EU RISK MANAGEMENT PLAN (RMP)

KERENDIA®

BAY No. 94-8862
(Finerenone)

No. 3.3

Date of Report:

10 DEC 2025

[redacted]

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EU Risk Management Plan

EU Risk Management Plan for Kerendia® (Finerenone)

RMP version to be assessed as part of this application:

RMP Version number: 3.3

Data lock point for this RMP: 08 JUL 2024

Date of final sign-off: 10 DEC 2025

Rationale for submitting an updated RMP: Update of the EU RMP with the results from Phase III FINEARTS-HF study.

The CKD-T2D Phase III data (FIDELIO-DKD, FIGARO-DKD and pooled FIDELIO-DKD & FIGARO-DKD) presented in this RMP retrospectively excludes data from 34 participants due to a GCP violation identified in 2023 that affected the FIDELIO-DKD and FIGARO-DKD studies. This integrated analysis also excludes data from another 2 participants in FIDELIO-DKD who had been flagged for potential GCP violations after data release in 2020. Thus, a total of 36 participants have been retrospectively excluded.

Summary of significant changes in this RMP:

All modules: Update of the EU RMP with the results from Phase III FINEARTS-HF study and with retrospective exclusion of 36 participants in the CKD-T2D Phase III data (FIDELIO-DKD, FIGARO-DKD and pooled FIDELIO-DKD & FIGARO-DKD).

Part I: This module has been updated in line with the latest version of the SmPC.

Part II Module SI: Updated with the new indication HF with ≥40% LVEF.

Part II Module SII: Update of non-clinical studies and relevance to human usage in the indication HF with ≥40% LVEF including the results of Phase I studies which are relevant for 40 mg dose.

Part II Module SIII: Update of the exposure data for the clinical development programme.

Part II Module SIV: Module was updated to reflect the changes in the clinical development programme.

Part II SV: Post-marketing exposure data was updated.

Part II Module SVII: All sections of the module were updated with retrospective exclusion of 36 participants in the CKD-T2D Phase III data (FIDELIO-DKD, FIGARO-DKD and pooled FIDELIO-DKD & FIGARO-DKD). Module SVII.3 was updated to include clinical trial data from Phase III FINEARTS-HF study and post-marketing data.

Part VI: Summary was updated to reflect the changes introduced to the respective modules of this RMP.

Annexes:

Previous Annex **7.2** (Case descriptions of life-threatening treatment-emergent hyperkalemia events in Phase III studies FIDELIO-DKD and FIGARO-DKD) was removed due to anonymisation of protected personal data since individual study participant/patient level

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information is neither required nor expected in RMPs. Annex **7.2** to **7.4** were updated to include clinical trial data from Phase III FINEARTS-HF study and with retrospective exclusion of 36 participants in the CKD-T2D Phase III data (FIDELIO-DKD, FIGARO-DKD and pooled FIDELIO-DKD & FIGARO-DKD).

Annex **8** was updated.

Other RMP versions under evaluation: Not applicable

Details of the currently approved RMP:

RMP Version number: 2.2

Approved with procedure: EMEA/H/C/005200/II/0001/G

Date of approval: 06 FEB 2023

QPPV signature:

EU QPPV name	Dr. Jutta Pospisil
Contact person for this RMP	[redacted]
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Electronic QPPV signature is attached at the end of the document.

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List of abbreviations

ACC	American College of Cardiology
ACEi	Angiotensin-converting-enzyme inhibitor
ACR	Albumin-to-creatinine ratio
ADME	Absorption, distribution, metabolism and excretion
ADR	Adverse drug reaction
AE	Adverse event
AER	Albumin excretion rate
AF	Atrial fibrillation
AFL	Atrial flutter
AHA	American Heart Association
Apo	Apolipoprotein
ARB	Angiotensin receptor blocker
ARIC	Atherosclerosis Risk in Communities
ARNi	Angiotensin receptor-neprilysin inhibitor
ARTS	miner**A**locorticoid-**R**eceptor antagonist **T**olerability **S**tudy
AUC	Area under the plasma concentration vs time curve
BCRP	Breast cancer resistance protein
BID	Twice daily
C_{max}	Maximum drug concentration in plasma
Caco-2 cell	Human colon adenocarcinoma cells
CAD	Coronary Artery Disease
CARDIA	Coronary Artery Risk Development in Young Adults
CHF	Chronic heart failure

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CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CKD	Chronic kidney disease
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
CREDENCE	Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation
CV	Cardiovascular
CVD	Cardiovascular disease
CYP	Cytochrome P450
DAPA-CKD	Dapagliflozin And Prevention of Adverse outcomes in chronic kidney disease
DBP	Diastolic blood pressure
DCCT	Diabetes Control and Complications
DDI	Drug-drug interaction
DEMAND	Developing Education on Microalbuminuria for Awareness of renal and cardiovascular risk in Diabetes
DKD	Diabetic kidney disease
DLP	Data lock point
DN	Diabetic nephropathy
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency

ENTRED	Échantillon national témoin représentatif des personnes diabétiques
EPAR	European Public Assessment Report
EOD	Every other day
ESC	European Society of Cardiology
ESRD	End-stage renal disease
EU	European Union
F	Female
FIDELIO-DKD	**FI**nerenone in reducing ki**D**n**E**y fai**L**ure and d**I**sease pr**O**gression in **D**iabetic **K**idney **D**isease
FIGARO-DKD	**FI**nerenone in reducin**G** c**A**rdiovascular mo**R**tality and m**O**rbidity in Diabetic Kidney Disease
Folfox	Folinic acid, fluorouracil, and oxaliplatin
G	Grade
GCP	Good clinical practice
GDMT	Guideline-directed medical therapy
GFR	Glomerular filtration rate
GLP-1	Glucagon-like peptide 1
GWTG-HF	Get With The Guidelines Heart Failure
HbA1c	Glycated haemoglobin
HCV	Hepatitis C virus
HDL	High-density lipoprotein
hERG	Human ether-a-go-go-related gene
HF	Heart Failure

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HFmrEF	Heart Failure with mid-range left ventricular Ejection Fraction 41-49%
HFpEF	Heart Failure with preserved left ventricular Ejection Fraction ≥50%
HFrEF	Heart Failure with reduced left ventricular Ejection Fraction ≤40%
HFSA	Heart Failure Society of America
IDNT	Irbesartan Diabetic Nephropathy Trial
IV	Intravenous
K^+	Potassium ion
KDOQI	Kidney Disease Outcomes Quality Initiative
LVEF	Left ventricular ejection fraction
LVSD	Left ventricular systolic dysfunction
M	Male
M-1a, M-1b, M-2a, and M-3a	M-1a, M-1b, M-2a, and M-3a are major, pharmacologically inactive metabolites of finerenone in plasma
MAH	Marketing authorisation holder
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MESA	Multi-Ethnic Study of Atherosclerosis
MLG	MedDRA Labelling Grouping
MR	Mineralocorticoid receptor
MRA	Mineralocorticoid receptor antagonist
N	Number
Na^+	Sodium ion
NHANES	National Health and Nutrition Examination Survey

NYHA	New York Heart Association (classification)
OATP	Organic anion transporting polypeptide
OD/od	Once daily
PBPK	Physiologically based pharmacokinetic modelling
P-gp	Permeability glycoprotein
PBRER	Periodic Benefit-Risk Evaluation Report
PIP	Paediatric Investigation Plan
PO	*Per os* (orally)
PQ	PQ interval in ECG, the time between the beginning of atrial depolarisation and the beginning of ventricular depolarisation
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PT	Preferred term
PY	Patient-Years
QPPV	Qualified Person for Pharmacovigilance
QRS	QRS interval, distance in time on the ECG tracing from the start of the Q-wave to the end of S-wave
QT	QT interval in ECG
QTc	Corrected QT interval in ECG
RAS	Renin-angiotensin system
RENAAL	Reduction in Endpoints in Noninsulin- Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan
RMP	Risk Management Plan
ROW	Rest of the World
SAE	Serious adverse event

SAF	Safety analysis set
SARS-CoV-2	Severe acute respiratory syndrome coronavirus type 2
SBP	Systolic blood pressure
SD	Standard deviation
SGLT2i	Sodium glucose cotransporter inhibitor
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA query
SOC	System Organ Class
SwedeHF	Swedish Heart Failure Registry
T2D	Type 2 diabetes
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
UACR	Urine albumin-to-creatinine ratio
UK	United Kingdom
US	United States (of America)
USRDS	United States Renal Data System

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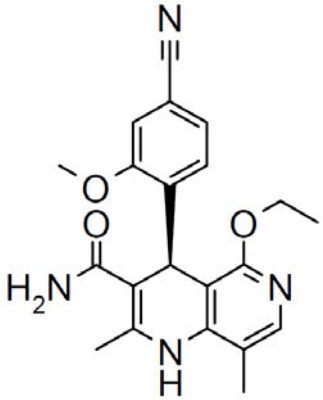
Part I – Product(s) overview

Part I: Product(s) overview

Table Part I.1 – Product(s) overview

Active substance(s) (INN or common name)	Finerenone
Pharmacotherapeutic group(s) (ATC Code)	C03DA05
Marketing Authorisation Holder	Bayer AG
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Kerendia®
Marketing authorisation procedure	Centralised
Brief description of the product	<u>Chemical class</u> Finerenone has the empirical formula of $C_{21}H_{22}N_4O_3$ and a molecular mass of 378.43 g/mol. The chemical name is (*4S*)-4-(4-cyano-2-methoxyphenyl)-5-ethoxy-2,8-dimethyl-1,4-dihydro-1,6-naphthyridine-3-carboxamide). Chemical structure of finerenone: 
	<u>Summary of mode of action</u> Finerenone is a non-steroidal, selective antagonist of the mineralocorticoid receptor (MR) which is activated by aldosterone and cortisol and regulates gene transcription. Its binding to the MR leads to a specific receptor ligand complex that blocks

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	recruitment of transcriptional coactivators implicated in the expression of pro-inflammatory and pro-fibrotic mediators.
	Important information about its composition: The active substance is finerenone. Each film-coated tablet contains 10 mg, 20 mg or 40 mg finerenone. The other ingredients are: Tablet core: lactose monohydrate, microcrystalline cellulose, croscarmellose-sodium, hypromellose 2910, magnesium stearate, sodium laurylsulfate Film-coat: hypromellose 2910, talc, titanium dioxide, iron oxide red (Kerendia® 10 mg and 40 mg), iron oxide yellow (Kerendia® 20 mg and 40 mg).
Hyperlink to the Product Information	Module 1.3.1
Indication(s) in the EEA	Current: *Chronic kidney disease* 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. *Heart failure* Kerendia® is indicated for the treatment of symptomatic chronic heart failure with left ventricular ejection fraction (LVEF) ≥40% in adults
Dosage in the EEA	Current: Serum potassium and estimated glomerular filtration rate (eGFR) have to be measured to determine if finerenone treatment can be initiated and to determine starting dose. *Chronic kidney disease* If serum potassium ≤4.8 mmol/L, finerenone treatment can be initiated. If serum potassium >4.8 to 5.0 mmol/L, initiation of finerenone treatment may be considered with additional serum potassium monitoring within the first 4 weeks based on patient characteristics and serum potassium levels. The recommended starting dose of finerenone is based on eGFR: • 20 mg once daily if eGFR ≥60 mL/min/1.73 m^2 • 10 mg once daily if eGFR ≥25 to <60 mL/min/1.73 m^2 Serum potassium and eGFR have to be remeasured four weeks after initiation or re-start of finerenone treatment or change in

