1%)	0.55	29 (1.0%)	0.47	121 (1.9%)	0.73	88 (1.4%)	0.52
Any AE leading to discontinuation of study drug	96 (3.2%)	1.55	83 (2.8%)	1.33	414 (6.4%)	2.49	350 (5.4%)	2.08
Any SAE	1157 (38.7%)	22.91	1213 (40.5%)	24.29	2054 (31.7%)	14.74	2181 (33.7%)	15.53
Results in Death	204 (6.8%)	3.29	239 (8.0%)	3.83	109 (1.7%)	0.65	151 (2.3%)	0.89
Requires or Prolongs Hospitalization	1045 (34.9%)	20.50	1071 (35.8%)	21.23	1968 (30.3%)	14.03	2078 (32.1%)	14.69
Life-threatening	115 (3.8%)	1.87	114 (3.8%)	1.85	100 (1.5%)	0.60	125 (1.9%)	0.74
Persist or Signif Disability/Incapacity	36 (1.2%)	0.58	35 (1.2%)	0.56	53 (0.8%)	0.32	65 (1.0%)	0.39
Other Medically Important Serious Event	166 (5.5%)	2.75	166 (5.5%)	2.73	347 (5.3%)	2.13	415 (6.4%)	2.53
Any study drug-related SAE	54 (1.8%)	0.88	24 (0.8%)	0.38	83 (1.3%)	0.50	61 (0.9%)	0.36
Any SAE related to procedures required by the protocol	0	0.00	2 (<0.1%)	0.03	5 (<0.1%)	0.03	4 (<0.1%)	0.02
Any SAE leading to discontinuation of study drug	37 (1.2%)	0.60	35 (1.2%)	0.56	145 (2.2%)	0.87	154 (2.4%)	0.91
Drug-related SAE with outcome death	0	0.00	0	0.00	0	0.00	2 (<0.1%)	0.01

Most frequently reported adverse events

The most commonly reported AEs that were reported more for frequently for finerenone than for placebo were "hyperkalaemia" (8.8% vs. 3.8%), "hypotension" (7.3% vs. 4.5%), "renal impairment" (6.6% vs. 3.9%), "dizziness" (5.8% vs. 4.7%), "diarrhoea" (5.7% vs. 4.4%), "GFR decreased" (5.2% vs. 3.6%), "constipation" (3.8% vs. 2.7%), "acute kidney injury (AKI)" (3.7% vs. 2.1%), "renal failure" (2.6% vs. 1.6%), "hyponatremia" (1.8% vs. 0.8%) and "blood creatinine increased (1.2% vs. 0.8%) (**Table 37**).

Table 34 TEAEs with a difference in reporting of ≥1% of participants between the treatment groups by preferred term (SAF) – FINEARTS-HF

Preferred Term MedDRA Version 27.0	**Finerenone** **N=2993 (100%)**	**Placebo** **N=2993 (100%)**
Difference of ≥1% of participants: higher frequency in finerenone		
Hyperkalaemia	264 (8.8%)	113 (3.8%)
Hypotension	218 (7.3%)	134 (4.5%)
Renal impairment	199 (6.6%)	117 (3.9%)
Dizziness	174 (5.8%)	141 (4.7%)
Diarrhoea	172 (5.7%)	132 (4.4%)
Glomerular filtration rate decreased	157 (5.2%)	108 (3.6%)
Constipation	114 (3.8%)	82 (2.7%)
Acute kidney injury	111 (3.7%)	64 (2.1%)
Renal failure	78 (2.6%)	47 (1.6%)
Hyponatraemia	54 (1.8%)	25 (0.8%)
Blood creatinine increased	36 (1.2%)	25 (0.8%)
Difference of ≥1% of participants: higher frequency in placebo		
Cardiac failure	129 (4.3%)	182 (6.1%)
Hypertension	108 (3.6%)	185 (6.2%)
Hypokalaemia	89 (3.0%)	200 (6.7%)
Iron deficiency anaemia	30 (1.0%)	59 (2.0%)

Adverse drug reactions

The incidence of drug-related TEAEs was higher for finerenone compared to placebo for "hyperkalaemia" (6.1% vs. 1.9%), "renal impairment" (2.8% vs. 1.2%), "hypotension (2.1% vs. 0.9%), "GFR decreased" (2.1% vs. 1.0%), "renal failure" (1.0% vs. 0.4%), "acute kidney injury" (1.0% vs. 0.2%), "dizziness" (1.0% vs. 0.7%), "diarrhoea" (0.9% vs. 0.4%), "blood potassium increased" (0.6% vs. 0.2%), "blood creatinine increased" (0.5% vs. 0.3%) and "constipation" (0.4% vs. <0.1%) (***Table 38***).

Table 35 Treatment-related TEAEs occurring in at least 0.5% of participants per study treatment group: number of participants and incidence rates by preferred term (SAF) – FINEARTS-HF and FIDELITY

	FINEARTS-HF				FIDELITY			
Preferred Term MedDRA Version 27.0	**Finerenone N=2993 (100%) n (%)**	**Finerenone EAIR per 100 pt-yrs**	**Placebo N=2993 (100%) n (%)**	**Placebo EAIR per 100 pt-yrs**	**Finerenone N=6489 (100%) n (%)**	**Finerenone EAIR per 100 pt-yrs**	**Placebo N=6474 (100%) n (%)**	**Placebo EAIR per 100 pt-yrs**
Number (%) of participants with at least one treatment-related TEAE	576 (19.2%)	10.65	324 (10.8%)	5.59	1204 (18.6%)	8.16	859 (13.3%)	5.53
Hyperkalaemia	182 (6.1%)	3.04	58 (1.9%)	0.94	496 (7.6%)	3.09	214 (3.3%)	1.29
Renal impairment	85 (2.8%)	1.40	36 (1.2%)	0.58	45 (0.7%)	0.27	38 (0.6%)	0.23
Hypotension	64 (2.1%)	1.05	28 (0.9%)	0.45	92 (1.4%)	0.56	33 (0.5%)	0.20
Glomerular filtration rate decreased	62 (2.1%)	1.01	30 (1.0%)	0.48	67 (1.0%)	0.40	33 (0.5%)	0.20
Renal failure	30 (1.0%)	0.49	13 (0.4%)	0.21	7 (0.1%)	0.04	9 (0.1%)	0.05
Acute kidney injury	29 (1.0%)	0.47	7 (0.2%)	0.11	53 (0.8%)	0.32	26 (0.4%)	0.15
Dizziness	29 (1.0%)	0.47	22 (0.7%)	0.35	52 (0.8%)	0.31	48 (0.7%)	0.29
Diarrhoea	26 (0.9%)	0.42	13 (0.4%)	0.21	54 (0.8%)	0.33	45 (0.7%)	0.27
Blood potassium increased	19 (0.6%)	0.31	6 (0.2%)	0.10	83 (1.3%)	0.50	39 (0.6%)	0.23
Blood creatinine increased	14 (0.5%)	0.23	9 (0.3%)	0.14	68 (1.0%)	0.41	57 (0.9%)	0.34
Constipation	12 (0.4%)	0.19	2 (<0.1%)	0.03	31 (0.5%)	0.19	35 (0.5%)	0.21

Adverse events are sorted by descending frequency in the FINEARTS-HF finerenone group.
EAIR = exposure-adjusted incidence rate, pt-yrs = patient-years, TEAE = treatment-emergent adverse event

Based on data from the FINEARTS-HF study, "diarrhoea" and "constipation" have been adequately included in the SmPC for Kerendia.

Adverse events of special interest

Hyperkalaemia

The incidence for finerenone versus placebo was approximately 2 times increased for TEAEs of hyperkalaemia (9.7% vs. 4.2%) and about 3 times increased for treatment-related hyperkalaemia (6.6% vs. 2.1%). Serious TEAEs of hyperkalaemia were reported 0.7% for finerenone and 0.2% for placebo. A higher proportion of patients in the finerenone group compared to placebo had incidences of serum potassium >5.5 mmol/L (14.0% vs 6.6%) and >6.0 mmol/L (2.9% vs 1.4%). The incidences of serum potassium >5.5 mmol/L and >6.0 mmol/L are in line with FIDELITY (**Table 39**).

Subgroup analyses of treatment-emergent hyperkalemia for FINEARTS-HF are presented in **Table 40**.

Table 36 Number of participants with treatment-emergent hyperkalaemia (based on MLG hyperkalaemia) including serum potassium values by category (SAF) – FINEARTS-HF and FIDELITY

	FINEARTS-HF		FIDELITY	
	Finerenone N=2993 (100%)	Placebo N=2993 (100%)	Finerenone N=6489 (100%)	Placebo N=6474 (100%)
Any treatment-emergent event	**289 (9.7%)**	**125 (4.2%)**	**908 (14.0%)**	**448 (6.9%)**
Treatment-related	197 (6.6%)	63 (2.1%)	571 (8.8%)	249 (3.8%)
Leading to permanent discontinuation	**13 (0.4%)**	**5 (0.2%)**	**110 (1.7%)**	**38 (0.6%)**
Serious	20 (0.7%)	6 (0.2%)	69 (1.1%)	16 (0.2%)
Treatment-related	16 (0.5%)	4 (0.1%)	43 (0.7%)	8 (0.1%)
Leading to permanent discontinuation	0	0	10 (0.2%)	2 (<0.1%)
Leading to hospitalization	**16 (0.5%)**	**6 (0.2%)**	**61 (0.9%)**	**10 (0.2%)**
Life-threatening	3 (0.1%)	0	4 (<0.1%)	5 (<0.1%)
Fatal	0	0	0	0
PT Hyperkalaemia	**264 (8.8%)**	**113 (3.8%)**	**779 (12.0%)**	**382 (5.9%)**
Treatment-related	182 (6.1%)	58 (1.9%)	496 (7.6%)	214 (3.3%)
Serious	19 (0.6%)	6 (0.2%)	65 (1.0%)	16 (0.2%)
Life-threatening	3 (0.1%)	0	3 (<0.1%)	5 (<0.1%)
PT Blood potassium increased	**30 (1.0%)**	**14 (0.5%)**	**149 (2.3%)**	**75 (1.2%)**
Treatment-related	19 (0.6%)	6 (0.2%)	83 (1.3%)	39 (0.6%)
Serious [b]	<1%	<1%	<1%	<1%
Life-threatening [b]	<0.1%	<0.1%	<0.1%	<0.1%
Serum potassium [a]	**Num/Den (%)**	**Num/Den (%)**	**Num/Den (%)**	**Num/Den (%)**
>5.5 mmol/L	401/2866 (14.0%)	190/2868 (6.6%)	1072/6382 (16.8%)	470/6355 (7.4%)
>6.0 mmol/L	85/2891 (2.9%)	41/2885 (1.4%)	211/6419 (3.3%)	80/6398 (1.3%)

Table 37 Number of subjects with treatment-emergent hyperkalaemia for selected subgroups (safety analysis set)

	FINEARTS-HF		FIDELITY	
Subgroup	Finerenone n/N (%)	Placebo n/N (%)	Finerenone n/N (%)	Placebo n/N (%)
Overall	289 /2993 (9.7%)	125 /2993 (4.2%)	908 /6489 (14.0%)	448 /6474 (6.9%)
Age group (years)				
<65 years	51 /641 (8.0%)	18 /619 (2.9%)	358 /2942 (12.2%)	238 /2914 (8.2%)
65 – <75 years	100 /1072 (9.3%)	40 /1103 (3.6%)	418 /2623 (15.9%)	158 /2577 (6.1%)
75 – <85 years	110 /1054 (10.4%)	56 /1029 (5.4%)	127 /877 (14.5%)	50 /928 (5.4%)
≥85 years	28 /226 (12.4%)	11 /242 (4.5%)	5 /47 (10.6%)	2 /55 (3.6%)
Sex				
Male	171 /1643 (10.4%)	72 /1619 (4.4%)	643 /4458 (14.4%)	304 /4583 (6.6%)
Female	118 /1350 (8.7%)	53 /1374 (3.9%)	265 /2031 (13.0%)	144 /1891 (7.6%)
Race				
White	212 /2357 (9.0%)	91 /2366 (3.8%)	539 /4441 (12.1%)	223 /4410 (5.1%)
Black or African American	3 /49 (6.1%)	1 /39 (2.6%)	42 /250 (16.8%)	12 /269 (4.5%)
Asian	61 /496 (12.3%)	30 /497 (6.0%)	285 /1414 (20.2%)	185 /1442 (12.8%)
Other	13 /91 (14.3%)	3 /91 (3.3%)	42 /384 (10.9%)	28 /353 (7.9%)
Baseline BMI (kg/m²)				
<25 kg/m²	67 /661 (10.1%)	30 /643 (4.7%)	146 /793 (18.4%)	86 /800 (10.8%)
25 – <30 kg/m²	100 /992 (10.1%)	43 /991 (4.3%)	306 /2138 (14.3%)	172 /2169 (7.9%)
30 – <35 kg/m²	68 /764 (8.9%)	38 /778 (4.9%)	253 /2020 (12.5%)	104 /1969 (5.3%)
≥35 kg/m²	54 /569 (9.5%)	14 /575 (2.4%)	199 /1517 (13.1%)	84 /1526 (5.5%)
Baseline eGFR (mL/min/1.73 m²) (KDIGO) category				
<30 mL/min/1.73 m²	27 /98 (27.6%)	9 /123 (7.3%)	114 /437 (26.1%)	56 /447 (12.5%)
30 – <60 mL/min/1.73 m²	165 /1348 (12.2%)	87 /1313 (6.6%)	598 /3460 (17.3%)	277 /3448 (8.0%)
60 – <90 mL/min/1.73 m²	86 /1273 (6.8%)	25 /1271 (2.0%)	175 /1934 (9.0%)	99 /1919 (5.2%)
≥90 mL/min/1.73 m²	11 /274 (4.0%)	4 /286 (1.4%)	21 /658 (3.2%)	16 /659 (2.4%)
Baseline eGFR (mL/min/1.73m²)				
<60 mL/min/1.73m²	192/1446 (13.3%)	96/1436 (6.7%)	712/3897 (18.3%)	333/3895 (8.5%)
≥60 mL/min/1.73m²	97/1547 (6.3%)	29/1557 (1.9%)	196/2592 (7.6%)	115/2578 (4.5%)
Medical history: Hyperkalemia				
NO	285/2980 (9.6%)	123/2985 (4.1%)	865/6377 (13.6%)	429/6362 (6.7%)
YES	4/13 (30.8%)	2/8 (25.0%)	43/112 (38.4%)	19/112 (17.0%)
Baseline serum potassium (mmol/L) category				
≤4.5 mmol/L	126/1965 (6.4%)	46/1954 (2.4%)	489/4505 (10.9%)	218/4454 (4.9%)
>4.5 mmol/L	163/1028 (15.9%)	79/1039 (7.6%)	419/1984 (21.1%)	230/2018 (11.4%)
Baseline albuminuria (mg/g) category				
Normal (UACR <30 mg/g)	139/1757 (7.9%)	51/1743 (2.9%)	15/120 (12.5%)	2/109 (1.8%)
High (30 mg/g – <300 mg/g)	77 /843 (9.1%)	49 /868 (5.6%)	294/2063 (14.3%)	134/2009 (6.7%)
Very high (≥300 mg/g)	63/292 (21.6%)	21/281 (7.5%)	599/4305 (13.9%)	312/4354 (7.2%)
SGLT-2 inhibitors use at baseline				
No	246/2601 (9.5%)	102/2570 (4.0%)	863/6054 (14.3%)	436/6037 (7.2%)
Yes	43/392 (11.0%)	23/423 (5.4%)	45/435 (10.3%)	12/437 (2.7%)
Loop diuretic use at baseline				
No	30/383 (7.8%)	14/377 (3.7%)	682/5110 (13.3%)	344/5061 (6.8%)
Yes	259/2610 (9.9%)	111/2616 (4.2%)	226/1379 (16.4%)	104/1413 (7.4%)
Thiazide diuretic use at baseline				
No	254/2567 (9.9%)	112/2592 (4.3%)	693/4888 (14.2%)	375/4937 (7.6%)
Yes	35/426 (8.2%)	13/401 (3.2%)	215/1601 (13.4%)	73/1537 (4.7%)

BMI = body mass index, eGFR = estimated glomerular filtration rate, KDIGO = Kidney Disease Improving Global Outcomes, SGLT-2 = sodium-glucose co-transporter-2, UACR = urinary albumin-to-creatinine ratio

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

Worsening of renal function

TEAEs related to "worsening of renal function" were reported more frequently in the finerenone group (17.7%) than in the placebo group (10.9%), including "renal impairment" (6.6% vs. 3.9%), "acute kidney injury" (3.7% vs. 2.1%), "renal failure" (2.6% vs. 1.6%), "decreased GFR" (5.2% vs. 3.6%) and "blood creatinine increased" (1.2% vs. 0.8%).

Serious TEAEs of "worsening renal function" were increased for finerenone (2.4%) compared to placebo (1.5%), including serious TEAEs of AKI (1.8% vs. 0.9%).

The incidence of treatment-related TEAEs of "worsening of renal function" was higher for finerenone (7.1%) compared to placebo (3.0%), including for "renal impairment" (2.8% vs. 1.2%), "acute kidney injury" (1.0 vs 0.2%), "renal failure" (1.0% vs. 0.4%) and "GFR decreased" (2.1% vs. 1.0%).

TEAEs of "worsening of renal function" requiring hospitalization were more frequent in the finerenone group (2.0%) than in the placebo group (1.3%), of which "acute kidney injury" was the most frequently reported renal event with the incidence 1.6% for finerenone and 0.8% for placebo (**Table 41**).

There was a more pronounced decrease in eGFR in the finerenone group compared with placebo group, with a mean difference of approximately 3-4 mL/min/1.73 m^2 from week 4 to 28. From week 28 and onwards the eGFR declined slightly more in the placebo group, with a mean difference between finerenone and placebo of approximately 2-3 mL/min/1.73 m^2 (**Figure 7**). More subjects in the finerenone group compared to placebo had a relative eGFR decrease of ≥30% (33.5% vs. 20.4%), ≥40% (16.3% vs. 9.5%), ≥50 % (6.9% vs. 4.0%) and ≥57 % (3.4% vs. 2.1%) (**Table 41**).

The cumulative incidence for time to first TEAE of worsening of renal function (PTs "renal impairment", "renal failure", "postrenal failure", "prerenal failure", "AKI", "glomerular filtration rate decreased" and "blood creatinine increased") was 23.7% for finerenone and 15.0% for placebo, whereas in FIDELITY, the cumulative incidence was 17.5% and 15.7% for finerenone and placebo (**Figure 8**).

Subgroup analyses of TEAEs of worsening of renal function for FINEARTS-HF are presented in **Table 42**. The incidence of TEAEs of "worsening of renal function" was increased in the finerenone group compared to placebo in both the eGFR ≤60 (23.6% vs. 15.5%) and eGFR >60 (12.2% vs. 6.7%) subgroups. In addition, the incidence of TEAEs of "worsening of renal function" was higher for finerenone compared to placebo in both subgroups, i.e., with and without, background medication of SGLT-2 inhibitors, NSAIDs, loop diuretics and thiazides diuretics, respectively.

The exposure differs between patients in FINEARTS-HF and patients in FIDELITY, meaning that patients exposed to 20 mg finerenone in FINEARTS-HF corresponds to approximately 35-40% higher exposure compared to patients exposed to 20 mg finerenone in FIDELITY. Due to confounding factors, no firm conclusions could be drawn from the performed PK exposure-response analysis as to whether the risk is increased in patients with documented higher exposure. There was no indication of a dose-dependent difference in the incidence of TEAEs of "worsening of renal function" between subjects who had received a higher versus a lower dose of finerenone at the time of the reported renal event.

The outcome of TEAEs of "worsening of renal function" was reported as not recovered/resolved or resolved with sequelae in 20-22% for "GFR decreased", in 29-33% for "renal impairment", in 21-25% for "AKI" and in 37-38% for "renal failure" for finerenone and placebo (**Table 43**). Approximately one third (27%) of the finerenone cases reporting TEAEs of "worsening of renal function" had the outcome "not resolved/ resolved with sequelae). In some cases where finerenone was permanently discontinued, eGFR did not return to baseline levels. This has been reflected in the product information.

Table 38 Number of participants with treatment-emergent worsening of renal function including serum laboratory eGFR values by category (SAF) – FINEARTS-HF and FIDELITY

	FINEARTS-HF		FIDELITY	
	Finerenone N=2993 (100%)	**Placebo N=2993 (100%)**	**Finerenone N=6489 (100%)**	**Placebo N=6474 (100%)**
Any treatment-emergent event	**530 (17.7%)**	**327 (10.9%)**	**885 (13.6%)**	**790 (12.2%)**
Treatment-related	212 (7.1%)	91 (3.0%)	225 (3.5%)	155 (2.4%)
Leading to permanent discontinuation	9 (0.3%)	10 (0.3%)	52 (0.8%)	42 (0.6%)
Serious	71 (2.4%)	44 (1.5%)	125 (1.9%)	128 (2.0%)
Treatment-related	24 (0.8%)	9 (0.3%)	23 (0.4%)	15 (0.2%)
Leading to permanent discontinuation	2 (<0.1%)	3 (0.1%)	15 (0.2%)	10 (0.2%)
Leading to hospitalization	59 (2.0%)	40 (1.3%)	110 (1.7%)	112 (1.7%)
Life-threatening	8 (0.3%)	3 (0.1%)	0	4 (<0.1%)
Fatal	1 (<0.1%)	0	0	1 (<0.1%)
Relevant PTs				
Renal impairment	**199 (6.6%)**	**117 (3.9%)**	**177 (2.7%)**	**159 (2.5%)**
Treatment-related	85 (2.8%)	36 (1.2%)	45 (0.7%)	38 (0.6%)
Leading to hospitalization	7 (0.2%)	10 (0.3%)	9 (0.1%)	10 (0.2%)
Leading to permanent discontinuation	5 (0.2%)	3 (0.1%)	10 (0.2%)	10 (0.2%)
SAE	10 (0.3%)	11 (0.4%)	10 (0.2%)	12 (0.2%)
Leading to death	0	0	0	0
Glomerular filtration rate decreased	**157 (5.2%)**	**108 (3.6%)**	**348 (5.4%)**	**274 (4.2%)**
Treatment-related	62 (2.1%)	30 (1.0%)	67 (1.0%)	33 (0.5%)
Leading to hospitalization	1 (<0.1%)	1 (<0.1%)	6 (<0.1%)	4 (<0.1%)
Leading to permanent discontinuation	1 (<0.1%)	3 (0.1%)	16 (0.2%)	12 (0.2%)
SAE	1 (<0.1%)	1 (<0.1%)	9 (0.1%)	5 (<0.1%)
Leading to death	0	0	0	0
Acute kidney injury	**111 (3.7%)**	**64 (2.1%)**	**220 (3.4%)**	**234 (3.6%)**
Treatment-related	29 (1.0%)	7 (0.2%)	53 (0.8%)	26 (0.4%)
Leading to hospitalization	48 (1.6%)	25 (0.8%)	85 (1.3%)	86 (1.3%)
Leading to permanent discontinuation	1 (<0.1%)	2 (<0.1%)	14 (0.2%)	10 (0.2%)
SAE	54 (1.8%)	28 (0.9%)	94 (1.4%)	97 (1.5%)
Leading to death	1 (<0.1%)	0	0	1 (<0.1%)
Renal failure	**78 (2.6%)**	**47 (1.6%)**	**42 (0.6%)**	**36 (0.6%)**
Treatment-related	30 (1.0%)	13 (0.4%)	7 (0.1%)	9 (0.1%)
Leading to hospitalization	5 (0.2%)	4 (0.1%)	10 (0.2%)	9 (0.1%)
Leading to permanent discontinuation	2 (<0.1%)	2 (<0.1%)	5 (<0.1%)	5 (<0.1%)
SAE	8 (0.3%)	5 (0.2%)	11 (0.2%)	9 (0.1%)
Leading to death	0	0	0	0
Blood creatinine increased	**36 (1.2%)**	**25 (0.8%)**	**169 (2.6%)**	**151 (2.3%)**
Treatment-related	14 (0.5%)	9 (0.3%)	68 (1.0%)	57 (0.9%)
Leading to hospitalization	0	0	2 (<0.1%)	5 (<0.1%)
Leading to permanent discontinuation	0	0	7 (0.1%)	6 (<0.1%)
SAE	0	0	3 (<0.1%)	7 (0.1%)
Leading to death	0	0	0	0
Treatment-emergent relative eGFR decrease [a]	**n=2897 n* (%)**	**n=2888 n* (%)**	**n=6422 n* (%)**	**n=6402 n* (%)**
≥30%	971 (33.5%)	590 (20.4%)	2728 (42.5%)	2365 (36.9%)
≥40%	472 (16.3%)	273 (9.5%)	1395 (21.7%)	1302 (20.3%)
≥50%	201 (6.9%)	116 (4.0%)	632 (9.8%)	683 (10.7%)
≥57%	98 (3.4%)	62 (2.1%)	316 (4.9%)	404 (6.3%)

[a] n = participants at risk for a treatment-emergent laboratory abnormality (participants must have both a baseline and post-baseline treatment-emergent value); n* = number of participants with treatment-emergent safety event; % = n*/n

Table 39 Number of participants with treatment-emergent worsening renal function events by list of PTs by selected subgroups (SAF) – FINEARTS-HF and FIDELITY