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	dose. Thereafter, serum potassium has to be remeasured periodically and as needed based on patient characteristics and serum potassium levels. The recommended target dose is 20 mg finerenone once daily. *Heart failure* If serum potassium ≤5.0 mmol/L, finerenone treatment can be initiated. The recommended starting dose of finerenone is based on eGFR: • 20 mg once daily if eGFR ≥60 mL/min/1.73 m^2 • 10 mg once daily if eGFR ≥25 to <60 mL/min/1.73 m^2 Serum potassium and eGFR have to be remeasured four weeks after initiation or re-start of finerenone treatment or change in dose. Thereafter, serum potassium and eGFR have to be remeasured periodically and as needed based on patient characteristics. The recommended target dose depends on renal function (eGFR) at initiation of finerenone treatment: • 40 mg once daily if eGFR ≥60 mL/min/1.73 m^2 • 20 mg once daily if eGFR ≥25 to <60 mL/min/1.73 m^2
Pharmaceutical form(s) and strengths	Current: Kerendia® 10 mg film-coated tablets: Pink, oval-oblong film-coated tablet with a length of 10 mm and a width of 5 mm, marked ‘10’ on one side and ‘FI’ on the other side. Kerendia® 20 mg film-coated tablets: Pale yellow, oval-oblong film-coated tablet with a length of 10 mm and a width of 5 mm, marked ‘20’ on one side and ‘FI’ on the other side. Kerendia® 40 mg film-coated tablets: Grey-orange, oval-oblong film-coated tablet with a length of 11 mm and a width of 5 mm, marked ‘40’ on one side and ‘FI’ on the other side.
Is/will the product be subject to additional monitoring in the EU?	Yes

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Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

SI.1 Indications

Kerendia® is indicated:

- for the treatment of chronic kidney disease (with albuminuria) associated with type 2 diabetes in adults.
- for the treatment of symptomatic chronic heart failure with left ventricular ejection fraction (LVEF) ≥40% in adults.

SI.1.1 Chronic kidney disease (with albuminuria) associated with type 2 diabetes in adults

SI.1.1.1 Incidence and prevalence

In 2015 it was estimated that type 2 diabetes (T2D) affected more than 415 million patients worldwide, and it is expected that this number will grow to 642 million in 2040 (1). Approximately 20 to 40% of patients with T2D develop chronic kidney disease (CKD) (2). Among patients with T2D enrolled in the large international study Developing Education on Microalbuminuria for Awareness of renal and cardiovascular risk in Diabetes (DEMAND), 22% had impaired renal function and only 51% had normoalbuminuria (3). Overall, the prevalence of CKD in persons with T2D in European countries is approximately 30 to 60%, depending on the definition of CKD used (4, 5).

Table SI.1: Percentage and 95% confidence intervals of persons with CKD-T2D by eGFR and UACR categories in a US population (6)

		UACR categories		
	eGFR categories, ml/min/1.73 m²	**Normal to mildly increased <30 mg/g**	**Moderately increased 30-300 mg/g**	**Severely increased >300 mg/g**
G1 (Normal or high)	≥90	29.1 (27.0-31.2)	9.2 (7.8-10.5)	1.4 (0.9-1.9)
G2 (Mildly decreased)	60-89	27.4 (25.1-29.6)	8.4 (7.0-9.7)	2.6 (1.9-3.2)
G3a (Mildly to moderately decreased)	45-59	8.0 (6.9-9.2)	3.6 (2.8-4.3)	1.4 (0.8-1.9)
G3b (Moderately to severely decreased)	30-44	2.7 (2.1-3.3)	2.1 (1.5-2.6)	1.0 (0.5-1.5)
G4 (Severely decreased)	15-29	0.6 (0.2-0.9)	1.2 (0.6-1.7)	1.0 (0.5-1.6)
G5 (Kidney failure)	<15	0.0 (0.0-0.1)	0.0 (0.0-0.0)	0.4 (0.1-0.6)

Colours: green=low risk, yellow=moderately increased risk, orange=high risk, red=very high risk

Abbreviations: CKD=chronic kidney disease, eGFR=estimated glomerular filtration rate, G=grade, T2D=type 2 diabetes, UACR=urine albumin-to-creatinine ratio, US=United States.

A population-based study in Romania showed that 7.32% of general population had an estimated glomerular filtration rate (eGFR) below 60 ml/min/1.73 m^2, including 1.35% of persons with a eGFR below 45 ml/min/1.73 m^2 (7). Another population-based study from Iceland calculated the eGFR using the Modification of Diet in Renal Disease (MDRD) equation and showed that 24.9% of male subjects and 14.6% of females are in stage 1 of Kidney Disease Outcomes Quality Initiative (KDOQI) classification (eGFR >90 ml/min/1.73 m^2) (8), around 70% of subjects were placed in stage 2 (eGFR 60-89 ml/min/1.73 m^2), stage 3 (eGFR 30-59 ml/min/1.73 m^2) included 3.7% of males and 11.0% of females, and for stages 4 and 5, the numbers were below 0.5% (9). According to the Échantillon national témoin représentatif des personnes diabétiques (ENTRED) 2007 data, around two-thirds of T2D patients in France had a reduced GFR, but only 22% had a GFR less than 60 mL/min/1.73 m^2 and 8% a GFR less than 45 mL/min/1.73 m^2 (estimated using the Cockroft-Gault equation; MDRD corresponding figures are 23% and 6%, respectively) (10). A French study reported that at least 29% of persons with T2D had CKD based on doctors' data (11). A Finnish study reported a prevalence of CKD stages 1-5 and/or albuminuria in patients with T2D seen in primary care settings to be as high as 68.6% (12). When considering only those with eGFR below 60 ml/min/1.73 m^2, namely CKD stages 3-5, this percentage drops to 34.7%. In Spain, a study conducted in primary care patients with T2D showed a prevalence of CKD of 37.2% based on the presence of eGFR below 60 ml/min/1.73 m^2 or the urine albumin-to-creatinine ratio (UACR) higher than 30 mg/g (13). In a random sample of 2,642 primary care patients with T2D in the Mediterranean area, 34.1% had kidney disease, 22.9% had renal impairment, 19.5% had albuminuria, and 16.4% had diabetic nephropathy (14).

In an early longitudinal study conducted in Denmark among patients with T2D and high albuminuria, 22% developed very high albuminuria during a 10-year follow-up period (15). A study in the United Kingdom (UK) followed 5,102 patients with T2D for a median time of 15 years. Among 4,032 without albuminuria at baseline, 38% developed albuminuria, and among 5,032 with normal plasma creatinine at baseline, 28% developed renal impairment (eGFR ≤60 mL/min/1.73 m^2 or doubling of plasma creatinine levels from baseline). Of 4,006 patients without renal impairment or albuminuria at baseline, 14% developed both albuminuria and renal impairment during follow-up (16). Similar results were observed in 2011 in a Swedish cohort of patients with T2D with no baseline renal disease. Of 3,667 patients, 20% developed albuminuria, and 16% of those patients developed renal impairment (eGFR <60 mL/min/1.73 m^2); overall, 11% of the study population developed renal impairment at an annual rate of 2.2% (17). In Spain, prevalence of CKD among a cohort of T2D patients was 28%, overall (18). In Italy, the 4-year incidence of CKD among persons with T2D ranged from 16 to 37%, depending on the definition of CKD (19, 20).

According to data from the United States of America (US) Renal Data System, new-onset end-stage renal disease (ESRD) is caused by T2D in 42.5% of cases. In the US in 2012, diabetes accounted for most of the prevalent cases (close to 250,000 patients in the US) and incident cases (around 150 new cases per million every year in the US) of ESRD (21). Overall, population-based studies show that the prevalence of high albuminuria in T2D is 25% to 35% and the prevalence of very high albuminuria is 3.5% to 20.5% (22). Further

analyses of more recent National Health and Nutrition Examination Survey (NHANES) data demonstrated a maintained prevalence in the US around 40%, what is interpreted as a suggestion that efforts to prevent CKD can be improved (23). A detailed picture of this problem by renal function stage shows that for the more recent data (2007-2012), the majority of CKD in individuals with T2D is in stages 1-2 (18.5%) and 3a (11.2%). For more advanced stages, the distribution of cases among patients with T2D is: 5.5% for stage 3b, 2.4% for stage 4, and 0.7% for stage 5 (23). Analysis of data from the third NHANES demonstrated a prevalence of kidney disease among patients with diabetes of 42.3%, overall (24).

In a cohort study conducted in India among patients with T2D, the prevalence of overt nephropathy and the prevalence of high albuminuria were 2.2% and 27%, respectively (25). In the coming years, an increase in the prevalence of diabetes (and along with it, CKD) is expected in India and China (22). In Australia, the prevalence of CKD and the prevalence of albuminuria in adults with diabetes have been reported to be 27% and 25%, respectively, and are expected to rise in the coming years (26).

SI.1.1.2 Demographics of the population in the proposed indication – stratified by age, gender, race/ethnic origin

Results from the NHANES III showed that patients with CKD and T2D had a mean age of 62 years, whereas patients with kidney disease without diabetes had a mean age of 57 years (24). In Australia, the prevalence of CKD among adults with diabetes was reported to be 22% in those aged 25-44 years, 19% in those aged 45-64 years, and 35% in those aged 65 or more years (26). A large retrospective cohort study in primary care patients from the UK with T2D and incident CKD showed that mean age at CKD diagnosis was 64 years and 49.4% of them were male. These figures vary substantially when stratifying by eGFR stage resulting in an older population – 51 years old at stage 1 vs 74 at stage 4 – with higher proportion of male – 44.1% at stage 1 vs 59.6% at stage 4 – as the diagnosis is made at a more advanced stage (27).

In the NHANES III, a slightly higher proportion of women was observed in the CKD group compared with the general population (57% in CKD and T2D and 60% in CKD without T2D) (24). In a US-based prospective cohort study of 4,400 patients with diabetes in a managed care setting, overall CKD with eGFR <60 mL/min/1.73 m^2 or high albuminuria was less common in women (49.6%) than in men (56.9%), but CKD with eGFR <30 mL/min/1.73 m^2 was more common in women (3.6%) than in men (2.3%) (28).

A cross-sectional study in a cohort of 32,208 patients with T2D showed that the highest prevalence of increased albuminuria was found in Asian (56%) and Hispanic subgroups (54%) and the lowest was found in Caucasians (41%) (3). A smaller study of 1,978 patients with T2D conducted in the UK showed marked differences between White European and South Asian subpopulations in the prevalence of high and very high albuminuria as well as in risk factor profiles (29). People from Hispanic, Black, Asian, Indian, indigenous, Maori, and Pacific Island ethnic backgrounds have been reported to have an increased prevalence of albuminuric CKD and T2D compared with Europeans (22). In a US-based study of health records from 15,683 individuals with T2D and no prior history of kidney disease, the age- and sex adjusted prevalence of proteinuric CKD and T2D was 24.8% in non-Hispanic White

people, 24.8% in Asian Indian people, 27.6% in Chinese people, 37.9% in Filipino people, 32.5% in Hispanic people, and 35.3% in non-Hispanic Black people (30).