	FINEARTS-HF		FIDELITY	
Subgroup	Finerenone n/N (%)	Placebo n/N (%)	Finerenone n/N (%)	Placebo n/N (%)
Overall	**530 /2993 (17.7%)**	**327 /2993 (10.9%)**	**885 /6489 (13.6%)**	**790 /6474 (12.2%)**
Age group (years)				
<65 years	82 /641 (12.8%)	53 /619 (8.6%)	383 /2942 (13.0%)	353 /2914 (12.1%)
65 – <75 years	178 /1072 (16.6%)	111 /1103 (10.1%)	382 /2623 (14.6%)	316 /2577 (12.3%)
75 – <85 years	217 /1054 (20.6%)	130 /1029 (12.6%)	112 /877 (12.8%)	114 /928 (12.3%)
≥85 years	53 /226 (23.5%)	33 /242 (13.6%)	8 /47 (17.0%)	7 /55 (12.7%)
Sex				
Male	305 /1643 (18.6%)	176 /1619 (10.9%)	615 /4458 (13.8%)	578 /4583 (12.6%)
Female	225 /1350 (16.7%)	151 /1374 (11.0%)	270 /2031 (13.3%)	212 /1891 (11.2%)
Race				
White	407 /2357 (17.3%)	262 /2366 (11.1%)	607 /4441 (13.7%)	508 /4410 (11.5%)
Black or African American	11 /49 (22.4%)	7 /39 (17.9%)	41 /250 (16.4%)	47 /269 (17.5%)
Asian	97 /496 (19.6%)	42 /497 (8.5%)	139 /1414 (9.8%)	159 /1442 (11.0%)
Other	15 /91 (16.5%)	16 /91 (17.6%)	98 /384 (25.5%)	76 /353 (21.5%)
Baseline BMI (kg/m^2)				
<25 kg/m^2	118 /661 (17.9%)	69 /643 (10.7%)	90 /793 (11.3%)	89 /800 (11.1%)
25 – <30 kg/m^2	172 /992 (17.3%)	110 /991 (11.1%)	281 /2138 (13.1%)	243 /2169 (11.2%)
30 – <35 kg/m^2	120 /764 (15.7%)	81 /778 (10.4%)	276 /2020 (13.7%)	244 /1969 (12.4%)
≥35 kg/m^2	118 /569 (20.7%)	66 /575 (11.5%)	235 /1517 (15.5%)	213 /1526 (14.0%)
Baseline eGFR (mL/min/1.73 m^2) (KDIGO)				
<30 mL/min/1.73 m^2	35 /98 (35.7%)	23 /123 (18.7%)	79 /437 (18.1%)	92 /447 (20.6%)
30 – <60 mL/min/1.73 m^2	306 /1348 (22.7%)	200 /1313 (15.2%)	565 /3460 (16.3%)	480 /3448 (13.9%)
60 – <90 mL/min/1.73 m^2	169 /1273 (13.3%)	95 /1271 (7.5%)	201 /1934 (10.4%)	178 /1919 (9.3%)
≥90 mL/min/1.73 m^2	20 /274 (7.3%)	9 /286 (3.1%)	40 /658 (6.1%)	40 /659 (6.1%)
Baseline eGFR (mL/min/1.73 m^2) category				
eGFR <60	341/1446 (23.6%)	223/1436 (15.5%)	644/3897 (16.5%)	572/3895 (14.7%)
eGFR ≥60	189/1547 (12.2%)	104/1557 (6.7%)	241/2592 (9.3%)	218/2578 (8.5%)
Baseline albuminuria (mg/g) category				
Normal (UACR < 30 mg/g)	245/1757 (13.9%)	150/1743 (8.6%)	13/120 (10.8%)	5/109 (4.6%)
High (30 mg/g - < 300 mg/g)	175/843 (20.8%)	110/868 (12.7%)	281/2063 (13.6%)	236/2009 (11.7%)
Very high (≥300 mg/g)	87/292 (29.8%)	54/281 (19.2%)	591/4305 (13.7%)	549/4354 (12.6%)
SGLT-2 inhibitors use at baseline				
No	455/2601 (17.5%)	278/2570 (10.8%)	841/6054 (13.9%)	750/6037 (12.4%)
Yes	75/392 (19.1%)	49/423 (11.6%)	44 /435 (10.1%)	40/437 (9.2%)
NSAIDs (excl. acetylsalicylic acid) use at baseline				
No	494/2844 (17.4%)	308/2858 (10.8%)	825/6077 (13.6%)	749/6067 (12.3%)
Yes	36/149 (24.2%)	19/135 (14.1%)	60/412 (14.6%)	41/407 (10.1%)
Loop diuretic use at baseline (yes/no)				
No	56/383 (14.6%)	33 /377 (8.8%)	600/5110 (11.7%)	546/5061 (10.8%)
Yes	474/2610 (18.2%)	294/2616 (11.2%)	285/1379 (20.7%)	244/1413 (17.3%)
Thiazide diuretic use at baseline (yes/no)				
No	462/2567 (18.0%)	278/2592 (10.7%)	654/4888 (13.4%)	591/4937 (12.0%)
Yes	68/426 (16.0%)	49/401 (12.2%)	231/1601 (14.4%)	199/1537 (12.9%)

The following PTs were searched: Acute kidney injury, Blood creatinine increased, Glomerular filtration rate decreased, Postrenal failure, Prerenal failure, Renal failure, Renal impairment

BMI = body mass index, eGFR = estimated glomerular filtration rate, KDIGO = Kidney Disease Improving Global Outcomes, NSAIDs = nonsteroidal anti-inflammatory drugs, PT = preferred term, SGLT-2 = sodium-glucose co-transporter-2, UACR = urinary albumin-to-creatinine ratio

Figure 7 eGFR (mL/min/1.73 m^2, in blood) - CKD-EPI: mean change from baseline by visit with 95% CIs (SAF) – FINEARTS-HF

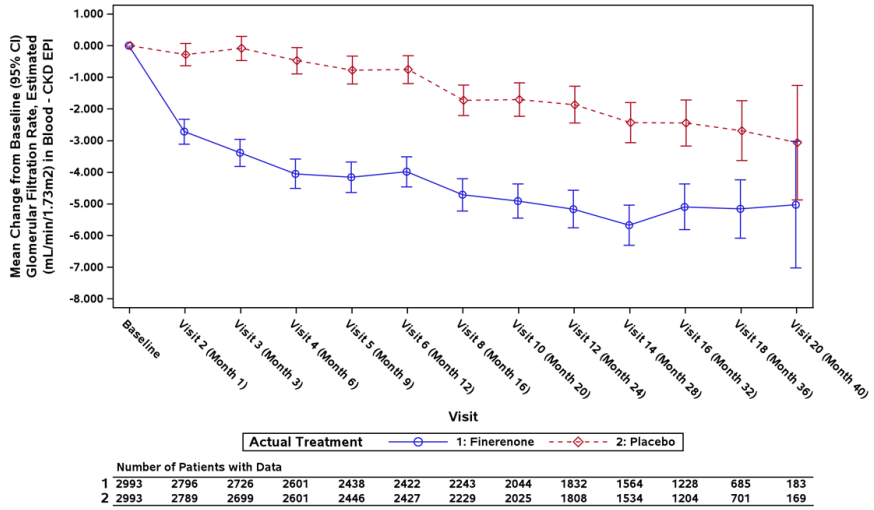
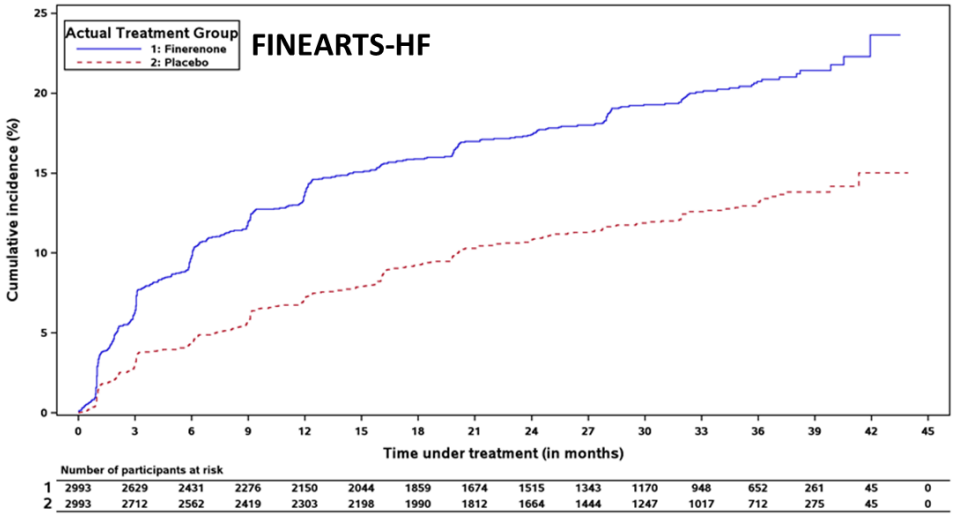


Figure 8 Cumulative incidence based on Aalen-Johansen estimates for time to first treatment-emergent worsening of renal function event (SAF) – FINEARTS-HF and FIDELITY



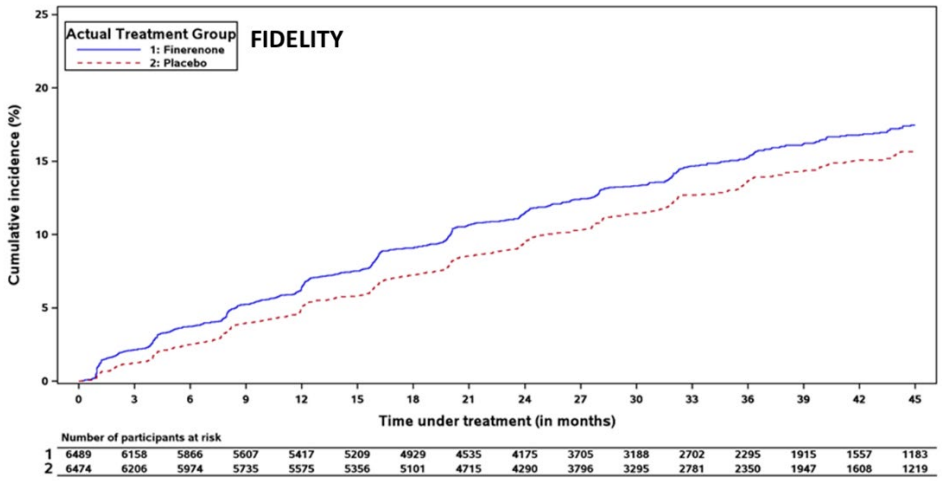


Table 40 Worsening renal function: Treatment-emergent adverse events by worst outcome

Primary system organ class / Preferred term / MedDRA version 27.0	Worst outcome	FINEARTS-HF Finerenone N=2993 (100%)	FINEARTS-HF Placebo N=2993 (100%)	FIDELITY Finerenone N=6489 (100%)	FIDELITY Placebo N=6474 (100%)
Glomerular filtration rate decreased	UNKNOWN	3 (0.1%)	1 (<0.1%)	3 (<0.1%)	3 (<0.1%)
	RECOVERED/ RESOLVED	87 (2.9%)	62 (2.1%)	204 (3.1%)	149 (2.3%)
	RECOVERING/ RESOLVING	35 (1.2%)	21 (0.7%)	40 (0.6%)	33 (0.5%)
	RECOVERED/ RESOLVED WITH SEQUELAE	3 (0.1%)	0	4 (<0.1%)	2 (<0.1%)
	NOT RECOVERED/ NOT RESOLVED	29 (1.0%)	24 (0.8%)	97 (1.5%)	87 (1.3%)
	Total	157 (5.2%)	108 (3.6%)	348 (5.4%)	274 (4.2%)
Renal impairment	UNKNOWN	0	1 (<0.1%)	1 (<0.1%)	5 (<0.1%)
	RECOVERED/ RESOLVED	108 (3.6%)	57 (1.9%)	98 (1.5%)	76 (1.2%)
	RECOVERING/ RESOLVING	33 (1.1%)	20 (0.7%)	22 (0.3%)	13 (0.2%)
	RECOVERED/ RESOLVED WITH SEQUELAE	3 (0.1%)	4 (0.1%)	3 (<0.1%)	1 (<0.1%)
	NOT RECOVERED/ NOT RESOLVED	55 (1.8%)	35 (1.2%)	53 (0.8%)	64 (1.0%)
	Total	199 (6.6%)	117 (3.9%)	177 (2.7%)	159 (2.5%)
Renal failure	RECOVERED/ RESOLVED	40 (1.3%)	21 (0.7%)	25 (0.4%)	22 (0.3%)
	RECOVERING/ RESOLVING	9 (0.3%)	8 (0.3%)	1 (<0.1%)	1 (<0.1%)
	RECOVERED/ RESOLVED WITH SEQUELAE	1 (<0.1%)	0	0	0
	NOT RECOVERED/ NOT RESOLVED	28 (0.9%)	18 (0.6%)	16 (0.2%)	13 (0.2%)
	Total	78 (2.6%)	47 (1.6%)	42 (0.6%)	36 (0.6%)
Acute kidney injury	RECOVERED/ RESOLVED	85 (2.8%)	47 (1.6%)	188 (2.9%)	183 (2.8%)
	RECOVERING/ RESOLVING	3 (0.1%)	1 (<0.1%)	13 (0.2%)	11 (0.2%)
	RECOVERED/ RESOLVED WITH SEQUELAE	1 (<0.1%)	2 (<0.1%)	4 (<0.1%)	7 (0.1%)
	NOT RECOVERED/ NOT RESOLVED	21 (0.7%)	14 (0.5%)	15 (0.2%)	32 (0.5%)
	FATAL	1 (<0.1%)	0	0	1 (<0.1%)
	Total	111 (3.7%)	64 (2.1%)	220 (3.4%)	234 (3.6%)
Blood creatinine increased	UNKNOWN	0	0	2 (<0.1%)	1 (<0.1%)
	RECOVERED/ RESOLVED	20 (0.7%)	16 (0.5%)	95 (1.5%)	72 (1.1%)
	RECOVERING/ RESOLVING	6 (0.2%)	1 (<0.1%)	14 (0.2%)	15 (0.2%)
	RECOVERED/ RESOLVED WITH SEQUELAE	1 (<0.1%)	0	1 (<0.1%)	3 (<0.1%)
	NOT RECOVERED/ NOT RESOLVED	9 (0.3%)	8 (0.3%)	57 (0.9%)	60 (0.9%)
	Total	36 (1.2%)	25 (0.8%)	169 (2.6%)	151 (2.3%)

The current section 4.8 of the SmPC for Kerendia includes "GFR decreased" (common). The MAH has proposed to include "blood creatinine increased" (frequency: common) in section 4.8 of the SmPC. This is endorsed. Increased blood creatinine is expected as serum creatinine is a marker of renal function, and creatinine increases with decreases in renal function. Based on data from the FINEART-HF study, "renal impairment" and " acute kidney injury" have been included in the SmPC for Kerendia.

2.6.8.3. Serious adverse event/deaths/other significant events

Serious adverse events

The incidence of serious TEAEs was comparable for finerenone (39%) and placebo (40%) (**Table 44**). The most common serious TEAEs for finerenone compared to placebo were pneumonia (2.9% vs. 3.7%), atrial fibrillation (2.6% vs. 2.4%), and COVID-19 (2.3% vs. 2.4%) were reported with no differences between the treatment groups or less frequently in the placebo arm. AKI as a serious TEAE was reported more frequently in participants in the finerenone group (1.8%) compared to participants receiving placebo (0.9%).

Table 41 Serious TEAEs occurring in at least 1% per study treatment group: number of participants and incidence rates by preferred term (SAF) – FINEARTS-HF and FIDELITY

	FINEARTS-HF				FIDELITY			
Preferred Term MedDRA Version 27.0	**Finerenone N=2993 (100%) n (%)**	**Finerenone EAIR per 100 pt-yr**	**Placebo N=2993 (100%) n (%)**	**Placebo EAIR per 100 pt-yr**	**Finerenone N=6489 (100%) n (%)**	**Finerenone EAIR per 100 pt-yr**	**Placebo N=6474 (100%) n (%)**	**Placebo EAIR per 100 pt-yr**
Number (%) of participants with at least one serious TEAE	1157 (38.7%)	22.91	1213 (40.5%)	24.29	2054 (31.7%)	14.74	2181 (33.7%)	15.53
Pneumonia	87 (2.9%)	1.41	110 (3.7%)	1.78	142 (2.2%)	0.86	216 (3.3%)	1.30
Atrial fibrillation	77 (2.6%)	1.26	73 (2.4%)	1.19	3 (<0.1%)	0.02	4 (<0.1%)	0.02
COVID-19	69 (2.3%)	1.13	71 (2.4%)	1.15	17 (0.3%)	0.10	22 (0.3%)	0.13
Acute kidney injury	54 (1.8%)	0.88	28 (0.9%)	0.45	94 (1.4%)	0.57	97 (1.5%)	0.58
Angina unstable	38 (1.3%)	0.62	36 (1.2%)	0.58	4 (<0.1%)	0.02	6 (<0.1%)	0.04
Anaemia	34 (1.1%)	0.55	31 (1.0%)	0.50	32 (0.5%)	0.19	34 (0.5%)	0.20
Death	29 (1.0%)	0.47	52 (1.7%)	0.83	10 (0.2%)	0.06	10 (0.2%)	0.06
COVID-19 pneumonia	28 (0.9%)	0.45	30 (1.0%)	0.48	8 (0.1%)	0.05	11 (0.2%)	0.07
Hyperkalaemia	19 (0.6%)	0.31	6 (0.2%)	0.10	65 (1.0%)	0.39	16 (0.2%)	0.09
Cellulitis	17 (0.6%)	0.27	24 (0.8%)	0.38	66 (1.0%)	0.40	50 (0.8%)	0.30

Adverse events are sorted by descending frequency in the FINEARTs-HF finerenone group.
EAIR = exposure-adjusted incidence rate, p-yr = patient-years, TEAE = treatment-emergent adverse event

Deaths

The incidence of fatal outcome or AEs was 16.5% in the finerenone group and 17.6% in the placebo group. There were more fatal cases in FINEARTS-HF, in both treatment groups, compared to FIDELITY due to the underlying HF condition (**Table 45**).

Table 42 Deaths: overview of number of participants with a fatal event (SAF) – FINEARTS-HF and FIDELITY

	FINEARTS-HF		FIDELITY	
	Finerenone N=2993 (100%)	Placebo N=2993 (100%)	Finerenone N=6489 (100%)	Placebo N=6474 (100%)
Total number of deaths	**494 (16.5%)**	**528 (17.6%)**	**557 (8.6%)**	**631 (9.7%)**
TEAE with fatal outcome	204 (6.8%)	239(8.0%)	109 (1.7%)	151 (2.3%)
Post-intervention fatal AE	178 (5.9%)	164 (5.5%)	136 (2.1%)	140 (2.2%)
Deaths not attributed to an AE	112 (3.7%)	125 (4.2%)	312 (4.8%)	340 (5.3%)

All investigator-reported deaths are included in this table.
Death not attributed to an AE could be an event cardiovascular death collected separately as efficacy event or death outside the AE collection period. Post-treatment AEs: FINEARTS-HF: AEs occurring more than 3 days after permanent stop of study intervention. FIDELITY: AEs occurring more than 3 days after any temporary stop of study intervention are included.
If a participant experienced both a TEAE and a post-treatment AE with fatal outcome, event is only counted as a TEAE with fatal outcome in this table.AE = adverse event, TEAE = treatment-emergent adverse event

2.6.8.4. Laboratory findings

Haematology

In FINEARTS-HF, the decrease in TEAE mean haemoglobin was 0.2% in the finerenone group and 0.5% in the placebo group. The decrease in mean haematocrit was <0.1% in the finerenone group and placebo group, respectively.

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

Serum sodium

An initial decrease in mean serum sodium of approximately 0.8 mmol/L was observed in the finerenone group at month 1 and remained lower thereafter. In FINEARTS-HF, hyponatraemia occurred more frequently for finerenone (1.8%) compared to placebo (0.8%).

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

Serum potassium

See section 3.3.7.2 (Adverse events of special interest: Hyperkalaemia).

eGFR changes

See section 3.3.7.2 (Adverse events of special interest: Worsening of renal function).

Creatinine changes

See section 3.3.7.2 (Adverse events of special interest: Worsening of renal function).

Vital signs

Blood pressure

In FINEARTS-HF, blood pressure decreased in the finerenone group compared to placebo (mean SBP by approximately 2-3 mmHg and mean DPB by approximately 1-2 mmHg).

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

ECG

In FINEARTS-HF, a local ECG was only done at baseline to assess the selection criteria for the study. Adverse events related to QT prolongation were infrequent and balanced between the finerenone group and the placebo group (each 0.1%).

2.6.8.5. In vitro biomarker test for patient selection for safety

N/A

2.6.8.6. Safety in special populations

Effect by age

In FINEARTS-HF, the reporting rate generally increased with increasing age in both treatment groups. The incidence of TEAEs of "hyperkalaemia" (age group <65 years: 8.0% vs. 2.9%; 65≤75 years: 9.3% vs. 3.6%; 75≤85 years: 10.4% vs 5.4%) and "worsening of renal function" (age group <65 years: 12.8% vs. 8.6%; 65≤75 years: 16.6% vs. 10.1%; 75≤85 years: 20.6% vs 12.6%) was higher in older patients compared to younger and was increased for finerenone compared to placebo across the age groups (**Table 40, Table 42**). Elderly HF patients and patients with impaired renal function (eGFR <60 mL/min/1.73 m²) are considered to be at higher risk of TEAEs of worsening of renal function and more frequent monitoring is recommended.

Effect by race

In FINEARTS-HF, the incidence of TEAEs was balanced between treatment groups in White and Asian and was slightly higher for finerenone compared to placebo in Black and Other subjects. However, the portion of Black participants and Other subjects, respectively, were small and results should be interpreted with caution. A slightly higher proportion of participants with TEAEs across the various TEAE categories was observed in participants of Asian race compared to other race groups as well as to the overall population **Table 46**.

Table 43 Overview of TEAEs by race (SAF) – FINEARTS-HF

	White		Black		Asian		Other	
Number (%) of participants with TEAE	Finerenone N=2357	Placebo N=2366	Finerenone N=49	Placebo N=39	Finerenone N=496	Placebo N=497	Finerenone N=91	Placebo N=91
Any AE	1940 (82.3%)	1913 (80.9%)	42 (85.7%)	28 (71.8%)	452 (91.1%)	450 (90.5%)	81 (89.0%)	73 (80.2%)
Maximum intensity for any AE								
Mild	608 (25.8%)	532 (22.5%)	7 (14.3%)	3 (7.7%)	179 (36.1%)	168 (33.8%)	27 (29.7%)	13 (14.3%)
Moderate	842 (35.7%)	876 (37.0%)	25 (51.0%)	9 (23.1%)	177 (35.7%)	164 (33.0%)	37 (40.7%)	40 (44.0%)
Severe	490 (20.8%)	505 (21.3%)	10 (20.4%)	16 (41.0%)	96 (19.4%)	118 (23.7%)	17 (18.7%)	20 (22.0%)
Any study treatment-related AE	425 (18.0%)	241 (10.2%)	9 (18.4%)	4 (10.3%)	127 (25.6%)	71 (14.3%)	15 (16.5%)	8 (8.8%)
Maximum intensity for study treatment-related AE								
Mild	220 (9.3%)	138 (5.8%)	3 (6.1%)	3 (7.7%)	88 (17.7%)	44 (8.9%)	10 (11.0%)	6 (6.6%)
Moderate	172 (7.3%)	93 (3.9%)	6 (12.2%)	1 (2.6%)	35 (7.1%)	20 (4.0%)	4 (4.4%)	2 (2.2%)
Severe	33 (1.4%)	10 (0.4%)	0	0	4 (0.8%)	7 (1.4%)	1 (1.1%)	0
Any AE related to procedures required by the protocol	20 (0.8%)	20 (0.8%)	1 (2.0%)	0	12 (2.4%)	8 (1.6%)	1 (1.1%)	1 (1.1%)
Any AE leading to discontinuation of study treatment	79 (3.4%)	67 (2.8%)	2 (4.1%)	1 (2.6%)	14 (2.8%)	12 (2.4%)	1 (1.1%)	3 (3.3%)
Any SAE	910 (38.6%)	939 (39.7%)	16 (32.7%)	22 (56.4%)	202 (40.7%)	220 (44.3%)	29 (31.9%)	32 (35.2%)
Results in death	175 (7.4%)	192 (8.1%)	2 (4.1%)	3 (7.7%)	25 (5.0%)	39 (7.8%)	2 (2.2%)	5 (5.5%)
Requires or prolongs hospitalization	814 (34.5%)	825 (34.9%)	15 (30.6%)	20 (51.3%)	187 (37.7%)	197 (39.6%)	29 (31.9%)	29 (31.9%)
Life-threatening	102 (4.3%)	101 (4.3%)	0	1 (2.6%)	9 (1.8%)	11 (2.2%)	4 (4.4%)	1 (1.1%)
Any study treatment-related SAE	45 (1.9%)	19 (0.8%)	0	0	8 (1.6%)	5 (1.0%)	1 (1.1%)	0
Any SAE leading to discontinuation of study treatment	32 (1.4%)	28 (1.2%)	0	1 (2.6%)	4 (0.8%)	5 (1.0%)	1 (1.1%)	1 (1.1%)
Treatment-related SAE with outcome death	0	0	0	0	0	0	0	0

The treatment-emergent period is defined as the time from study intervention start until the end of study intervention + 3 days.
TEAE = treatment-emergent adverse event

Effect by renal impairment

In FINEARTS-HF, the starting dose of finerenone was assigned based on the eGFR level at baseline: finerenone was initiated at 10 mg OD for participants with eGFR ≤60 mL/min/1.73 m^2 and at 20 mg OD for participants with eGFR >60 mL/min/1.73 m^2. Up-titration to the next higher dose was allowed if potassium was <5.0 mmol/L and eGFR decrease <30% (since the last visit). The target dose was

20 mg for participants with baseline eGFR ≤60 mL/min/1.73 m^2 and 40 mg for participants with baseline eGFR >60 mL/min/1.73 m^2.

The incidence of TEAEs and serious TEAEs increased with decreasing GFR, respectively, in both treatment groups. In FINEARTS-HF, the incidence of *treatment-related TEAEs* was higher in the finerenone group compared to placebo across eGFR strata: eGFR <30 (28.6% vs. 15.4%), eGFR 30-60 (22.6% vs. 12.9%), eGFR 60-90 (17.0% vs. 9.0%) eGFR ≥90 (9.9% vs. 7.0%) (**Table 47**).

The incidence of TEAEs of "hyperkalaemia" and "worsening of renal function" increased with decreasing eGFR and was higher for finerenone compared to placebo across eGFR subgroups (>90, 60-90, 30-60 and <30) (**Table 40**, **Table 41**). The incidence of TEAEs of "worsening of renal function" was increased in the finerenone group compared to placebo in both subgroups eGFR ≤60 (23.6% vs. 15.5%) and eGFR >60 (12.2% vs. 6.7%).

The incidence of treatment-emergent relative eGFR decrease was higher in the finerenone group compared to placebo in all categories of relative eGFR decrease (≥30%, ≥40%, ≥50% and ≥57%) across all subgroups (**Table 48**).