SI.1.1.3 Risk factors for the disease

In patients with T2D, the main independent risk factors for high advanced CKD include ethnicity, retinopathy, duration of diabetes, kidney function, and body height (3). Baseline smoking habit, glycated haemoglobin (HbA1c), systolic blood pressure, proteinuria and serum uric acid together with the presence of vascular comorbidities, and blood lipid levels are strongly and independently associated with faster diabetic kidney disease (DKD) progression (3, 31, 32). Beyond baseline levels, high intrapersonal variability of these physiological parameters is also associated with a higher risk of developing CKD in T2D patients (33).

Hypertension and especially poorly controlled hypertension increase the risk of developing CKD in patients with T2D (19). Blood pressure rises in parallel with the increase in urinary albumin excretion rate (AER), although some data show that high blood pressure might even precede the onset of DKD (31). The renoprotective effects in diabetic patients of blood pressure lowering and blockade of the renin-angiotensin system (RAS) are confirmed by large interventional studies such as Reduction in Endpoints in Noninsulin-Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan (RENAAL) study (34) and Irbesartan Diabetic Nephropathy Trial (IDNT), which showed retardation of DKD with effective blood pressure control and RAS blockade (35, 36).

The Diabetes Control and Complications (DCCT) study showed renal benefits following improved glycaemic control in patients with type 1 diabetes. In the primary prevention cohort, intensive treatment reduced the mean adjusted risk of the cumulative incidence of microalbuminuria (≥28 µg/min) by 34% (95% confidence interval [CI] 2, 56%; P=0.04). Furthermore, intensive treatment decreased the AER by 15% after the first year of therapy (6.5 vs 7.7 µg/min, P <0.001) (37). Appropriate glycaemic management has been shown to delay the onset and progression of increased UACR and reduced eGFR in patients with T2D (38).

Patients with DKD usually present lipoprotein abnormalities such as higher plasma levels of low and very low-density lipoprotein, intermediate-density lipoprotein, and triglycerides, and lower high-density lipoprotein (HDL) concentrations (31). Patients with diabetes but without CKD typically have normal or even elevated HDL cholesterol. The lipid abnormalities related to DKD are not necessarily the same at all DKD stages. Thus, high triglycerides, apolipoprotein (Apo) B, ApoA-II, and HDL3-cholesterol predict incident microalbuminuria, whereas high triglycerides and ApoB predict the progression to macroalbuminuria (39, 40). This lipid metabolic impairment relates also to glycaemic regulation (41).

SI.1.1.4 The main existing treatment options

Currently available and proven pharmacological strategies for CKD and T2D prevention and treatment include the reduction of hyperglycaemia, hypertension, hyperlipidaemia, and the inhibition of the RAS alongside with nutritional management (42, 43). Hyperlipidaemia is addressed with dietary modification and statin therapy (in non-dialysis-dependent CKD and

T2D), and hypertension is generally treated with a RAS blocker (alongside lifestyle modifications) (23, 44, 45). Approximately 60 to 70% of individuals with CKD and T2D receive either angiotensin-converting-enzyme inhibitors (ACEis) or angiotensin receptor blockers (ARBs) (11, 23, 32). Sodium glucose cotransporter inhibitors (SGLT2i), such as canagliflozin, dapagliflozin, ertugliflozin, and empagliflozin, are recommended for the management of glycemia in patients with T2D. Recent results of the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) and the Dapagliflozin And Prevention of Adverse outcomes in CKD (DAPA-CKD) trials showed a significant treatment benefit of the SGLT2i canagliflozin and dapagliflozin, respectively, on renal and cardiovascular (CV) outcomes for patients with CKD with or without T2D (46, 47). According to recent updates in American Diabetes Association and joint European Society of Cardiology/European Association for the Study of Diabetes guidelines from 2019 (48, 49), the use of SGLT2is is recommended for patients with T2D and CKD. Despite standard of care therapy and recent emerging therapies, there remains a high need for additional treatment options to further reduce cardiorenal morbidity and mortality in patients with CKD and T2D. For patients with comorbid CKD, recommendations vary according to the eGFR level; dose adjustments may be required and, in patients with severe renal impairment or ESRD, SGLT2i should be avoided according to label recommendations (50). Recent publications show that initiation of novel anti-hyperglycaemic agents such as SGLT2i is not common among individuals with T2D and renal disease (45). A multinational analysis published in 2019 and conducted in 382 centres in Germany, 11 centres in Austria, and one centre in Luxembourg reported the utilisation rates of SGLT2is in patients with T2D and kidney disease. In this cross-sectional study, just 2.6% of 343,675 patients with T2D received SGLT2i. In this study population, among the subgroup of patients with T2D and comorbid CKD (eGFR <60 mL/min/1.73 m^2 and/or albuminuria [≥30 mg/g]), 2.0% of the 171,930 patients received SGLT2i, suggesting that the diagnosis of CKD did not have a significant impact on the utilisation rate of SGLT2i (51). More recently, the DAPA-CKD trial found that dapagliflozin significantly reduced the risk of kidney function decline, end-stage kidney disease, cardiovascular death, and hospitalisation for HF in CKD patients (hazard ratio: 0.61), regardless of diabetes status (47).

SI.1.1.5 Natural history of the indicated condition in the untreated population, including mortality and morbidity

In Westernised countries, CKD is the leading cause of ESRD in patients with T2D (21, 52). In the NHANES III, mortality in individuals with diabetes but without kidney disease was 11.5% (95% CI: 7.9-15.2) whereas the rate in individuals with CKD and T2D was 31.1% (95% CI: 24.7-37.5), which represents an absolute risk difference of 23.4% compared with individuals without diabetes or kidney disease (24). All-cause, CV and non-CV mortality has been associated with lower eGFR levels in CKD and T2D patients (52). Higher mortality has also been associated with lower eGFR and higher albumin-to-creatinine ratio (ACR) independently of diabetes status in kidney disease patients (52). Proteinuria is a major risk factor for CV mortality in patients with T2D (26, 52). In Australia, among deaths attributed to diabetes, kidney failure was reported as the third most common cause of death after coronary heart disease and hypertension (26).

SI.1.1.6 Concomitant medication(s) in the target population

ACEis and ARBs are considered as standard of care therapy in patients with CKD and T2D and are often prescribed to patients with CKD and T2D at early stages (23, 42, 43, 53). Besides insulin and ACEis, treatment of CV complications in CKD and T2D is common. Beta blockers, statins, and oral antiplatelet agents are used in approximately 50% of patients with CKD and T2D (23, 42, 43, 53). Use of beta blockers increases with progression of CKD from 15.4% in stage 1 to 82.2% in stage 5 CKD (23). Use of diuretics (thiazide diuretics, loop diuretics or potassium-sparing diuretics) increases from CKD stage 1 (21.6%) to CKD stage 4 (76.1%) and drops among CKD stage 5 patients (33.9%) (23). It has been suggested that statins may be cost-effective for CV primary prevention in CKD patients (54). These findings are reflected in guidance from Kidney Disease Improving Global Outcomes (55). Overall, around eight of every ten patients with CKD and T2D are prescribed (32). Noninsulin anti-hyperglycaemic agents used in CKD and T2D (with dose adjustment in some cases) include second-generation sulfonylureas, meglitinides, biguanides, thiazolidinediones, and dipeptidyl peptidase 4 inhibitors in addition to SGLT2i and glucagon-like peptide 1 (GLP-1), yet with limited use in patients with CKD and T2D (43, 45).

SI.1.1.7 Important comorbidities

Patients with mildly or moderately impaired kidney function as defined by quartiles of eGFR levels are 20 times more likely to die of cardiovascular disease (CVD) than of direct renal causes (56). Chronic heart failure is strongly associated with CKD among all CVDs as well as with the severity of the kidney disease. Hypertension, retinopathy, and previous stroke are also risk factors for CKD among T2D patients (21, 23, 57). Severity of CKD is associated also with the presence of coronary heart disease in patients with T2D and CKD (23). The United States Renal Data System (USRDS) 2014 publication reported that elderly CKD patients have a greater burden of CVD than do their non-CKD counterparts for a wide range of conditions, being twice as prevalent for any given CVD (21). The same report shows an increased risk for developing CKD among patients with a previous acute kidney injury (25). A recent analysis of NHANES data corresponding to the period 2007-2012 among T2D patients showed an increase in the prevalence of CV comorbidities along with an increase of CKD disease severity (23). These results are comparable to findings from European countries (58). In a study of primary care patients with T2D in the Mediterranean area, the prevalence of coronary heart disease and stroke were 19.2% and 5.2%, respectively, in patients with albuminuria without renal impairment (the latter defined as eGFR <60 ml/min/1.73 m^2), and 9.8% and 6.9%, respectively, in patients with non-albuminuric renal impairment (14). In a cohort study conducted in India among patients with T2D, hypertension was present in 59.7% of those with high albuminuria and 86.8% of those with very high albuminuria and diabetic retinopathy (25). In a cohort of Swedish patients with T2D who developed albuminuria or renal impairment during 5 years of follow-up, hypertension, previous coronary heart disease, and previous stroke were reported in 94%, 29%, and 10-11%, respectively (17). In a clinical trial population of patients with T2D, CKD, and anaemia, 63-68% had CVD, 41-46% had coronary disease, 30-37% had heart failure, 20-22% had peripheral vascular disease, 17-19% had myocardial infarction, 11% had stroke, and 9-12% had atrial fibrillation reported in their

medical history (56). Anaemia is associated with impaired renal function, and hence a common comorbidity in patients with CKD (59). Overall, 50% of patients with CKD develop anaemia, and this proportion rises up to 90% in patients with CKD stage 5 (60). These figures are similar in patients with CKD and diabetes, although the presentation of anaemia appears to be more severe in patients with both CKD and T2D than in patients with non-diabetic CKD (61). According to a large study conducted in a US claims database during 2011-2013, patients with CKD and T2D were at higher risk of infection, and the magnitude of the association increased with the kidney function stage (62). A more recent report from the Atherosclerosis Risk in Communities (ARIC) study showed a consistent association of hospitalisation due to infection and stage of CKD (63). There are also reports showing an association between CKD and specific viral infections: Severe acute respiratory syndrome coronavirus type 2 infection (SARS-CoV-2) in CKD patients seems to be associated with an enhanced risk of severe coronavirus disease 2019 (COVID-19) disease (64). Furthermore, hepatitis C virus (HCV) is linked to a higher risk of developing and shorter time to CKD (65).

SI.1.2 Heart failure

SI.1.2.1 Incidence and prevalence

Several guidelines that have been written by the European Society of Cardiology (ESC) as well as by American College of Cardiology (ACC)/American Heart Association (AHA) define heart failure (HF) as a “clinical syndrome characterised by typical symptoms (e.g., breathlessness, ankle swelling and fatigue) and signs (e.g., elevated jugular venous pressure, pulmonary crackles and peripheral oedema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress” (66, 67).

Generally, the LVEF determines how HF is classified, which treatments are given, and what the prognosis may be. The ESC Guidelines separate HF into a) HF with reduced LVEF ≤40% (HFrEF), b) HF with mid-range LVEF 41-49% (HFmrEF) and c) HF with preserved LVEF ≥50% (HFpEF) (66). The ACC/AHA guidelines recommend subcategorizing of HF into a) HFrEF with LVEF ≤40%, b) HFimpEF (HF with improved ejection fraction) with previous LVEF ≤40% and a follow-up measurement of LVEF >40%, c) HFmrEF (HF with mildly reduced EF) with LVEF 41-49% and d) HFpEF with LVEF ≥50% (67).

From observational research, recent data on incidence of HFpEF and/or HFmrEF are scarce with only one identified study conducted in the US. In the US, a single study described the cumulative incidence of advanced HFrEF, HFpEF and HFmrEF at 6 years as 14.4%, 11.7% and 11.4%, respectively in a cohort of adult residents of Olmsted County (68).

Overall, the prevalence of HF is reported to increase, which can be attributed to ageing and lifestyle of the population incurring higher prevalence of risk factors (e.g., arterial hypertension, T2D, and obesity). So far, HF affects approximately 64 million people worldwide with the prevalence increasing due to the ageing of the population, improved survival after MI and improved treatment and survival of patients with HF (69). Approximately 50% of patients with HF are reported to have a preserved EF (HFpEF), while HFmrEF is less common (10-25%). However, estimates of HFpEF prevalence vary depending

on the study population, comorbidity burden and settings (outpatient or hospitalised patients) (70, 71).

In the US, the prevalence of HFpEF among the adult patients with HF differs widely between different reports, but in the majority HFpEF is described in around 50% of patients. In the US NCDR PINNACLE Registry, HFpEF cases accounted for 44.6% of HF cases (72), Arnold *et al*., reported 55.5% HFpEF patient among T2D patients with HF (73). A similar rate of HFpEF patients (49.4%) was reported among adult patients hospitalised for worsening of HF (74). A temporal trends evaluation of HF phenotype prevalence from 2005 to 2018 showed increased rates of HFpEF over the years, from 38.2% to 45% among patients hospitalised for HF in the Get With The Guidelines Heart Failure (GWTG-HF) registry (75).

The prevalence of HFmrEF among adults with HF is 14-15% (73, 76) and 11.6% among adult patients hospitalised for worsening of HF (74). The proportion of HFmrEF among patients hospitalised for HF increased from 7.4% to 9.7% between 2005 and 2018 (75). The regional distribution of HF phenotypes across the US regions is heterogenous and likely reflects the difference in the prevalence of main risk factors (including obesity, hypertension, or diabetes), HFpEF was most prevalent in the South (48.5%) followed by the Midwest (21.8%), the West (15.2%), and least prevalent in the Northeast (14.6%). Similarly, HFmrEF was most prevalent in the South (46.6%) and least prevalent in the Northeast (12.8%) (72).

In Europe, the prevalence of HFpEF among the adult patients with HF ranged between 18.7% (77) and 50% (78). In the UK, HFpEF was prevalent in 33% of patients with suspected heart failure from the SHEAF registry (79). In France, the prevalence of HFpEF among patient with decompensated HF was 36.1%. Across a multitude of European reports, the prevalence of HFpEF among adult patients hospitalised for congestive HF (80) was 42.57%. The prevalence of HFmrEF among the adult patients with HF ranged between 19% (78) and 45.3% (81). The prevalence of HFmrEF among adult patients hospitalised for congestive HF was 12.61% (80), while among decompensated HF it was 18.7% (77).

In Japan, HFpEF prevalence was high across patients hospitalised due to HF (43%) (82) or on maintenance haemodialysis (44.3%) (83), while it ranged between 18.6% and 25% (84) across HF adults with comorbid DM and HF. Amongst decompensated HF patients, HFpEF prevalence ranged between 43% (85) and 55.1% (86). The prevalence of HFmrEF ranged between 14.9% (82) and 21% (78).

SI.1.2.2 Demographics of the population in the proposed indication – stratified by age, gender, race/ethnic origin

The mean age for patients diagnosed with HFmrEF is 70.1 years, similar to that of HFpEF patients (69.7 years) (72). The age for advanced heart failure patients with HFmrEF is older with 80.4 years, compared to 78.6 years for HFpEF patients (87).

In HFmrEF, 66.9% of patients are male, whereas in HFpEF, the percentage of males decreases to 48.5% (72). In advanced heart failure, the proportion of males decreases to 57.5% in HFmrEF and 38.4% in HFpEF (87).

Race varied depending on the population included in the respective observational study, suggesting potential racial disparities in the prevalence of HFmrEF and HFpEF. The majority of patients in both HFmrEF and HFpEF appear to be White. The range of White patients in HFmrEF spans from 64.8% to 98.5%, while in HFpEF, it ranges from 67.4% to 92.9%.

African American participants in the Multi-Ethnic Study of Atherosclerosis (MESA) had a 4.6 per 1,000 person-years incidence of HF, followed by Hispanic, White, and Chinese participants with 3.5, 2.4, and 1.0 per 1,000 person-years, respectively (88). In the ARIC Community Surveillance data, African American men and women had the highest burden of new-onset HF cases and the highest age-adjusted 30-day case fatality rate compared to White men and women (89). The Coronary Artery Risk Development in Young Adults (CARDIA) study showed a 20-fold higher incidence of HF in young Black women and men before the age of 50 (cumulative incidence 1.1% and 0.9%, respectively) versus White women and men (0.08% and 0%, respectively) (90).

SI.1.2.3 Risk factors for the disease

Heart failure risk factors encompass hypertension (91), coronary artery disease (CAD) (92), diabetes (93), obesity (94), smoking (95), previous heart attack (91), heart valve problems (96), cardiomyopathy (97), excessive alcohol use (98) and family history (99).

SI.1.2.4 The main existing treatment options

An overview of current treatments for HF with LVEF ≥40% that are included in the most recent recommendations provided by the AHA/ACC/Heart Failure Society of America (HFSA) 2022 Guidelines for the Management of HF, as well as the 2021 ESC Guidelines for the diagnosis and treatment of Acute and Chronic HF is provided in the Table SI.2.

In HF with LVEF 40%-49% (HFmrEF), the AHA/ACC/HFSA Guidelines recommend diuretics as Class 1 treatment, SGLT2i as Class 2a treatment, and ACEi (or ARB or angiotensin receptor-neprilysin inhibitor [ARNi]), MRA and beta blockers as Class 2b treatment (67). The ESC Guidelines recommend loop diuretics (for fluid retention), SGLT2i (dapagliflozin or empagliflozin), intravenous (IV) iron supplementation (for iron deficiency) and finerenone in patients with CKD/T2D as Class I treatment. As Class IIa treatment, the ESC Guidelines recommend IV iron supplementation with ferric carboxymaltose or ferric derisomaltose, and as Class IIb treatment ACEi (or ARB or ARNi), beta blockers and MRA (66, 100).

In comparison in HF with LVEF ≥50% (HFpEF), the AHA/ACC/HFSA Guidelines recommend diuretics as Class 1 treatment. In patients with hypertension, medication should be titrated to achieve blood pressure targets (in alignment with guidelines). As Class 2a, the AHA/ACC/HFSA guidelines recommend SGLT2i and management of AF to improve symptoms; and as Class 2b, MRA and ARB (or ARNi) in patients with lower LVEF range (67). For HF with LVEF ≥50% (HFpEF), only Class I treatment is recommended in the ESC Guidelines: loop diuretics (for fluid retention), treatment of etiologies and cardiovascular or non-cardiovascular comorbidities, SGLT2i (dapagliflozin or empagliflozin), and finerenone in patients with CKD/T2D (66, 100).

Notably, since 2013, multiple new agent classes have been added to the guidelines for treatment of HF patients, including ARNi (sacubitril/valsartan, as an alternative to ACEis/ARBs), SGLT2i, and vericiguat, among others.

SGLT2is are now recognized in European and American guidelines with level 1a and 2a recommendations, respectively (66, 67). SGLT2is are now indicated in adults for the treatment of symptomatic chronic HF, following the results of two randomised clinical trials (EMPEROR-Preserved and DELIVER) each involving around 6,000 patients with an ejection fraction of more than 40% , which demonstrated that the SGLT2is, empaglifozin and dapaglifozin, significantly reduced the primary composite endpoint of hospitalisation for HF and CV death (101, 102). In the SOLOIST-WHF trial, sotagliflozin also demonstrated a significant reduction in total HHF/CV death in patients across the range of EFs, although this trial was underpowered for HFpEF patients and included only patients with diabetes (103).

In addition, ARNIs are recommended as a Class 2b option in the 2022 ACC/AHA/HFSA and the 2023 update of the 2021 ESC Guidelines for HF with LVEF with 40%-49% patients to lower HF hospitalisation and CV mortality risks. This is informed by the PARAGON-HF trial findings, where sacubitril/valsartan significantly reduced CV death and total HF hospitalisations by 22% in patients with an EF ≤57%, compared to valsartan alone (67).

Furthermore, the 2022 AHA HF guidelines advise HF self-care education, and for patients with overt congestion, recommend diuretics (Class 1) and steroidal MRAs (Class 2b), particularly for patients with HFpEF at the lower end of the LVEF spectrum. The current ESC Guidelines also consider MRAs for HFpEF patients, balancing benefits against hyperkalemia risks (103), drawing on insights from the TOPCAT trial (66).

Table SI.2: Guideline-directed medical therapy (GDMT) for HF with LVEF ≥40 %

HF sub-type	AHA/ACC/HFSA (2022)[1]	2021 ESC Guidelines[2] ***(with new ESC guidance from 2023 "focused update")***
HF with LVEF 40%-49% (HFmrEF)	**Class 1:** - Diuretics, as needed **Class 2a:** - SGLT2i **Class 2b:** - ACEi or ARB or ARNi - MRA - Beta Blockers	**Class I:** - Loop diuretics (for fluid retention) - SGLT2i: Dapagliflozin/Empagliflozin (based on updated guidance from 2023) - IV iron supplementation, in those with iron deficiency (based on updated guidance from 2023) - Finerenone (non-steroidal MRA) in patients with CKD/T2D, (based on updated guidance from 2023) **Class IIa:** - IV iron supplementation with ferric carboxymaltose or ferric derisomaltose, in those with iron deficiency (based on updated guidance from 2023) **Class IIb:** - ACEi or ARB or ARNi - Beta Blockers - MRA

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Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Table SI.2: Guideline-directed medical therapy (GDMT) for HF with LVEF ≥40 %

HF sub-type	AHA/ACC/HFSA (2022)[1]	2021 ESC Guidelines[2] ***(with new ESC guidance from 2023 "focused update")***
HF with LVEF ≥50% (HFpEF)	**Class 1:** - Diuretics, as needed - In patients with hypertension, medication should be titrated to achieve blood pressure targets (in alignment with guidelines) **Class 2a:** - SGLT2i - Management of AF, to improve symptoms **Class 2b:** - MRA (in patients with lower LVEF ranges) - ARB or ARNi (those with lower LVEF ranges)	**Class I:** - Loop diuretics (for fluid retention) - Treatment of etiologies and CV/non-CV comorbidities - SGLT2i: Dapagliflozin/Empagliflozin (based on updated guidance from 2023) - Finerenone (non-steroidal MRA) in patients with CKD/T2D, (based on updated guidance from 2023)

[1] AHA/ACC/HFSA Guidelines (2022) (67): Class 1 = Strong; Class 2A = Moderate; Class 2B = Weak; Class 3 = No Benefit; Class 4 = Harmful.