Table 44 Overview of TEAEs by baseline eGFR (KDIGO, SAF) – FINEARTS-HF

	<30 mL/min/1.73 m^2		30 – <60 mL/min/1.73 m^2		60 – <90 mL/min/1.73 m^2		≥90 mL/min/1.73 m^2	
Number (%) of participants with TEAEs	Finerenone N=98	Placebo N=123	Finerenone N=1348	Placebo N=1313	Finerenone N=1273	Placebo N=1271	Finerenone N=274	Placebo N=286
Any AE	86 (87.8%)	112 (91.1%)	1186 (88.0%)	1120 (85.3%)	1029 (80.8%)	1019 (80.2%)	214 (78.1%)	213 (74.5%)
Maximum intensity for any AE								
Mild	22 (22.4%)	29 (23.6%)	343 (25.4%)	279 (21.2%)	362 (28.4%)	333 (26.2%)	94 (34.3%)	75 (26.2%)
Moderate	44 (44.9%)	39 (31.7%)	515 (38.2%)	505 (38.5%)	444 (34.9%)	454 (35.7%)	78 (28.5%)	91 (31.8%)
Severe	20 (20.4%)	44 (35.8%)	328 (24.3%)	336 (25.6%)	223 (17.5%)	232 (18.3%)	42 (15.3%)	47 (16.4%)
Any treatment-related AE	28 (28.6%)	19 (15.4%)	305 (22.6%)	170 (12.9%)	216 (17.0%)	115 (9.0%)	27 (9.9%)	20 (7.0%)
Maximum intensity for treatment-related AE								
Mild	13 (13.3%)	13 (10.6%)	169 (12.5%)	93 (7.1%)	127 (10.0%)	69 (5.4%)	12 (4.4%)	16 (5.6%)
Moderate	10 (10.2%)	5 (4.1%)	117 (8.7%)	69 (5.3%)	77 (6.0%)	38 (3.0%)	13 (4.7%)	4 (1.4%)
Severe	5 (5.1%)	1 (0.8%)	19 (1.4%)	8 (0.6%)	12 (0.9%)	8 (0.6%)	2 (0.7%)	0
Any AE related to procedures required by the protocol	2 (2.0%)	1 (0.8%)	18 (1.3%)	15 (1.1%)	14 (1.1%)	11 (0.9%)	0	2 (0.7%)
Any AE leading to discontinuation of study intervention	6 (6.1%)	6 (4.9%)	50 (3.7%)	48 (3.7%)	35 (2.7%)	27 (2.1%)	5 (1.8%)	2 (0.7%)
Any SAE	43 (43.9%)	67 (54.5%)	616 (45.7%)	594 (45.2%)	426 (33.5%)	459 (36.1%)	72 (26.3%)	93 (32.5%)
Results in death	9 (9.2%)	18 (14.6%)	104 (7.7%)	125 (9.5%)	75 (5.9%)	89 (7.0%)	16 (5.8%)	7 (2.4%)
Requires or prolongs hospitalization	36 (36.7%)	59 (48.0%)	566 (42.0%)	530 (40.4%)	380 (29.9%)	395 (31.1%)	63 (23.0%)	87 (30.4%)
Life-threatening	6 (6.1%)	7 (5.7%)	70 (5.2%)	52 (4.0%)	29 (2.3%)	46 (3.6%)	10 (3.6%)	9 (3.1%)
Any treatment-related SAE	5 (5.1%)	2 (1.6%)	31 (2.3%)	14 (1.1%)	17 (1.3%)	8 (0.6%)	1 (0.4%)	0
Any SAE leading to discontinuation of study treatment	1 (1.0%)	4 (3.3%)	18 (1.3%)	13 (1.0%)	15 (1.2%)	18 (1.4%)	3 (1.1%)	0
Treatment-related SAE with outcome death	0	0	0	0	0	0	0	0

eGFR = estimated glomerular filtration rate, KDIGO = Kidney Disease Improving Global Outcomes, TEAE = treatment-emergent adverse event

Table 45 Worsening renal function: Number of participants with treatment-emergent relative decrease in eGFR ≥30%, ≥40%, ≥50% or ≥57% by Baseline eGFR (mL/min/1.73m2) (KDIGO) category (safety analysis set) - FINEARTS-HF and FIDELITY

		FINEARTS-HF		FIDELITY	
Relative decrease in eGFR	Baseline eGFR (mL/min/1.73m2) (KDIGO) category	Finerenone (N=2993) Num/Den(%)	Placebo (N=2993) Num/Den(%)	Finerenone (N=6489) Num/Den(%)	Placebo (N=6474) Num/Den(%)
>= 30%	< 30 mL/min/1.73m2	24/ 94 (25.5%)	16/ 119 (13.4%)	187/ 432 (43.3%)	183/ 443 (41.3%)
	30 - < 60 mL/min/1.73m2	444/1295 (34.3%)	265/1251 (21.2%)	1459/3424 (42.6%)	1256/3402 (36.9%)
	60 - < 90 mL/min/1.73m2	438/1241 (35.3%)	258/1240 (20.8%)	858/1915 (44.8%)	741/1903 (38.9%)
	>= 90 mL/min/1.73m2	65/ 267 (24.3%)	51/ 278 (18.3%)	224/ 651 (34.4%)	185/ 654 (28.3%)
>= 40%	< 30 mL/min/1.73m2	12/ 94 (12.8%)	5/ 119 (4.2%)	103/ 432 (23.8%)	103/ 443 (23.3%)
	30 - < 60 mL/min/1.73m2	216/1295 (16.7%)	124/1251 (9.9%)	740/3424 (21.6%)	675/3402 (19.8%)
	60 - < 90 mL/min/1.73m2	211/1241 (17.0%)	122/1240 (9.8%)	433/1915 (22.6%)	413/1903 (21.7%)
	>= 90 mL/min/1.73m2	33/ 267 (12.4%)	22/ 278 (7.9%)	119/ 651 (18.3%)	111/ 654 (17.0%)
>= 50%	< 30 mL/min/1.73m2	3/ 94 (3.2%)	3/ 119 (2.5%)	52/ 432 (12.0%)	64/ 443 (14.4%)
	30 - < 60 mL/min/1.73m2	82/1295 (6.3%)	55/1251 (4.4%)	331/3424 (9.7%)	361/3402 (10.6%)
	60 - < 90 mL/min/1.73m2	99/1241 (8.0%)	52/1240 (4.2%)	199/1915 (10.4%)	204/1903 (10.7%)
	>= 90 mL/min/1.73m2	17/ 267 (6.4%)	6/ 278 (2.2%)	50/ 651 (7.7%)	54/ 654 (8.3%)
>= 57%	< 30 mL/min/1.73m2	0/ 94 (0.0%)	1/ 119 (0.8%)	27/ 432 (6.3%)	39/ 443 (8.8%)
	30 - < 60 mL/min/1.73m2	45/1295 (3.5%)	30/1251 (2.4%)	158/3424 (4.6%)	204/3402 (6.0%)
	60 - < 90 mL/min/1.73m2	44/1241 (3.5%)	27/1240 (2.2%)	101/1915 (5.3%)	128/1903 (6.7%)
	>= 90 mL/min/1.73m2	9/ 267 (3.4%)	4/ 278 (1.4%)	30/ 651 (4.6%)	33/ 654 (5.0%)

Effect by hepatic function

The incidence of subjects with any AE and any SAE, respectively, was slightly higher in subjects with hepatic impairment (AEs:90%; SAEs:38%-39%) compared to those without hepatic impairment in the medical history (AEs:85%-86%; SAEs:30%-33%), in both treatment groups.

Monitoring of renal function is recommended periodically during treatment and as needed based on patient characteristics. Elderly patients and patients with impaired renal function (eGFR <60 mL/min/1.73 m²) are at higher risk for worsening of renal function and should be monitored more frequently.

2.6.8.7. Immunological events

N/A

2.6.8.8. Safety related to drug-drug interactions and other interactions

Finerenone is considered a weak inhibitor of CYP3A4 and CYP2C8 at doses of 40 mg, but not at 20 mg, see section PK. Concomitant use of finerenone with medications that impair potassium excretion and increase serum potassium, may increase the risk of hyperkalaemia. This is reflected in the SmPC for Kerendia.

2.6.8.9. Discontinuation due to adverse events

In FINEARTS-HF, TEAEs resulting in permanent discontinuation of study drug were reported slightly more frequently for finerenone (3.2%) than for placebo (2.8%), driven mostly by hyperkalaemia (0.4% vs. 0.2% for finerenone vs placebo) (**Table 49**).

Table 46 TEAEs leading to permanent discontinuation of study intervention occurring in ≥0.1% of participants per study intervention group

	FINEARTS-HF				FIDELITY			
Preferred Term MedDRA Version 27.0	Finerenone N=2993 (100%) n (%)	Finerenone EAIR per 100 pt-yr	Placebo N=2993 (100%) n (%)	Placebo EAIR per 100 pt-yr	Finerenone N=6489 (100%) n (%)	Finerenone EAIR per 100 pt-yr	Placebo N=6474 (100%) n (%)	Placebo EAIR per 100 pt-yr
Number (%) of participants with at least 1 such TEAE	96 (3.2%)	1.55	83 (2.8%)	1.33	414 (6.4%)	2.49	350 (5.4%)	2.08
Hyperkalaemia	12 (0.4%)	0.19	5 (0.2%)	0.08	87 (1.3%)	0.52	31 (0.5%)	0.18
Asthenia	5 (0.2%)	0.08	0	0.00	2 (<0.1%)	0.01	2 (<0.1%)	0.01
Renal impairment	5 (0.2%)	0.08	3 (0.1%)	0.05	10 (0.2%)	0.06	10 (0.2%)	0.06
Diarrhoea	4 (0.1%)	0.06	4 (0.1%)	0.06	14 (0.2%)	0.08	13 (0.2%)	0.08
Dyspnoea	3 (0.1%)	0.05	1 (<0.1%)	0.02	2 (<0.1%)	0.01	3 (<0.1%)	0.02
Hypotension	3 (0.1%)	0.05	0	0.00	3 (<0.1%)	0.02	0	0.00
Nausea	3 (0.1%)	0.05	3 (0.1%)	0.05	5 (<0.1%)	0.03	14 (0.2%)	0.08
Acute kidney injury	1 (<0.1%)	0.02	2 (<0.1%)	0.03	14 (0.2%)	0.08	10 (0.2%)	0.06
Blood potassium increased	1 (<0.1%)	0.02	0	0.00	23 (0.4%)	0.14	7 (0.1%)	0.04
Cardiac failure	1 (<0.1%)	0.02	3 (0.1%)	0.05	1 (<0.1%)	0.01	4 (<0.1%)	0.02
Dementia	1 (<0.1%)	0.02	2 (<0.1%)	0.03	4 (<0.1%)	0.02	7 (0.1%)	0.04
Dizziness	1 (<0.1%)	0.02	2 (<0.1%)	0.03	6 (<0.1%)	0.04	7 (0.1%)	0.04
Glomerular filtration rate decreased	1 (<0.1%)	0.02	3 (0.1%)	0.05	16 (0.2%)	0.10	12 (0.2%)	0.07
Rash	1 (<0.1%)	0.02	1 (<0.1%)	0.02	8 (0.1%)	0.05	4 (<0.1%)	0.02
Blood creatinine increased	0	0.00	0	0.00	7 (0.1%)	0.04	6 (<0.1%)	0.04
Chronic kidney disease	0	0.00	1 (<0.1%)	0.02	2 (<0.1%)	0.01	8 (0.1%)	0.05
Pneumonia	0	0.00	3 (0.1%)	0.05	2 (<0.1%)	0.01	6 (<0.1%)	0.04

Adverse events are sorted by descending frequency in the FINEARTs-HF finerenone group.
EAIR = exposure-adjusted incidence rate, p-yr = patient-years, TEAE = treatment-emergent adverse event

Discontinuations due to hyperkalaemia

In FINEARTS-HF, serum potassium levels were closely monitored. The doses were down-titrated if potassium levels were ≥5.5 to <6.0 mmol/L or interrupted if potassium levels were ≥6.0 mmol/L. Treatment-emergent hyperkalaemia events by action taken is presented in **Table 50**. The number of TEAEs of hyperkalaemia was 289 in the finerenone group and 125 in the placebo group, of which the *dose was reduced* in 20% (58/289) and 22% (28/125), the *dose was temporarily discontinued* in 50% (143/289) and 40% (50/125) and the *dose was permanently discontinued* in 4.5% (13/289) and 4.0%

(5/125) for finerenone and placebo, respectively. The dose was not changed in 24% (70/289) in the finerenone group and in 32% (40/125) in the placebo group.

The dose adjustments related to potassium levels that were applied in in FINEARTS-HF are proposed to be recommended in the SmPC (**section 4.2)**. **This is endorsed**.

Table 47 Treatment-emergent hyperkalaemia events by action taken

Action taken	**Any TEAE of hyperkalaemia in the finerenone group** **N=289**	**Any TEAE of hyperkalaemia in the placebo group** **N=125**
Intervention withdrawn	13 (4.5%)	5 (4.0%)
Intervention interrupted	143 (49.5%)	50 (40.0%)
Dose reduced	58 (20.1%)	28 (22.4%)
Dose not changed	70 (24.2%)	40 (32.0%)
Not applicable	5 (1.7%)	1 (0.8%)
Unknown	0	1 (0.8%)

Discontinuations due to worsening of renal function

The number of TEAEs of worsening of renal function was 530 in the finerenone group and 327 in the placebo group, of which the dose was **permanently discontinued** in 1.7% (9/530) of the subjects in the finerenone group and in 3.1% (10/327) of the subjects in the placebo group. The renal PTs reported in the finerenone (n=9) were: "renal impairment" (n=5), "renal failure" (n=2), "AKI" (n=1) and "GFR decreased" (n=1) (**Table 51**).

Table 48 Number of participants permanently discontinuing study intervention due to treatment-emergent worsening of renal function via selected PTs (SAF) – FINEARTS-HF and FIDELITY

	FINEARTS-HF		**FIDELITY**	
Primary system organ class **Preferred Term**	**Finerenone**	**Placebo**	**Finerenone**	**Placebo**
MedDRA Version 27.0	**=2993 (100%)**	**=2993 (100%)**	**=6489 (100%)**	**=6474 (100%)**
Number (%) of participants with at least 1 TEAE	**9 (0.3%)**	**10 (0.3%)**	**52 (0.8%)**	**42 (0.6%)**
Investigations	1 (<0.1%)	3 (0.1%)	23 (0.4%)	18 (0.3%)
Blood creatinine increased	0	0	7 (0.1%)	6 (<0.1%)
Glomerular filtration rate decreased	1 (<0.1%)	3 (0.1%)	16 (0.2%)	12 (0.2%)
Renal and urinary disorders	8 (0.3%)	7 (0.2%)	29 (0.4%)	24 (0.4%)
Acute kidney injury	1 (<0.1%)	2 (<0.1%)	14 (0.2%)	10 (0.2%)
Renal failure	2 (<0.1%)	2 (<0.1%)	5 (<0.1%)	5 (<0.1%)
Renal impairment	5 (0.2%)	3 (0.1%)	10 (0.2%)	10 (0.2%)

2.6.8.10. Post marketing experience

The estimated cumulative exposure to the marketed product since market launch until 08 JUL 2024 (data lock point of finerenone PBRER/PSUR 5.0) was 549,550 PY. Finerenone 10 mg film-coated tablet is currently authorized to be marketed in 90 countries and is marketed in 76 countries. Finerenone 20 mg film-coated tablet is currently authorized to be marketed in 89 countries and is marketed in 75 countries.

In the previous PSUR, covering the period 9 July 2023 to 8 July 2024, cumulative reviews on "anaphylactic reactions" and "acute kidney injury"/ "function kidney decreased" were provided as a request from National Agencies. No new safety issues could be identified from these reviews at that point. The MAH was asked to return to these issues if new relevant information became available in future PSURs.

2.6.9. Discussion on clinical safety

The established safety profile of finerenone is based on the studies FIDELIO-DKD and FIGARO-DKD (the pooled analysis named FIDELITY) to support the treatment of CKD with T2D.

The MAH has provided a safety evaluation of finerenone in HF patients from the FINEARTS-HF study. Overall, the safety profile in the HF population was similar to that of finerenone known from previous trials in T2D patients with CKD. The major safety concern is the risk of hyperkalaemia that increases with decreasing renal function, which is handled with serum potassium monitoring and dose adjustments (routine risk minimisation). An initial decrease in GFR, caused by a hemodynamic effect, is also a known adverse reaction for finerenone. However, from the data provided, a new safety concern emerged regarding "worsening of renal function", i.e., a more significant and prolonged eGFR reduction and an increased risk of renal adverse events (acute kidney injury [AKI], renal failure) associated with finerenone-treatment.

In FINEARTS-HF, 5,986 patients were included, of which 2,993 exposed to finerenone. The median duration of treatment and patient-year of exposure were similar between finerenone (28 months; 6184 patient-years) and placebo (28 months; 6227 patient years). The mean duration of treatment was 25 months. Approximately 80% of the study population was exposed for at least 12 months and 60% for at least 24 months.

The incidence of TEAEs was similar for finerenone (84.0%) and placebo (82.3%); however, treatment-related TEAEs were increased for finerenone (19.2%) compared to placebo (10.8%). Most of the TEAEs (about 75%) were mild or moderate in intensity. The most reported TEAEs for finerenone compared to placebo were hyperkalaemia (8.8% vs. 3.8%), hypotension (7.3% vs. 4.5%) and renal impairment (6.6% vs. 3.9%).

The frequency of serious TEAEs was similar in the finerenone group (38.7%) and placebo group (40.5%), of which acute kidney injury was reported more frequently for finerenone (1.8%) compared to placebo (0.9%). The frequency of fatal outcome or AEs was 16.5% in the finerenone group and 17.6% in the placebo group.

TEAEs resulting in permanent discontinuation of study drug were reported slightly more frequently for finerenone (3.2%) than for placebo (2.8%), driven mostly by hyperkalaemia (0.4% vs. 0.2% for finerenone vs. placebo).

Hyperkalaemia

The incidence of any treatment-emergent "hyperkalaemia" (9.7% vs. 4.2%) and treatment-related TEAEs of hyperkalaemia (6.6% vs. 2.1) were increased for finerenone compared to placebo. The

incidence of hyperkalaemia increased with decreasing renal function across eGFR strata: eGFR ≥90 mL/min/1.73m^2 (4.0% vs. 1.4%), eGFR 60 ≤90 mL/min/1.73m^2 (6.8% vs. 2.0%) and eGFR 30≤60 mL/min/1.73m^2 (12.2% vs. 6.6%) and eGFR <30 mL/min/1.73m^2 (27.6% vs. 7.3%).

Information on the risk of hyperkalaemia is included in the current SmPC for Kerendia.

Worsening of renal function

In FINEARTS-HF, TEAEs related to "worsening of renal function" were reported more frequently in the finerenone group (17.7%) than in the placebo group (10.9%), including "renal impairment" (6.6% vs. 3.9%), "acute kidney injury" (3.7% vs. 2.1%), "renal failure" (2.6% vs. 1.6%), "decreased GFR" (5.2% vs. 3.6%) and "blood creatinine increased" (1.2% vs. 0.8%). Serious TEAEs of "worsening renal function" were increased for finerenone (2.4%) compared to placebo (1.5%), including serious TEAEs of AKI (1.8% vs. 0.9%).

The incidence of treatment-related TEAEs of "worsening of renal function" was higher for finerenone (7.1%) compared to placebo (3.0%) for "renal impairment" (2.8% vs. 1.2%), "acute kidney injury" (1.0 vs 0.2%), "renal failure" (1.0% vs. 0.4%) and "GFR decreased" (2.1% vs. 1.0%).

TEAEs of "worsening of renal function" requiring hospitalization were more frequent in the finerenone group (2.0%) than in the placebo group (1.3%), of which "acute kidney injury" was the most frequently reported renal event with the incidence 1.6% for finerenone and 0.8% for placebo.

There was a more pronounced decrease in eGFR in the finerenone group compared with placebo group, with a mean difference of approximately 3-4 mL/min/1.73 m^2 from week 4 to 28. From week 28 and onwards the eGFR declined slightly more in the placebo group, with a mean difference between finerenone and placebo of approximately 2-3 mL/min/1.73 m^2. More subjects in the finerenone group compared to placebo had a relative eGFR decrease of ≥30% (33.5% vs. 20.4%), ≥40% (16.3% vs. 9.5%), ≥50 % (6.9% vs. 4.0%) and ≥57 % (3.4% vs. 2.1%).

The cumulative incidence for time to first TEAE of worsening of renal function (PTs "renal impairment", "renal failure", "postrenal failure", "prerenal failure", "AKI", "glomerular filtration rate decreased" and "blood creatinine increased") was 23.7% for finerenone and 15.0% for placebo

The increased risk of "worsening of renal function" was not seen in the previously performed FIDELITY trial supporting the indication in patients with CKD associated with type 2 diabetes. Potential underlying causes to the documented increased risk of "worsening of renal function" in FINEARTS-HF was discussed during the procedure. In particular, the importance of higher exposure (35-40%) in patients treated for heart failure compared to the previously approved target population. Due to confounding factors, no firm conclusions could be drawn from the performed PK exposure-response analysis as to whether the risk is increased in patients with documented higher exposure. There were no relevant differences in the incidence of TEAEs of worsening of renal function between different weight subgroups. There was no indication of a dose-dependent difference in the incidence of TEAEs of "worsening of renal function" between subjects who had received a higher versus a lower dose of finerenone at the time of the reported renal event. However, given that patients were continuously up- and down-titrated during the study, comparison between subgroups by dose is difficult and associated with confounding factors. Approximately one third (27%) of the finerenone cases reporting TEAEs of "worsening of renal function" had the outcome "not resolved" or "resolved with sequelae". In some cases where finerenone was permanently discontinued, eGFR did not return to baseline levels. This has been reflected in the product information.

Monitoring of renal function is recommended periodically during treatment and as needed based on patient characteristics. Elderly patients and patients with impaired renal function (eGFR <60

mL/min/1.73 m²) are at higher risk for worsening of renal function and should be monitored more frequently as recommended in Section 4.4 of the SmPC.

Gastrointestinal events

In FINEARTS-HF, the incidence of TEAEs of "diarrhoea" (5.7% vs. 4.4%) and "constipation" (3.8% vs. 2.7%), including drug-related TEAEs of "diarrhoea" (0.9% vs. 0.4%) and constipation (0.4% vs. <0.1%), was increased for finerenone compared to placebo.

Laboratory findings, vital signs

Blood pressure

In FINEARTS-HF, blood pressure decreased in the finerenone group compared to placebo (mean SBP by approximately 2-3 mmHg and mean DPB by approximately 1-2 mmHg). Hypotension as a TEAE occurred more frequently in participants in the finerenone group (7.3%) compared with placebo (4.5%).

Hypotension is included in section 4.8 of the current SmPC for Kerendia with corresponding frequency: "common".

Serum sodium

An initial decrease in mean serum sodium of approximately 0.8 mmol/L was observed in the finerenone group at month 1 and remained lower thereafter. In FINEARTS-HF, TEAEs of hyponatraemia occurred more frequently in participants in the finerenone group (1.8%) compared with placebo (0.8%).

Hyponatremia is included in section 4.8 of the current SmPC for Kerendia with corresponding frequency "common".

Subgroups

Effect by age

The reporting rate generally increased with increasing age in both treatment groups. The incidence of TEAEs of "hyperkalaemia" (age group <65 years: 8.0% vs. 2.9%; 65≤75 years: 9.3% vs. 3.6%; 75≤85 years: 10.4% vs 5.4%) and "worsening of renal function" (age group <65 years: 12.8% vs. 8.6%; 65≤75 years: 16.6% vs. 10.1%; 75≤85 years: 20.6% vs 12.6%) was higher in older patients compared to younger and was increased for finerenone compared to placebo across the age groups. In addition, there should be a cross-reference from section 4.2 to 4.4. Due to age-related decline in renal function and the fact that eGFR is not regularly monitored in all patients, there is a risk that decline in renal function may not be identified. Elderly are considered to be at higher risk. Therefore, a periodically monitoring of renal function in elderly is recommended.

Effect by race

The incidence of TEAEs was balanced between treatment groups in White (81-82%) and Asian (89-91%) and was slightly higher for finerenone compared to placebo in Black (86% vs. 72%) and Other subjects (89% vs 80%). However, the portion of Black participants (n=88) and Other subjects (n=182) were small, and results should be interpreted with caution. A slightly higher proportion of participants with TEAEs across the various TEAE categories was observed in participants of Asian race (90-91%) compared to other race groups as well as to the overall population (79-85%).

Effect by renal function

In FINEARTS-HF, the starting dose of finerenone was assigned based on the eGFR level at baseline: finerenone was initiated at 10 mg OD for participants with eGFR ≤60 mL/min/1.73 m^2 and at 20 mg OD for participants with eGFR >60 mL/min/1.73 m^2. Up-titration to the next higher dose was allowed if

potassium was <5.0 mmol/L and eGFR decrease <30% (since the last visit). The target dose was 20 mg for participants with baseline eGFR ≤60 mL/min/1.73 m^2 and 40 mg for participants with baseline eGFR >60 mL/min/1.73 m^2.

Subjects with lower eGFR at baseline reported overall more TEAEs and serious TEAEs compared to subjects with higher eGFR at baseline although the incidences were similar for finerenone and placebo. The incidence of *treatment-related TEAEs* was higher in the finerenone group compared to placebo across eGFR (ml/min/1.73m^2) strata: eGFR <30 (28.6% vs. 15.4%), eGFR 30 ≤60 (22.6% vs. 12.9%), eGFR 60≤90 (17.0% vs. 9.0%) and eGFR ≥90 (9.9% vs. 7.0%).

The incidence of *treatment-emergent relative eGFR decrease* was higher in the finerenone group compared to placebo in all categories of relative eGFR decrease (≥30%, ≥40%, ≥50% and ≥57%) across eGFR (ml/min/1.73m^2) strata. The incidence of a relative eGFR decrease of ≥30%: eGFR <30 (25.5% vs. 13.4%), eGFR 30-60 (34.3% vs. 21.2%), eGFR 60-90 (35.3% vs. 20.8%) eGFR ≥90 (24.3% vs. 18.3%) and the incidence of eGFR decrease of ≥40%: eGFR <30 (12.8% vs. 4.2%), eGFR 30-60 (16.7% vs. 9.9%), eGFR 60-90 (17.0% vs. 9.8%) eGFR ≥90 (12.4% vs. 7.9%).