[2] ESC Guidelines (2021) Recommendations (66, 100): Class I = "Is recommended"; Class IIa = "Should be considered"; Class IIb = "May be considered"; Class III = "Is not recommended"

Abbreviations: ACC=American College of Cardiology, ACEi=angiotensin-converting enzyme inhibitors, AF=atrial fibrillation, AHA=American Heart Association, ARB=angiotensin (II) receptor blocker, ARNi=angiotensin receptor-neprilysin inhibitor, CKD=chronic kidney disease, CV=cardiovascular, ESC=European Society of Cardiology, GDMT=Guideline-directed medical therapy, HF=Heart failure, HFmrEF=heart failure with mildly reduced ejection fraction, HFpEF=heart failure with preserved ejection fraction, HFSA=Heart Failure Society of America, IV=intravenous, LVEF=left ventricular ejection fraction, MRA=mineralocorticoid receptor antagonist, SLGT2i=sodium glucose cotransporter-2 inhibitors, T2D=type-2 diabetes.

SI.1.2.5 Natural history of the indicated condition in the untreated population, including mortality and morbidity

According to Fayol *et al*. 2022 who evaluated mortality in patients hospitalised for congestive HF, a total of 383 (41.3%) deaths during the follow-up period (2.17 ± 1.38 years) were identified across patients with HFpEF. As for patients with HFmrEF, a total of 108 (39.3%) deaths were observed during follow-up. The all-cause mortality did not differ significantly among the two groups of patients (HFmrEF vs HFpEF) (80).

As for HFpEF with comorbidities, a specific study presented patients with five phenotypic clusters of HFpEF patients from the Swedish registry (SwedeHF), including 6,909 patients: a young-low comorbidity burden cluster, an atrial fibrillation-hypertensive cluster, an older-atrial fibrillation cluster, an obese-diabetic cluster, and a cardiorenal cluster. The event rate for all-cause mortality ranged from 10% (95% CI: 7.1-13) to 58.7% (95% CI 55.4-62.0), depending on phenotyping cluster. Patients in the young-low comorbidity burden cluster had

the lowest, while patients in the older-atrial fibrillation and cardiorenal cluster had the highest event rates (104).

In a study comparing the risk of all-cause death in specialty care vs primary care for patients with HFpEF and HFmrEF between 2000-2018 registered in the SwedeHF. Follow-up in specialty care was associated with 50% lower mortality rate compared to primary care (13.2 vs 22.7 events/100 PY). Similar results have been observed in patients with HFmrEF (10.3 vs 21.3 events/100 PY). This difference was related to the youth of the patients referred to specialty care, the fact that they were more often male, had higher socioeconomic status, lower EF, more severe HF but fewer comorbidities, and were more likely to receive guideline-recommended HF therapies. Referral to specialty care was independently associated with better survival but paradoxically higher risk of first HF hospitalisation, suggesting that rigorous monitoring may entail earlier hospitalisations that avert subsequent death (105).

SI.1.2.6 Concomitant medication(s) in the target population

In Europe, beta blockers seem to the most used concomitant drugs (52.4% to 89.8%), followed by RAS inhibitors (67.6% to 88.2%) and by diuretics (from 15.6% to 85%). Other treatments also commonly prescribed are nitrates, digoxin, and anticoagulants (81, 104, 105).

As for the US, the most prescribed concomitant drugs appear to be beta blockers (61.2% to 74.7%), ACEi/ARB (46.02% to 61.2%) then diuretics (43.4% to 60.1%). MRAs, digoxin, ARNi and anticoagulants were also used across different study populations (72, 106).

Overall, in terms of prescribed medications, there is no significant difference between patients with HFpEF and HFmrEF. In total, the most commonly used concomitant drugs are beta blockers, diuretics (loop or thiazide), ACEi/ARBs (in combination or separately), MRAs, digoxin, and anticoagulants. The use of SGLT2is in real-life in patients with HFpEF and/or HFmrEF was rarely reported as they were more recently approved. However, following the approval of Jardiance® in 2022, RWE for this class is expected to improve (107).

SI.1.2.7 Important comorbidities

The most commonly reported comorbidities among patients with HFpEF and/or HFmrEF are hypertension, AF, CAD, T2D, obesity, CKD, and chronic obstructive pulmonary disease (COPD).

In the large nationwide Swedish registry (2000-2018) collecting data from mainly secondary care inpatients, outpatient wards and clinics and from primary care for clinician-judged HF, the most frequently reported comorbidities among patients with HF with follow-up in specialty care vs primary care were: hypertension (62.2% vs76.6%), atrial fibrillation (AF) (54.8% vs 63.3%), ischaemic heart disease (54.3% vs 56.7%), kidney disease (44.3% vs 61.7%) and anaemia (33% vs 40.8%) (105).

The large US registry (PINNACLE; 2008-2016) reported results on comorbidities among 1,103,386 patients with HF. The most common comorbidities were hypertension (75.6%), CAD (59.5%), AF or atrial flutter (AFL) (34.4%) and diabetes (26.1%). It was observed that patients with HFmrEF were more likely to have higher prevalence of CAD, peripheral artery

disease, AF or AFL, CKD, diabetes and were more likely to have prior myocardial infarction compared to HFrEF or HFpEF patients (p<0.001) (72).

In another US-based, outpatient registry of patients with diabetes and prediabetes (2013-2016) prescribed at least one glucose-lowering medication, and with diagnosed HF (55.5% with LVEF ≥50%), CV comorbidities were common with 87.3% of patients having hypertension, 59.0% of patients having CAD, and 37% having AF/AFL (73).

Part II: Module SII - Non-clinical part of the safety specification

An extensive non-clinical safety pharmacology, pharmacokinetics, and toxicology programme was conducted to investigate the systemic toxicity as well as exaggerated pharmacological effects of finerenone and to support the filing and registration for its intended use for prevention of progression of CKD in patients with T2D. This programme also enables filing and registration in the indication of HF in patients with LVEF of ≥40%. A comprehensive non-clinical absorption, distribution, metabolism and excretion (ADME) profile of finerenone including victim and perpetrator drug-drug interaction (DDI) properties of parent drug and major human plasma metabolites was generated. The programme also included safety pharmacology studies in both *in vitro* and *in vivo* test systems to assess potential effects on main vital physiological functions, *in vitro* and *in vivo* genetic toxicity studies, as well as oral repeat-dose toxicity studies (up to 13-weeks duration in mice, up to 26-weeks duration in rats, and up to 39-weeks duration in dogs). In addition, the reproductive and developmental toxicity profile was determined in rats and rabbits and juvenile toxicity studies in rats were conducted. Finally, the carcinogenic potential of finerenone was determined in 2 years rat and mouse carcinogenicity studies. The toxicological programme was designed to support the chronic use of finerenone in humans.

Key safety findings from non-clinical studies and their relevance to human usage:

Table SII.1: Key safety findings from non-clinical studies and relevance to human usage

Key safety findings (from non-clinical studies)	Relevance to human usage
Single- and repeat-dose toxicity	
Finerenone was tested in oral single dose toxicity studies in rats and mice as well as in an intravenous (IV) single dose toxicity study in mice. The maximum non-lethal doses are 50 mg/kg in rats after oral administration and 2,000 mg/kg and 30 mg/kg in mice after oral and IV dosing, respectively. No specific signs of toxicity were observed.	Single dose toxicity studies in rats and mice revealed no organ-specific signs of toxicity.
After daily oral administration for up to 13-week in mice, 26-week in rats and 39-week in dogs, finerenone was generally well tolerated in all three species. The toxicological profile was mainly characterised by exaggerated pharmacological activity of finerenone. Target organs were adrenal glands, kidney, liver, urinary bladder, female genital tract, and prostate. Most effects were limited to high dose levels tested in the shorter-term studies in rats and not seen in the chronic study at multiples of up to 17 times the maximum human therapeutic exposure for the 20 mg dose and at multiples of up to 7 for the 40 mg dose. In the chronic study in dogs, multiples of 60 for the	In animal toxicity studies, finerenone caused an impaired water-electrolyte balance (increased K^+/Na^+ ratio) with a secondary response in adrenals, as expected for the mode of action. As with other mineralocorticoid receptor antagonists (MRAs) and due to mode of action, an impaired water-electrolyte balance (increased K^+/Na^+ ratio) may occur in humans at clinically relevant exposure levels. Other effects (degenerative effects in kidney, mild changes in serum liver enzymes, urinary bladder lesions, atrophic changes in female genital organs, decrease in prostate weights)

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Table SII.1: Key safety findings from non-clinical studies and relevance to human usage

Key safety findings (from non-clinical studies)	Relevance to human usage
20 mg dose and of 24 for the 40 mg dose were reached. The most prominent effects of finerenone were an imbalance in water and electrolyte homeostasis (increased K^+/Na^+ ratio) and a compensatory hypertrophy of the zona glomerulosa of the adrenal glands, which was shown to be reversible after 4 weeks recovery. After 4- and 13-week treatment in rats with doses of ≥10 mg/kg (about 8- to 19-fold of the human therapeutic exposure for the 20 mg dose and about 3- to 7-fold for the 40 mg dose), mild degenerative changes in the kidney were observed which were associated with a statistically significant increase of serum urea and µ-glutathione S-transferase after 4-week treatment and a slight and reversible increase in basophilic tubules. Also, in high dose female dogs in the 4-week study, an increase in serum urea was found without morphological alterations of the kidneys. In the chronic study in rats and in the subchronic and chronic study in dogs, no adverse effects on kidney were found. In the rat 4- and/or 13-week studies, mild changes in serum liver enzymes were found, which were not substantiated after longer treatment, and which were not accompanied by adverse morphological findings in liver. In the subacute and subchronic study in rats, urinary bladder lesions (focal or diffuse transitional cell hyperplasia, occasional inflammatory infiltration) were found at the high dose of 30 mg/kg, which were not observed in the chronic study, so that these lesions are regarded as an adaptive response. In the rat 4- and 13-week studies, the high dose resulting in signs of general toxicity also caused atrophic changes in female sex organ. The $AUC_{unbound}$ in female rats at the high dose was about 21 times the maximum human exposure for the 20 mg dose and about 9 times for the 40 mg dose. In the dog repeat-dose toxicity studies, there was no impact on female genital tract (high dose levels corresponded to 60-164 times the human therapeutic exposure for the 20 mg dose and 24-65 times for the 40 mg dose). In dogs, a decrease in prostate weights without	were observed at exposures considered sufficiently in excess to the maximum human exposure indicating little relevance to clinical use.

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Table SII.1: Key safety findings from non-clinical studies and relevance to human usage

Key safety findings (from non-clinical studies)	Relevance to human usage
correlating morphological changes was found starting at an $AUC_{unbound}$ of 10 times the maximum human therapeutic exposure for the 20 mg dose and 4 times for the 40 mg dose. There were not additional findings in the male genital tract at the high dose representing 24 or 60 times the maximum human exposure.	
Reproductive and developmental toxicity	
In the fertility studies in rats, signs of impaired female fertility (decreased number of corpora lutea and implantation sites) were found at high multiples of the human exposure (about 21 times for the 20 mg dose and about 9 times for the 40 mg dose), whereas no effects on male fertility were seen. In the chronic study in dogs, a decrease in prostate size and weight without any other morphological findings was found at an unbound AUC of about 10 times that in humans for the 20 mg dose and about 4 times for the 40 mg dose.	No human data on the effect of finerenone on fertility is available. Animal studies with finerenone did not indicate a risk of impaired male fertility. Animal studies with finerenone indicated impaired female fertility at exposures considered sufficiently in excess to the maximum human exposure indicating no clinical relevance.
In the embryo-foetal toxicity study in rats, finerenone resulted in reduced placental weights and signs of foetal toxicity, including reduced foetal weights and retarded ossification at the maternal toxic dose of 10 mg/kg/day corresponding to an $AUC_{unbound}$ of 19 times that in humans for the 20 mg dose and 7 times for the 40 mg dose. At 30 mg/kg/day, the incidence of visceral and skeletal variations was increased (slight oedema, shortened umbilical cord, slightly enlarged fontanelle) and one foetus showed complex malformations including a rare malformation (double aortic arch) at an $AUC_{unbound}$ of about 25 times that in humans humans for the 20 mg dose and about 10 times for the 40 mg dose. The doses free of any findings (low dose in rats, high dose in rabbits) provided safety margins of 10 to 13 times for $AUC_{unbound}$ for the 20 mg dose and 4 to 5 times for the 40 mg dose. When rats were exposed during pregnancy and lactation in the pre- and postnatal developmental toxicity study, pup mortality and other adverse effects (lower pup weight, delayed pinna unfolding) were increased at about 2 or 4 times the $AUC_{unbound}$ expected in humans. The dose free of findings provided a safety margin of about 2 for $AUC_{unbound}$ for the 20 mg dose and was in the	There are no data on the use of finerenone in pregnant women. In studies on embryo-foetal development, effects in rats were observed at finerenone exposures considered sufficiently in excess to the maximum human exposure thereby not indicating an increased concern for teratogenicity or embryolethality. The variations observed in rats are expected to be reversible after birth. In addition, in the postnatal developmental toxicity study, slightly increased locomotor activity was found in the offspring after weaning, which may have been caused by exposure during pregnancy. Finerenone should not be used during pregnancy unless there has been careful consideration of the benefit for the mother and the risk to the foetus. Women of childbearing potential should use effective contraception during treatment with finerenone. Male patients do not have to use contraception when treated with finerenone. Embryo-foetal toxicity is considered as an **important potential risk**. Use in pregnancy and lactation is considered as **missing information**.

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Part II: Module SII – Non-clinical part of the safety specification

Table SII.1: Key safety findings from non-clinical studies and relevance to human usage

Key safety findings (from non-clinical studies)	Relevance to human usage
range of human exposure for the 40 mg dose. In addition, the offspring showed after weaning slightly increased locomotor activity with no other neurobehavioural changes. Based on the data on developmental toxicity of finerenone, there is no indication of a male mediated developmental toxicity in the corresponding sexual female partner.	
In juvenile rats, the pharmacological profile of finerenone is in line with the findings observed in adult rats with some effects on urinary volume and some adaptive findings in the adrenals. There were no adverse effects observed up to the high dose of 10 mg/kg. When comparing the toxicological profile in the juvenile animals with the results of the study in adult rats, there is no indication of any higher sensitivity of juvenile animals, on the contrary, juvenile animals had less findings than adult animals.	The juvenile toxicity studies do not indicate a risk for children. So far, there are no data regarding safety and efficacy in individuals less than 18 years of age. A Paediatric Investigation Plan (PIP) has been approved for finerenone for both CKD and HF.
Finerenone is excreted into the milk of lactating rats, resulting in exposure in pups. In the postnatal developmental toxicity study, when rats were exposed via milk, pup mortality was increased at about 2 or 4 times the $AUC_{unbound}$ expected in humans. The dose free of findings provided a safety margin of about 2 for $AUC_{unbound}$ for the 20 mg dose for CKD and was in the range of therapeutic exposure for the 40 mg dose for HF.	It is unknown whether finerenone or its metabolites are excreted in human breast milk. Available pharmacokinetic and toxicological data in animals have shown excretion of finerenone and its metabolites in milk. Rat pups exposed by this route showed adverse effects. A risk to the nursing infant cannot be excluded. Breastfeeding should be discontinued if use of finerenone is considered essential. Use in pregnancy and lactation is considered as **missing information**.
Genotoxicity	
The Salmonella/microsome test for point mutations, the cytogenetics *in vitro* assay as well as the micronucleus test *in vivo* for clastogenicity were negative.	Non-clinical tests found no evidence for a genotoxic risk to patients.
Carcinogenicity	
In 2-year carcinogenicity studies in rats and female mice, finerenone did not show a carcinogenic potential. In male mice, an increase in Leydig cell adenoma was observed at doses representing 26 times the $AUC_{unbound}$ in humans for the 20 mg dose in CKD and 10 times for the 40 mg dose in HF. A dose representing 17 times the $AUC_{unbound}$ in humans for the 20 mg dose in CKD or 7 times for the 40 mg dose in HF did not	Non-clinical data revealed no carcinogenic risk of finerenone for humans at the clinical doses. Based on the known sensitivity of rodents to develop Leydig cell tumours and the pharmacology-based mechanism at supratherapeutic doses as well as adequate safety margins, the increase in these tumours in male mice is not clinically relevant.

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Table SII.1: Key safety findings from non-clinical studies and relevance to human usage

Key safety findings (from non-clinical studies)	Relevance to human usage
cause any tumours.	
Safety pharmacology	
In dogs, finerenone did not affect blood pressure and heart rate. In the electrocardiogram (ECG), QRS, QT, and corrected QT interval in ECG (QTc) remained unaffected. The PQ interval was slightly shortened by 5 to 10% at maximal protein-unbound plasma concentrations >6-fold the maximum human levels. Finerenone as well as its major human plasma metabolites (M-1a, M-1b, M-2a, and M-3a) had no effects on cardiac repolarisation *in vitro* (human ether-a-go-go-related gene [hERG] K^+ current). After IV or oral (PO) administration of [^{14}C] finerenone to rats, low radioactivity concentrations were determined in the brain, indicating very low penetration of finerenone across the blood/brain barrier. Single treatment with finerenone (doses: 3 - 10 - 30 mg/kg) had no effects on the following parameters of CNS function in rats: behaviour, locomotor activity, body temperature, motor coordination, and chemoconvulsion threshold (pentylenetetrazole). The latter was confirmed by means of a second chemoconvulsion threshold (pentylenetetrazole) test at higher doses (30 - 60 - 100 mg/kg) in order to achieve the maximal feasible mean drug plasma concentrations (114 - 168 - 162 mg/L) at 5 h post-treatment. In rats, finerenone tested at the entire dose range (3 - 10 - 30 mg/kg) had no physiologically significant effects on respiration rate, tidal volume and minute volume.	In the safety pharmacology studies assessing CV, nervous and respiratory function, the only finding was a slight shortening of the PQ interval in dogs at free plasma concentrations of about 5 times or 13 times the human therapeutic concentration. Therefore, no clinical relevance is expected. In a thorough QT study #15113 in healthy subjects and a concentration-QTc analysis thereof, finerenone (single 20 mg and 80 mg oral dose) had no effect on the QTc interval.
Drug-drug interactions	
In vitro, finerenone was highly permeable in human colon adenocarcinoma (Caco-2) cells and classified as a permeability glycoprotein (P-gp) substrate.	In light of the virtually complete absorption in man (mass-balance study #14502 with ^{14}C-finerenone), an involvement of P-gp *in vivo* can be ruled out. Finerenone is not expected to be a victim of pharmacokinetic drug-drug interactions (DDIs) when co-administered with P-gp inhibitors during absorption.

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Table SII.1: Key safety findings from non-clinical studies and relevance to human usage

Key safety findings (from non-clinical studies)	Relevance to human usage
In vitro, oxidative metabolism of finerenone was predominantly catalysed by CYP3A4 (90%) with minor contributions by CYP2C8 (10%).	CYP3A4 inhibitors Concomitant use of finerenone with strong CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, ritonavir, nelfinavir, cobicistat, clarithromycin, telithromycin or nefazodone) is expected to result in more than 5-fold (i.e., more than 400%) increase in finerenone area under the plasma concentration vs time curve (AUC) and is contraindicated. Concomitant use of erythromycin (500 mg thrice daily), a moderate CYP3A4 inhibitor, increased finerenone mean AUC and C_{max} by 248% and 88%, respectively. Another moderate CYP3A4 inhibitor, verapamil (240 mg controlled-release tablet once daily), increased finerenone mean AUC and C_{max} by 170% and 120%, respectively. Monitoring of serum potassium during individual dose titration is recommended if finerenone is used concomitantly with moderate or weak CYP3A4 inhibitors. CYP3A4 inducers Concomitant use of finerenone with strong CYP3A4 inducers (e.g., phenytoin, carbamazepine, phenobarbitone or St. John's wort), or moderate CYP3A4 inducers (e.g., efavirenz) is expected to markedly decrease finerenone plasma concentrations and result in reduced therapeutic effect and should be avoided. CYP2C8 inhibitors Concomitant use of gemfibrozil (600 mg twice daily), a strong inhibitor of CYP2C8, increased finerenone mean AUC and C_{max} by 10% and 16%, respectively. This is not clinically relevant.
In vitro, competitive inhibition was observed on CYP2C8, CYP1A1, CYP3A4, CYP2C9 and CYP2C19 (rank order). In addition, irreversible inhibition was indicated for CYP3A4. Finerenone and its major human plasma metabolites showed an inductive potential on CYP3A4 in human hepatocytes.	*In vivo* relevance to human usage can be ruled out with regards to inhibition of CYP1A1 and CYP2C19 enzymes, based on *in vitro* data and accepted prediction algorithms. Finerenone 20 mg: A single dose of 20 mg finerenone had no effect on AUC and C_{max} of the CYP2C8 probe substrate repaglinide. Finerenone does not inhibit CYP2C8. In healthy subjects, a multiple-dose regimen of

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Table SII.1: Key safety findings from non-clinical studies and relevance to human usage

Key safety findings (from non-clinical studies)	Relevance to human usage
	20 mg finerenone once daily had no effect on the AUC of the CYP3A4 probe substrate midazolam. Finerenone neither inhibits nor induces CYP3A4. Lack of mutual pharmacokinetic interaction was demonstrated between 20 mg finerenone and the CYP2C9 substrate warfarin. <u>Finerenone 40 mg:</u> In healthy subjects, a multiple-dose regimen of 40 mg finerenone once daily resulted in 59% (AUC) and 30% (C_{max}) exposure increase of CYP2C8 probe substrate repaglinide (also a substrate for CYP3A4) and in 31% (AUC) and 15% (C_{max}) exposure increase of CYP3A4 probe substrate midazolam. Accordingly, finerenone at 40 mg once daily dose regimen is a weak inhibitor of CYP2C8 and CYP3A4.
In vitro, inhibition of P-gp, breast cancer resistance protein (BCRP) and organic anion transporting polypeptides (OATP)1B1/B3 by finerenone and/or its metabolites was observed.	<u>Finerenone 20 mg:</u> In healthy subjects for the 20 mg finerenone dose, lack of mutual pharmacokinetic interaction was demonstrated between finerenone and the P-gp substrate digoxin. <u>Finerenone 40 mg:</u> PBPK modelling demonstrated that also 40 mg finerenone does not have a clinically relevant effect on the P-gp substrate digoxin. *In vitro* data suggest a weak interaction potential of finerenone and/or its metabolites with BCRP and/or OATP transporter substrates according to pertinent guideline algorithms. Data of the clinical DDI study (#21429) indicate no or no relevant effect of multiple-dose regimen of 40 mg finerenone once daily on rosuvastatin, a BCRP and OATP substrate. Finerenone has no potential *in vivo* to inhibit these transporters.