Effect by hepatic function

The incidence of subjects with any AE and any SAE, respectively, was slightly higher in subjects with hepatic impairment (AEs:90%; SAEs:38%-39%) compared to those without hepatic impairment in the medical history (AEs:85%-86%; SAEs:30%-33%), in both treatment groups.

Section 4.2 and 4.4

Given that the TTO for most of the reported relevant renal PTs "AKI", "renal failure" and "renal impairment" was >6 months, more frequent monitoring of eGFR is considered during treatment with finerenone. Monitoring of renal function is recommended periodically during treatment and as needed based on patient characteristics. Elderly and patients with impaired renal function (eGFR <60 mL/min/1.73 m^2) are considered to be at higher risk, more frequent monitoring is recommended.

Section 4.8

Worsening of renal function

The current section 4.8 of the SmPC for Kerendia includes "GFR decreased" (frequency: common). The MAH has proposed to include "blood creatinine increased" (frequency: common) in section 4.8 of the SmPC and this is endorsed. Increased blood creatinine is expected as serum creatinine is a marker of renal function, and creatinine increases with decreases in renal function. Based on data from the FINEART-HF study, there is at least a reasonable possibility to support a causal relationship between finerenone and "renal impairment" (frequency: common) and "acute kidney injury" (frequency: common).

Gastrointestinal disorders

Based on data from the FINEART-HF study, there is at least a reasonable possibility to support a causal relationship between finerenone and "diarrhoea" (frequency: common) and "constipation" (frequency: common), respectively. In addition, "gastrointestinal ADRs" is labelled for the aldosterone antagonists spironolactone and eplerenone.

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics.

2.6.10. Conclusions on the clinical safety

The safety profile in the HF population was overall similar to that of finerenone known from previous trials in T2D patients with CKD, except for a new safety concern regarding "worsening of renal function" that emerged from the provided data from FINARTS-HF. However, decreases in eGFR, caused by hemodynamic effects, including adverse reactions of "impaired renal function" are labelled for other mineralocorticoid receptor antagonist (MRA) medicinal products approved for the treatment of heart failure. Given the same mechanism of action of finerenone, it is expected that TEAEs of "worsening of renal function" would also be a risk associated with finerenone. Approximately one third (27%) of the finerenone cases reporting TEAEs of "worsening of renal function" had the outcome "not resolved/ resolved with sequelae". It is challenging to draw definitive conclusions on reversibility due to the potential influence of comorbidities on the renal decline, as well as limitations in study design, including the lack of scheduled eGFR assessments after the last intake of the study drug in patients who completed the study. Nonetheless, to ensure transparency and accuracy, the product information states that in certain cases where finerenone was permanently discontinued, eGFR did not return to baseline levels.

Monitoring of renal function is recommended periodically during treatment and as needed based on patient characteristics. Elderly patients and patients with impaired renal function (eGFR <60 mL/min/1.73 m²) are at higher risk for worsening of renal function and should be monitored more frequently.

2.7. Risk Management Plan

2.7.1. Safety concerns

The applicant proposed the following summary of safety concerns in the RMP:

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Hyperkalaemia
Important potential risks	Embryo-foetal toxicity
Missing information	Use in pregnancy and lactation

2.7.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.7.3. Risk minimisation measures

Table Part V.49: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risk		

Table Part V.49: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
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	**Routine pharmacovigilance beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** 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	**Routine pharmacovigilance beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** 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	**Routine pharmacovigilance beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Abbreviations: SmPC=Summary of Product Characteristics.		

2.7.4. Conclusion

The CHMP considered that the risk management plan version 3.3 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by Bayer AG 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 list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. Product information

2.9.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Kerendia 10 and 20 mg film-coated tablets package leaflet. The bridging report submitted by Bayer AG has been found acceptable.

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 proposed new therapeutic indication for finerenone is:

"Kerendia is indicated for the treatment of symptomatic chronic heart failure with left ventricular ejection fraction (LVEF) ⩾ 40% in adults."

Chronic heart failure with LVEF ⩾ 40% encompass the subcategories HF with mildly reduced EF (HFmrEF; EF 40-49%) and HR with preserved EF (HFpEF; EF >50%).

3.1.2. Available therapies and unmet medical need

Current treatment recommendations for heart failure with mildly reduced and preserved ejection fraction (HFmrEF/HFpEF) include diuretics (class 1), as well as ACE inhibitors, ARBs, ARNIs, and beta blockers as class 2b options according to the *ESC 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure (https://doi.org/10.1093/eurheartj/ehad195).* SGLT-2 inhibitors have been approved during the last years and constitute a class 1 recommendation in the above ESC guidelines and a class 2a recommendation in the *2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure (https://doi.org/10.1161/CIR.000000000000106).* MRAs have a class 2b recommendation for HFmrEF in the ESC guidelines.

Even if treatments are already available there is still need for further effective therapies for HFmrEF/HFpEF.

3.1.3. Main clinical studies

The present application is supported by the single phase 3 FINEARTS-HF study that was a randomized, double-blind, placebo-controlled, parallel-group, event-driven study conducted at 654 centers across 37 countries including 6016 randomised patients. The study was designed to evaluate the effect of finerenone compared to placebo, when added to standard of care, in patients with a diagnosis of HF, NYHA II-IV and LVEF ⩾40%.

The primary objective was to demonstrate the superiority of finerenone to placebo in reducing the rate of the primary composite CV endpoint CV death and total (first and recurrent) HF events (HHF or urgent HF visit).

Exclusion criteria included eGFR <25 mL/min/1.73 m² and serum/plasma potassium >5.0 mmol/L.

For participants with an eGFR⩽60 mL/min/1.73 m2 at baseline, the starting dose was 10 mg OD. From Visit 2 (Month 1) onwards and if potassium ⩽5.0 mmol/l and eGFR decrease is <30%, the starting dose could be titrated to 20 mg OD.

For participants with an eGFR >60 mL/min/1.73 m2 at baseline, the starting dose was 20 mg OD. From Visit 2 (Month 1) onwards and if potassium is ⩽5.0 mmol/l and eGFR decrease is <30%, the starting dose can be titrated to 40 mg OD.

3.2. Favourable effects

Finerenone was superior to placebo in reducing the risk of the primary composite endpoint of CV death and total (first and recurrent) HF events (heart failure hospitalisation [HHF] or urgent HF visit) with on average 16% (RR=0.84; 95% CI 0.74; 0.95). The effect was mainly driven by an effect on HF events (RR=0.82 95% CI 0.71; 0.94) while the difference in CV death between the groups was small (242 vs. 260 events in finerenone vs. placebo; HR 0.93, 95% CI 0.78; 1.11).

The Nelson-Aalen estimates show an early curve separation and indicate a sustained effect.

The first secondary endpoint in the testing hierarchy was total (first and recurrent) HF events (HHF or urgent HF visit), which was also one of the components of the primary composite endpoint. The rate ratio was 0.82 (95% CI 0.71; 0.94) and the endpoint was statistically significant.

For the secondary endpoint change from baseline to month 6, 9 and 12 in Total Symptom Score (TSS) of the patient report outcome KCCQ, the mean change from baseline was 7.99 in the finerenone group

and 6.43 in the placebo group. The difference in LS mean was 1.56 (95% CI 0.79; 2.34) which was statistically significant.

3.3. Uncertainties and limitations about favourable effects

The effect of the primary endpoint was driven by HF events (HHF or urgent HF visits). The studied population has a high disease burden, and the effect was not apparent when looking at the total number of hospitalisations. An exploratory analysis on recurrent all-cause hospitalisation indicated no difference between the groups (RR 0.99 95% CI 0.92; 1.07) although a time to first analysis yielded a lower but not nominally significant point estimate (HR 0.94 95% CI 0.88; 1.02). There was no effect on the CV death component of the primary composite.

In FINEARTS-HF, 69% of patients were in NYHA class II and 30% in NYHA class III but only 47 participants (0.7%) were in NYHA class IV and the estimate of the effect in this group is thus uncertain. 36% of participants had EF 40-50% (HFmrEF). For patients with HFpEF, 45% of participants had EF ⩾50%-<60% and 19% had EF ⩾60%.

In the pre-specified subgroups analysed, the effect was in general consistent with the effect in the overall population. The relative risk (RR) was however higher in the subgroup of patients without index HF event (or patients that had one earlier than 3 months prior to randomisation) than in patients with an index HF event less than 7 days or between 7 days and 3 months before randomisation (RR 0.99 vs. RR 0.74 and 0.79).

For the secondary endpoint change from baseline to month 6, 9 and 12 in TSS of the patient report outcome KCCQ, the clinical relevance of the improvement is questionable (on average 1.56 points difference between the groups on the 100-point scale).

For all-cause mortality, there were no significant differences between the groups although the point estimate was below unity (HR=0.93 95% CI 0.83; 1.06) and no conclusions regarding an effect on mortality can be drawn.

The secondary renal composite endpoint time to first occurrence of the renal composite endpoint of sustained decrease in eGFR ⩾50% relative to baseline over at least 4 weeks, or sustained eGFR decline to <15 ml/min/1.73m2 or initiation of dialysis or renal transplantation was tested exploratively, and no significant difference was found between the groups (RR 1.33; 95% CI 0.94; 1.89). The point estimate was higher than unity and the early and sustained separated Aalen-Johansen estimate curves indicates an effect favouring placebo, however the events were relatively few. An exploratory analysis of the renal endpoint using the ⩾40% threshold yielded a nominally significant outcome in favour of placebo (HR = 1.55 95% CI 1.23; 1.94). The FINEARTS-HF study did not include an assessment of eGFR after study drug discontinuation limiting any conclusions on reversibility of the observed drug induced reductions in eGFR.

Data from an explorative time to first event analysis of CV death and non-fatal CV events indicated a slight imbalance in non-fatal MI and stroke in the finerenone group. The applicant has upon request provided an explorative time to first analysis of 3-point MACE which indicate a neutral effect on MACE from the treatment.

3.4. Unfavourable effects

The MAH has provided a safety evaluation of finerenone in HF patients from the FINEARTS-HF study. The safety profile in the HF population was overall similar to that of finerenone known from previous

trials in T2D patients with CKD, except for a new safety concern regarding "worsening of renal function" that emerged from the provided data.

Worsening of renal function

TEAEs related to "worsening of renal function" were reported more frequently in the finerenone group (17.7%) than in the placebo group (10.9%), including "renal impairment" (6.6% vs. 3.9%), "acute kidney injury" (3.7% vs. 2.1%), "renal failure" (2.6% vs. 1.6%), "decreased GFR" (5.2% vs. 3.6%) and "blood creatinine increased" (1.2% vs. 0.8%). Serious TEAEs of "worsening renal function" were increased for finerenone (2.4%) compared to placebo (1.5%), including serious TEAEs of AKI (1.8% vs. 0.9%).

The incidence of treatment-related TEAEs of "worsening of renal function" was higher for finerenone (7.1%) compared to placebo (3.0%), including "renal impairment" (2.8% vs. 1.2%), "acute kidney injury" (1.0 vs 0.2%), "renal failure" (1.0% vs. 0.4%) and "GFR decreased" (2.1% vs. 1.0%).

TEAEs of "worsening of renal function" requiring hospitalization were more frequent in the finerenone group (2.0%) than in the placebo group (1.3%), of which "acute kidney injury" was the most frequently reported renal event with the incidence 1.6% for finerenone and 0.8% for placebo.

More subjects in the finerenone group compared to placebo had a relative eGFR decrease of ≥30% (33.5% vs. 20.4%), ≥40% (16.3% vs. 9.5%), ≥50 % (6.9% vs. 4.0%) and ≥57 % (3.4% vs. 2.1%).

The cumulative incidence for time to first TEAE of "worsening of renal function" (PTs "renal impairment", "renal failure", "postrenal failure", "prerenal failure", "AKI", "glomerular filtration rate decreased" and "blood creatinine increased") was 23.7% for finerenone and 15.0% for placebo.

Hyperkalaemia

The incidence of any treatment-emergent "hyperkalaemia" (9.7% vs. 4.2%) and treatment-related TEAEs of hyperkalaemia (6.6% vs. 2.1) was increased for finerenone compared to placebo. The incidence of hyperkalaemia increased with decreasing renal function across eGFR strata: eGFR ≥90 mL/min/1.73m^2 (4.0% vs. 1.4%), eGFR 60 ≤90 mL/min/1.73m^2 (6.8% vs. 2.0%) and eGFR 30≤60 mL/min/1.73m^2 (12.2% vs. 6.6%) and eGFR <30 mL/min/1.73m^2 (27.6% vs. 7.3%).

Gastrointestinal events

TEAEs of "diarrhoea" (5.7% vs. 4.4%) and "constipation" (3.8% vs. 2.7%), including drug-related TEAEs of "diarrhoea" (0.9% vs. 0.4%) and constipation (0.4% vs. <0.1%), occurred more frequently in subjects in the finerenone group than in the placebo group.