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Table SII.1: Key safety findings from non-clinical studies and relevance to human usage

Key safety findings (from non-clinical studies)	Relevance to human usage
Other toxicity-related information or data	
Phototoxicity	
The initial *in vitro* assay for phototoxicity (3T3-Neutral Red Uptake assay) was slightly positive. Due to the variability of the results of the individual assays in this initial test, a second study was performed, which indicated that finerenone does not have any phototoxic potential. In addition, no relevant accumulation of finerenone was seen in the skin and pigmented tissue. Thus, taking all evidence together, finerenone is regarded as non-phototoxic.	Non-clinical data revealed that no precautions are needed with regard to exposure to sunlight.

Abbreviations: AUC=Area under the plasma concentration vs time curve, BCRP=Breast cancer resistance protein, CKD=Chronic kidney disease, Caco-2=human colon adenocarcinoma, CNS=Central nervous system, CV=coefficient of variation, CYP=Cytochrome P450, C_{max}=Maximum drug concentration in plasma, DDI=Drug-drug interaction, Herg=human ether-a-go-go-related gene, HF=Heart failure, IV=Intravenous, ECG=electrocardiogram, MRA=mineralocorticoid receptor antagonist, OATP=Organic anion transporting polypeptide, PBPK=Physiologically based pharmacokinetic modelling, P-gp=Permeability glycoprotein, PIP=Paediatric Investigation Plan, PO=*per os* (orally), QTc=corrected QT interval in ECG.

Conclusions on non-clinical data

The following list of safety concerns has been identified from non-clinical data and are included as important potential risk or missing information in Part II: Module SVII - Identified and potential risks:

Table SII.2: Safety concerns identified from non-clinical data

Important identified risk:
- None identified

Important potential risk:
- Embryo-foetal toxicity

Missing information:
- Use in pregnancy and lactation

Part II: Module SIII - Clinical trial exposure

Exposure data to finerenone includes datasets from five completed Phase II studies and three completed Phase III studies that were conducted in three different patient populations:

1) Stable chronic heart failure (CHF):

- One Phase IIa study ARTS (#14563) was conducted in patients with stable CHF with systolic left ventricular dysfunction and mild or moderate CKD: In this study, 313 subjects received at least one dose of finerenone (2.5 mg, 5 mg, or 10 mg once daily [OD] or 5 mg twice daily [BID]), 63 subjects received spironolactone, and 81 subjects received placebo with a mean treatment duration of approx. 30 days;

2) Worsening of CHF:

- Two Phase IIb studies ARTS-HF (#14564) and ARTS-HF Japan (#16815) were conducted in patients with worsening of CHF who also had either type 2 diabetes (T2D) with/without CKD or moderate CKD alone: In these studies (pooled data), 893 subjects received at least one dose of finerenone (2.5 mg, 5 mg, 7.5 mg, 10 mg 15 mg, or 20 mg OD) and 234 subjects received eplerenone with a mean treatment duration of approx. 75 days;

3) CKD and T2D:

- Two Phase IIb studies ARTS-DN (#16243) and ARTS-DN Japan (#16816) were conducted in patients with CKD and T2D: In these studies (pooled data), 811 subjects received at least one dose of finerenone (1.25 mg, 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, or 20 mg OD) and 106 subjects received placebo with a mean treatment duration of approx. 90 days;
- Two Phase III studies FIDELIO-DKD (#16244) and FIGARO-DKD (#17530) were conducted in patients with CKD and T2D: In FIDELIO-DKD study, 2,818 subjects received at least one dose of finerenone (10 mg or 20 mg) and 2,828 subjects received placebo with a mean treatment duration of 2.2 years. In FIGARO-DKD study, 3,671 subjects received at least 1 dose of finerenone (10 mg or 20 mg) and 3,646 subjects received placebo with a mean treatment duration of 2.9 years.

4) HF with LVEF ≥40%:

- One Phase III study FINEARTS-HF (#20103) conducted in patients with HF and a LVEF of ≥40%: In this study, 2,993 subjects received at least one dose of finerenone (10 mg or 20 mg OD or 10-20 mg, 10-40 mg, 20-40 mg OD), and 2,993 subjects received placebo with a mean treatment duration of approx. 2.1 years.

Detailed description of all completed Phase II and Phase III studies with finerenone is provided in Table SIII.1 below.

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Table SIII.1: Overview of completed Phase II and Phase III clinical studies of finerenone

Study number (status) number of study sites (regions)	Design (indication)	Number of participants by intervention group	Study population
Phase II			
Stable chronic heart failure			
Study 14563, ARTS (completed) Report A52945 54 sites (10 countries)	Phase IIa, randomised, double-blind, placebo-controlled, parallel-group, multicentre study (Parts A and B), with an additional open-label active comparator for Part B Duration (Mean ± SD): Part A, 28.0 ± 3.3 days; Part B: 26.2 ± 6.3 days Indication: Stable CHF with LVSD and mild CKD (Part A) or moderate CKD (Part B)	Part A: Finerenone 2.5 mg OD (65 randomised/ 16 treated/ 15 completed treatment) Finerenone 5 mg OD (65 randomised/ 16 treated/ 14 completed treatment) Finerenone 10 mg OD (65 randomised/ 17 treated/ 17 completed treatment) Placebo (65 randomised/ 16 treated/ 15 completed treatment) Part B: Finerenone 2.5 mg OD (393 randomised/ 66 treated/ 56 completed treatment) Finerenone 5 mg OD (393 randomised/ 67 treated/ 60 completed treatment) Finerenone 10 mg OD (393 randomised/ 67 treated/ 60 completed treatment) Finerenone 5 mg BID (393 randomised/ 65 treated/ 55 completed treatment) Spironolactone tablets 25 mg or 50 mg OD up-titrated (393 randomised/ 63 treated/ 51 completed treatment) Placebo (393 randomised/ 65 treated/ 57 completed treatment)	Part A Gender: 52 M / 13 F Average age (Mean ± SD): 66.3 ± 8.90 years Age range: 42-85 years Part B Gender: 312 M / 80 F Average age (Mean ± SD): 72.1 ± 7.80 years Age range: 40-89 years

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Table SIII.1: Overview of completed Phase II and Phase III clinical studies of finerenone

Study number (status) number of study sites (regions)	Design (indication)	Number of participants by intervention group	Study population
Worsening of chronic heart failure			
Study 14564, ARTS-HF (completed) Report-PH-38020 168 sites (25 countries)	Phase IIb, randomised, adaptive, double-blind, double-dummy, comparator-controlled, parallel-group, multicentre study Duration (Mean ± SD): 75.5 ± 28.7 days Indication: Worsening of CHF	Finerenone 2.5 mg OD, possibly up-titrated to 5 mg OD (1,066 randomised/ 173 treated/ 121 completed treatment) Finerenone 5 mg OD, possibly up-titrated to 10 mg OD (1,066 randomised/ 165 treated/ 122 completed treatment) Finerenone 7.5 mg OD, possibly up-titrated to 15 mg OD (1,066 randomised/ 169 treated/ 123 completed treatment) Finerenone 10 mg OD, possibly up-titrated to 20 mg OD (1,066 randomised/ 170 treated/ 134 completed treatment) Finerenone 15 mg OD, possibly up-titrated to 20 mg OD (1,066 randomised/ 165 treated/ 124 completed treatment) Eplerenone 25 mg EOD, possibly up-titrated to 25 mg OD on Day 30 if serum 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 serum potassium ≤5.0 mmol/L (1,066 randomised/ 224 treated/ 144 completed treatment)	Gender: 815 M / 240 F Average age (Mean ± SD): 71.2 ± 10.1 years Age range: 33-92 years

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Table SIII.1: Overview of completed Phase II and Phase III clinical studies of finerenone

Study number (status) number of study sites (regions)	Design (indication)	Number of participants by intervention group	Study population
Chronic kidney disease and type 2 diabetes			
Study 16815, ARTS-HF Japan (completed) Report PH-37594 31 sites (1 country)	Phase IIb, randomised, adaptive, double-blind, double-dummy, comparator-controlled, parallel-group, multicentre study Duration (Mean ± SD): 74.1 ± 29.6 days Indication: Worsening of CHF	Finerenone 2.5 mg OD, possibly up-titrated to 5 mg OD (72 randomised/ 13 treated/ 9 completed treatment) Finerenone 5 mg OD, possibly up-titrated to 10 mg OD (72 randomised/ 13 treated/ 11 completed treatment) Finerenone 7.5 mg OD, possibly up-titrated to 15 mg OD (72 randomised/ 11 treated/ 6 completed treatment) Finerenone 10 mg OD, possibly up-titrated to 20 mg OD (72 randomised/ 11 treated/ 7 completed treatment) Finerenone 15 mg OD, possibly up-titrated to 20 mg OD (72 randomised/ 11 treated/ 8 completed treatment) Eplerenone 25 mg EOD, possibly up-titrated to 25 mg OD on Day 30 if serum 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 serum potassium ≤5.0 mmol/L (72 randomised/ 13 treated/ 11 completed treatment)	Gender: 53 M / 19 F Average age (Mean ± SD): 73.1 ± 9.27 years Age range: 46-93 years

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Table SIII.1: Overview of completed Phase II and Phase III clinical studies of finerenone

Study number (status) number of study sites (regions)	Design (indication)	Number of participants by intervention group	Study population
Study 16243, ARTS-DN (completed) Report PH-37857 128 sites (23 countries)	Phase IIb, randomised, adaptive, double-blind, placebo-controlled, parallel-group, multicentre study Duration (Mean ± SD): 86.3 ± 16.9 days Indication: CKD and T2D	Finerenone 1.25 mg OD (823 randomised/ 96 treated/ 90 completed treatment) Finerenone 2.5 mg OD (823 randomised/ 92 treated/ 87 completed treatment) Finerenone 5 mg OD (823 randomised/ 100 treated/ 90 completed treatment) Finerenone 7.5 mg OD (823 randomised/ 98 treated/ 91 completed treatment) Finerenone 10 mg OD (823 randomised/ 98 treated/ 90 completed treatment) Finerenone 15 mg OD (823 randomised/ 125 treated/ 114 completed treatment) Finerenone 20 mg OD (823 randomised/ 120 treated/ 112 completed treatment) Placebo (823 randomised/ 94 treated/ 90 completed treatment)	Gender: 639 M / 182 F Average age (Mean ± SD): 64.2 ± 9.2 years Age range: 30-90 years
Study 16816, ARTS-DN Japan (completed) Report PH-38022 16 sites (1 country)	Phase IIb, randomised, adaptive, double-blind, placebo-controlled, parallel-group, multicentre study Duration (Mean ± SD): 88.1 ± 11.8 days Indication: CKD and T2D	Finerenone 1.25 mg OD (96 randomised/ 12 treated/ 11 completed treatment) Finerenone 2.5 mg OD (96 randomised/ 12 treated/ 12 completed treatment) Finerenone 5 mg OD (96 randomised/ 12 treated/ 12 completed treatment) Finerenone 7.5 mg OD (96 randomised/ 12 treated/ 11 completed treatment)	Gender: 77 M / 19 F Average age (Mean ± SD): 63.0 ± 9.8 years Age range: 41-83 years

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Table SIII.1: Overview of completed Phase II and Phase III clinical studies of finerenone