Laboratory findings, vital signs

Blood pressure

Blood pressure decreased in the finerenone group compared to placebo at month 1 (mean SBP by approximately 2-3 mmHg and mean DPB by approximately 1-2 mmHg). Hypotension as a TEAE occurred more frequently in subjects in the finerenone group (7.3%) compared with placebo (4.5%).

Subgroups

Effect of age

The reporting rate generally increased with increasing age in both treatment groups. The incidence of TEAEs of "hyperkalaemia" (age group <65 years: 8.0% vs. 2.9%; 65≤75 years: 9.3% vs. 3.6%; 75≤85 years: 10.4% vs 5.4%) and "worsening of renal function" (age group <65 years: 12.8% vs. 8.6%; 65≤75 years: 16.6% vs. 10.1%; 75≤85 years: 20.6% vs 12.6%) were higher in older patients compared to younger and was increased for finerenone compared to placebo across the age groups.

Effect by renal function

The starting dose of finerenone was assigned based on the eGFR level at baseline: finerenone was initiated at 10 mg OD for participants with eGFR ≤60 mL/min/1.73 m^2 and at 20 mg OD for participants with eGFR >60 mL/min/1.73 m^2. Up-titration to the next higher dose was allowed if potassium was <5.0 mmol/L and eGFR decrease <30% (since the last visit). The target dose was 20 mg for participants with baseline eGFR ≤60 mL/min/1.73 m^2 and 40 mg for participants with baseline eGFR >60 mL/min/1.73 m^2.

Subjects with lower eGFR at baseline reported overall more TEAEs and serious TEAEs compared to subjects with higher eGFR at baseline although the incidences were balanced for finerenone and placebo. The incidence of treatment-related TEAEs was higher in the finerenone group compared to placebo across eGFR strata: eGFR <30 (28.6% vs. 15.4%), eGFR 30≤60 (22.6% vs. 12.9%), eGFR 60≤90 (17.0% vs. 9.0%) and eGFR ≥90 (9.9% vs. 7.0%).

The incidence of treatment-emergent relative eGFR decrease was higher in the finerenone group compared to placebo in all categories of relative eGFR decrease (≥30%, ≥40%, ≥50% and ≥57%) across eGFR strata. The incidence of a relative eGFR decrease of ≥30% across eGFR strata: eGFR <30 (25.5% vs. 13.4%), eGFR 30≤60 (34.3% vs. 21.2%), eGFR 60≤90 (35.3% vs. 20.8%) eGFR ≥90 (24.3% vs. 18.3%) and the incidence of eGFR decrease of ≥40%: eGFR <30 (12.8% vs. 4.2%), eGFR 30≤60 (16.7% vs. 9.9%), eGFR 60≤90 (17.0% vs. 9.8%) eGFR ≥90 (12.4% vs. 7.9%).

Based on data from the FINEART-HF study, there is *at least a reasonable possibility to support a causal relationship* between finerenone and "renal impairment" (frequency: common), "acute kidney injury" (frequency: common), "renal failure" (frequency: common), "diarrhoea" (frequency: common) and "constipation" (frequency: common), respectively and this was reflected in section 4.8 of the agreed SmPC.

3.5. Uncertainties and limitations about unfavourable effects

In FINEARTS-HF, the incidence of TEAEs related to "worsening of renal function" (including the relevant PTs "renal impairment", "acute kidney injury", "renal failure" and "GFR decreased" was increased for finerenone compared to placebo. Although this was not seen in the previously performed FIDELITY trial, supporting the indication in patients with CKD associated with type 2 diabetes, TEAEs of "worsening of renal function" is expected for finerenone, in line with that impaired real function is an identified risk for MRAs on the market approved for treatment of heart failure. Approximately one third (27%) of the finerenone cases reporting TEAEs of "worsening of renal function" had the outcome "not resolved/ resolved with sequelae". It is challenging to draw definitive conclusions on reversibility due to the potential influence of comorbidities on the renal decline, as well as limitations in study design, including the lack of scheduled eGFR assessments after the last intake of the study drug in patients who completed the study. Nonetheless, to ensure transparency and accuracy, the product information clearly states that in certain cases where finerenone was permanently discontinued, eGFR did not return to baseline levels. Monitoring of renal function is recommended periodically during treatment and as needed based on patient characteristics. Elderly patients and patients with impaired renal function (eGFR <60 mL/min/1.73 m²) are at higher risk for worsening of renal function and should be monitored more frequently.

3.6. Effects Table

Table 50 Effects Table for Kerendia for the treatment of symptomatic chronic heart failure with left ventricular ejection fraction (LVEF) ≥ 40% in adults

Effect	Short Description	Unit	Kerendia	Placebo	Uncertainties/ Strength of evidence	References
Favourable Effects						
Primary endpoint	Composite of CV death and total (first and recurrent) HF events (HHF or urgent HF visit)	E/N (n, %)	1083/3003 (624, 20.8%)	1283/2998 (719, 24.0%)	RR 0.84 [95% CI 0.74; 0.95] p=0.0072	(1)
Secondary endpoint	Total (first and recurrent) HF events (HHF or urgent HF visit)	E/N (n,%)	842/3003 (479, 16.0%)	1024/2998 (573, 19.1%)	RR 0.82 (95% CI 0.71; 0.94) P=0.0062	(1)
	Change from baseline to month 6, 9 and 12 in TSS of KCCQ	LS Mean change from baseline [95% CI]	7.99 [7.37, 8.62]	6.43 [5.79, 7.07]	Difference in LS mean 1.56 [95% CI 0.79, 2.34] P<0.0001	(1)
	Improvement in NYHA class from Baseline to Month 12	Estimated proportion [95% CI]	0.179[0.163, 0.195]	0.178[0.162, 0.194]	OR 1.01 [0.88, 1.15]	(1)
	Time to first occurrence of the renal composite endpoint of sustained decrease in eGFR ⩾50% relative to baseline over at least 4 weeks, or sustained eGFR decline to <15 ml/min/1.73m^2 or initiation of dialysis or renal transplantation	n/N (%)	75/3003 (2.5%)	55/2998 (1.8%)	HR 1.33 [0.94; 1.89]	(1)
	All-cause mortality	n/N (%)	491/3003 (16.4%)	522/2998 (17.4%)	HR 0.93 [95% CI 0.83; 1.06]	(1)
Unfavourable Effects						

Effect	Short Description	Unit	Kerendia	Placebo	Uncertainties/ Strength of evidence	References
Hyperkalaemia	Incidence of hyperkalaemia	N (%)	289 (9.7%)	125 (4.2%)	The current section 4.8 of the SmPC for Kerendia (includes "hyperkalaemia" (frequency: very common [CKD with T2D] and common [HF with LVEF>40%]).	(1)
"Worsening of renal function"	Incidence of worsening of renal function	N (%)	540 (17.7%)	327 (10.9%)		(1)
Effect of renal function						
eGFR ≥60	Incidence of worsening of renal function	N (%)	189/1547 (12.2%)	104/1557 (6.7%)		(1)
eGFR <60	Incidence of worsening of renal function	N (%)	341/1446 (23.6%)	644/3897 (16.5%)		(1)
Relevant PTs of "worsening of renal function"						
PT Renal impairment	Incidence of renal impairment	N (%)	199 (6.6%)	117 (3.9%)		(1)
PT Acute kidney injury	Incidence of acute kidney injury	N (%)	111 (3.7%)	64 (2.1%)		(1)
PT Renal failure	Incidence of renal failure	N (%)	78 (2.7%)	47 (1.6%)		(1)
PT GFR decreased	Incidence of GFR decreased	N (%)	157 (5.2%)	108 (3.6%)		(1)
PT Blood creatinine increased	Incidence of blood creatinine increased	N (%)	36 (1.2%)	25 (0.8%)		(1)
Hypotension	Incidence of hypotension	N (%)	218 (7.3%)	134 (4.5%)	The current section 4.8 of the SmPC for Kerendia includes "hypotension" (frequency: common).	(1)

Abbreviations: N= Number of patients
Notes: (1) FINEARTS-HF

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Importance of favourable effects

HF affects approximately 64 million people worldwide, and its prevalence is increasing worldwide due to ageing and lifestyle factors that contribute to comorbidities such as hypertension, diabetes, obesity and renal dysfunction.

Current treatment recommendations for HFmrEF/HFpEF include diuretics and SGLT2 inhibitors (class 1), as well as ACE inhibitors, ARBs, ARNIs, MRA and beta blockers as class 2b options according to the ESC 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure (https://doi.org/10.1093/eurheartj/ehad613). Even if there are treatment options with class 1 recommendation, considering the high morbidity and mortality related to the condition, new treatment options are welcomed.

The FINEARTS-HF study encompassed 6016 randomised patients with a diagnosis of HF, NYHA II-IV and LVEF ⩾40% treated with standard of care. Nearly all patients were treated with diuretics (87% loop diuretics, 14% thiazides). The majority of patients were in NYHA class II and III while only 47 participants (0.7%) were in NYHA class IV and the estimate of the effect in this group is thus uncertain, which is reflected in the product information.

Finerenone was superior to placebo in reducing the risk of the primary composite endpoint of CV death and total (first and recurrent) HF events (HHF or urgent HF visit) with on average 16% lower risk compared with placebo. The effect was mainly driven by an effect on HF events and the difference in CV death between the groups was small. SGLT2 inhibitors emerged as class 1 recommendation during the conduct of the study and was administered to 14% of the population at baseline, the use slightly increasing during the study (19.8% vs. 21.9% in the finerenone group compared to placebo). The effect of finerenone in addition to SGLT2-inhibitors is therefore not fully characterised although subgroup analyses yielded a similar estimate of the primary endpoint. Regardless of SGLT2 inhibitor use at baseline, finerenone led to a larger NT-proBNP reduction compared to placebo up to Month 12. Concomitant use of other MRAs was not permitted during the study, and the relative efficacy of finerenone compared to currently available MRAs is not known.

The pivotal study is considered adequately designed and conducted. The effect on HF events is, albeit of limited magnitude, considered relevant and in line with results for other products recently approved for a similar target population.

For the secondary endpoint change from baseline to month 6, 9 and 12 in TSS of the patient report outcome KCCQ, the difference between the groups (on average 1.56 points difference between the groups on the 100-point scale) were statistically significant, but the clinical relevance questionable. Nevertheless, the findings indicate that treatment with finerenone is not related to a worsening in the patients' self-assessed health status.

Data from an explorative time to first event analysis of CV death and non-fatal CV events indicated a slight imbalance in non-fatal MI and stroke in the finerenone group. However, a 3-point MACE analysis indicates a neutral effect of the treatment.

Importance of unfavourable effects

The major known safety concern associated with the use of finerenone is the risk of hyperkalaemia that increases with decreasing renal function, which is handled with serum potassium monitoring and dose adjustments as routine risk minimisation measures. However, from the data provided in the current procedure, a new safety concern emerged regarding "worsening of renal function", i.e., a more significant and prolonged eGFR reduction and an increased risk of renal adverse events (e.g., AKI, renal failure) associated with finerenone-treatment. This risk was observed both in patients with GFR≤60 ml/min/1.73 m^2 and GFR>60 ml/min/1.73 m^2.

This was not seen in the previously performed FIDELITY trial supporting the indication in patients with CKD associated with type 2 diabetes. On the contrary, the currently approved indication is treatment of chronic kidney disease (with albuminuria) associated with type 2 diabetes in adults. However, decreases in eGFR, caused by hemodynamic effects, including adverse reactions of "impaired renal function" are labelled for MRA drugs approved for the treatment of heart failure. Given the same mechanism of action as finerenone, it is expected that TEAEs of "worsening of renal function" would also be a risk associated with finerenone.

A higher exposure (35-40%) in patients treated for heart failure compared to exposure in previously approved target population was identified. Due to confounding factors, no firm conclusions could be drawn from the performed PK exposure-response analysis as to whether the risk for "worsening of renal function" is increased in patients with documented higher exposure. There were no relevant

differences in the incidence of TEAEs of worsening of renal function between different weight subgroups. There was no indication of a dose-dependent difference in the incidence of TEAEs of "worsening of renal function" between subjects who had received a higher versus a lower dose of finerenone at the time of the reported renal event. However, given that patients were continuously up- and down-titrated during the study, comparison between subgroups by dose is difficult and associated with confounding factors.

Regular monitoring of renal function is recommended, as needed based on patient characteristics. Elderly patients and patients with impaired renal function (eGFR <60 mL/min/1.73 m²) are at higher risk for worsening of renal function and should be monitored more frequently.

3.7.2. Balance of benefits and risks

The outcomes from the FINEARTS-HF study indicate a beneficial effect of finerenone for treatment of symptomatic chronic heart failure in adults with HFmrEF/HFpEF. The increased risk of worsening of renal function can be mitigated with enhanced routine risk minimisation measures and a recommendation of regular eGFR monitoring. Therefore, the benefits are considered to outweigh the risks.

3.8. Conclusions

The overall benefit/risk balance of Kerendia is positive, subject to the conditions stated in section 'Recommendations'.

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 10, 20 and 40 mg mg film-coated tablets is favourable in the following indication:

Kerendia is indicated for the treatment of symptomatic chronic heart failure with left ventricular ejection fraction (LVEF) ≥ 40% in adults.

The CHMP therefore recommends the extension of the marketing authorisation for Kerendia subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

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.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

  Bayer AG 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.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0365/2022 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.