Study number (status) number of study sites (regions)	Design (indication)	Number of participants by intervention group	Study population
		Finerenone 10 mg OD (96 randomised/ 12 treated/ 11 completed treatment) Finerenone 15 mg OD (96 randomised/ 12 treated/ 12 completed treatment) Finerenone 20 mg OD (96 randomised/ 12 treated/ 12 completed treatment) Placebo (96 randomised/ 12 treated/ 12 completed treatment)	
Phase III			
Chronic kidney disease and type 2 diabetes			
Study 16244, FIDELIO-DKD (completed) Report PH-39746 1,023 sites (48 countries)	Phase III, randomised, double-blind, placebo-controlled, parallel-group, multicentre, event-driven study Duration (Mean ± SD): Finerenone: 26.91 ± 12.33 months Placebo: 27.25 ± 12.15 months Indication: CKD and T2D	Finerenone 10 or 20 mg OD (2,857 randomised/ 2,818 treated/ 2,815 completed study) Placebo (2,865 randomised/ 2,828 treated/ 2,829 completed study)	Gender: Finerenone: 1,943 M / 875 F Placebo: 2,021 M / 807 F Average age: (Mean ± SD): Finerenone: 65.45 ± 8.93 Age range: 32-90 Placebo: 65.67 ± 9.16 Age range: 28-97
Study 17530, FIGARO-DKD (completed) Report PH-39747 1,018 sites (48 countries)	Phase III, randomised, double-blind, placebo-controlled, parallel-group, multicentre, event-driven study Duration (Mean ± SD): Finerenone: 35.15 ± 14.85 months Placebo: 35.34 ± 14.60 months	Finerenone 10, 20 or 10-20 mg OD (3,711 randomised/ 3,671 treated/ 3,669 completed study) Placebo (3,702 randomised/ 3,646 treated/ 3,641 completed study)	Gender: Finerenone: 2,515 M / 1,156 F Placebo: 2,562 M / 1,084 F Average age: (Mean ± SD): Finerenone: 64.16 ± 9.66 Age range:

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Table SIII.1: Overview of completed Phase II and Phase III clinical studies of finerenone

Study number (status) number of study sites (regions)	Design (indication)	Number of participants by intervention group	Study population
			27-89 years Placebo: 64.14 ± 10.00 Age range: 23-93 years
HF with left ventricular ejection fraction (LVEF) ≥40%			
Study 20103, FINEARTS-HF (completed) Report PH-B002803 654 sites (37 countries)	Phase III, randomised, double-blind, placebo-controlled, parallel-group, multicentre, event-driven study <u>Duration</u> (Mean ± SD): Finerenone: 25.15 ± 12.42 months Placebo: 25.33 ± 12.35 months Indication: HF with LVEF ≥40%	Finerenone tablets 10, 20 or 40 mg OD (3,011 randomised/ 2,993 treated/ 2,050 completed study) Placebo OD tablets (3,005 randomised/ 2,993 treated/ 2,021 completed study)	<u>Gender:</u> Finerenone: 1,643 M / 1,350 F Placebo: 1,619 M / 1,374 F <u>Average age</u>: (Mean ± SD): 71.99 years (9.65) Finerenone: 71.93 ± 9.60 Age range: 40-96 years Placebo: 72.04 ± 9.70 Age range: 40-97 years

Abbreviations: ARTS= minerAlocorticoid-Receptor antagonist Tolerability Study, BID= Twice daily, CHF=chronic heart failure, CKD=chronic kidney disease, DKD=diabetic kidney disease, DN=diabetic nephropathy, EOD=every other day, F=female, FIDELIO-DKD= **FI**nerenone in reducing ki**D**n**E**y fai**L**ure and d**I**sease pr**O**gression in Diabetic Kidney Disease, FIGARO-DKD=**FI**nerenone in reducin**G** c**A**rdiovascular mo**R**tality and m**O**rbidity in Diabetic Kidney Disease, HF=Heart failure, LVEF=Left ventricular ejection fraction, M=male, LVSD= Left ventricular systolic dysfunction, OD=once daily, SD=standard deviation, T2D=type 2 diabetes.

Results from the five completed Phase II and three Phase III studies were not pooled because of the differences in the study designs, treatment durations, dosages as well as studied populations and – consequently – differing adverse event profiles. Since the Phase III studies FIDELIO-DKD and FIGARO-DKD are complementary with a reciprocal design and concept investigating the same disease and a combined analysis offers more robust insight into different CKD stages and albuminuria levels, data from both studies are pooled.

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In the tables below (Table SIII.2 through Table SIII.6), exposure data for the finerenone programme are presented per indication:

- *"Chronic kidney disease (CKD) and type 2 diabetes (T2D)"* included data from the pooled Phase IIb studies ARTS-DN and ARTS-DN Japan and the pooled Phase III studies FIDELIO-DKD and FIGARO-DKD,
- *"Worsening of chronic heart failure"* included data from the pooled Phase IIb studies ARTS-HF and ARTS-HF Japan,
- "Stable heart failure" included data from the Phase IIa study ARTS,
- "HF with LVEF ≥40%" included data from the Phase III study FINEARTS-HF.

Table SIII.2: Duration of exposure by indication and phase (Safety Analysis Set)

Chronic kidney disease and type 2 diabetes				
	Phase II studies (pooled Phase IIb studies ARTS-DN, #16243 and ARTS-DN Japan, #16816)		**Phase III studies (pooled Phase III studies FIGARO-DKD, #17530 and FIDELIO-DKD, #16244)**	
Duration of exposure	**Patients**	**Person time (months)**	**Patients**	**Person time (months)**
1 day	7	0.23	2	0.07
>1-7 days	8	1.10	18	2.70
>1-2 weeks	11	4.00	9	3.07
>2-4 weeks	5	3.80	32	24.07
>4-8 weeks	13	17.63	82	104.57
>8-12 weeks	15	34.97	61	139.17
>3-6 months (85-180 days)	752	2,270.10	202	881.53
>6-12 months (181-360 days)	–	–	312	2,763.60
>12-18 months (361-540 days)	–	–	359	5,356.77
>18-24 months (541-720 days)	–	–	719	15,256.23
>24-30 months (721-900 days)	–	–	1,043	28,164.40
>30-36 months (901-1,080 days)	–	–	1,006	33,102.93
>36-42 months (1,081-1,260 days)	–	–	809	31,459.87
>42-48 months (1,261-1,440 days)	–	–	881	39,648.57
>48-54 months (1,441-1,620 days)	–	–	491	24,838.07
>54-60 months (1,621-1,800 days)	–	–	444	25,050.77
>60-66 months (1,801-1,980 days)	–	–	19	1,153.23
Total person time		**2,331.83**		**207,949.60**

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Table SIII.2: Duration of exposure by indication and phase (Safety Analysis Set)

Worsening of chronic heart failure (pooled Phase IIb studies ARTS-HF, #14564 and ARTS-HF Japan, #16815)		
Duration of exposure	**Patients**	**Person time (months)**
1 day	8	0.27
>1-7 days	31	4.60
>1-2 weeks	35	11.87
>2-4 weeks	44	29.73
>4-8 weeks	54	67.93
>8-12 weeks	50	115.40
>3-6 months (85-180 days)	671	2,025.93
Total person time		**2,255.73**
Stable chronic heart failure (Phase IIa study ARTS, #14563)		
Duration of exposure	**Patients**	**Person time (months)**
1 day	2	0.07
>1-7 days	13	1.60
>1-2 weeks	8	2.97
>2-4 weeks	188	171.73
>4-8 weeks	102	99.27
Total person time		**275.63**

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Table SIII.2: Duration of exposure by indication and phase (Safety Analysis Set)

Heart failure with LVEF ≥40% (Phase III study FINEARTS-HF, #20103)		
Duration of exposure	**Patients**	**Person time (months)**
1 day	8	0.27
>1-7 days	19	2.40
>1-2 weeks	14	5.27
>2-4 weeks	36	26.73
>4-8 weeks	77	95.77
>8-12 weeks	50	117.90
>3-6 months (85-180 days)	145	613.63
>6-12 months (181-360 days)	222	1,974.33
>12-18 months (361-540 days)	298	4,630.27
>18-24 months (541-720 days)	367	7,727.00
>24-30 months (721-900 days)	401	10,892.53
>30-36 months (901-1,080 days)	634	21,177.53
>36-42 months (1,081-1,260 days)	675	26,022.10
>42-48 months (1,261-1,440 days)	47	2,002.70
Total person time		**75,288.43**

Treatment duration is defined as time from start of study drug to permanent stop of study drug.

30 days are considered as one month.

Abbreviations: ARTS=minerAlocorticoid-Receptor antagonist Tolerability Study, DKD=diabetic kidney disease, DN=diabetic nephropathy, FIDELIO-DKD=FInerenone in reducing kiDnEy faiLure and dIsease prOgression in Diabetic Kidney Disease, FIGARO-DKD=**FI**nerenone in reducin**G** c**A**rdiovascular mo**R**tality and m**O**rbidity in Diabetic Kidney Disease, HF=heart failure, LVEF=Left ventricular ejection fraction.

Source: Report B003525: Table 14.2/1.

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Table SIII.3: Duration of exposure by age group and gender (by indication and phase -Safety Analysis Set)

Chronic kidney disease and Type 2 Diabetes								
	Phase II studies (pooled Phase IIb studies ARTS-DN, #16243 and ARTS-DN Japan, #16816)				**Phase III studies (pooled Phase III studies FIGARO-DKD, #17530 and FIDELIO-DKD, #16244)**			
Age group	**Patients**		**Person time (months)**		**Patients**		**Person time (months)**	
	M	**F**	**M**	**F**	**M**	**F**	**M**	**F**
<65 years	303	79	873.33	225.57	1,9877	955	65,106.77	30,5437.23
65 - <75 years	273	66	793.83	192.03	1,852	771	59,781.73	24,666.03
75 - <85 years	57	29	153.40	81.83	596	281	18,433.83	8,087.37
≥85 years	4	0	11.83	0	23	24	694.67	635.97

Worsening of chronic heart failure (pooled Phase IIb studies ARTS-HF, #14564 and ARTS-HF Japan, #16815)				
Age group	**Patients**		**Person time (months)**	
	M	**F**	**M**	**F**
<65 years	194	33	488.03	97.07
65 - <75 years	226	65	580.50	152.47
75 - <85 years	232	90	572.23	229.20
≥85 years	34	19	91.30	44.93

Stable chronic heart failure (Phase IIa study ARTS, #14563)				
Age group	**Patients**		**Person time (months)**	
	M	**F**	**M**	**F**
<65 years	55	10	49.97	9.37
65 - <75 years	106	21	94.90	17.53
75 - <85 years	80	30	68.10	26.17
≥85 years	9	2	7.70	1.90

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Table SIII.3: Duration of exposure by age group and gender (by indication and phase -Safety Analysis Set)

Heart failure with LVEF ≥40% (Phase III study FINEARTS-HF, #20103)				
Age group	**Patients**		**Person time (months)**	
	M	**F**	**M**	**F**
<65 years	436	205	11,794.33	5,216.37
65 - <75 years	591	481	15,541.17	12,839.90
75 - <85 years	515	539	12,325.33	13,010.57
≥85 years	101	125	2,230.17	2,330.60

Treatment duration is defined as time from start of study drug to permanent stop of study drug.

30 days are considered as one month.

Abbreviations: ARTS=minerAlocorticoid-Receptor antagonist Tolerability Study, DKD=diabetic kidney disease, DN=diabetic nephropathy, F=Female, FIDELIO-DKD=FInerenone in reducing kiDnEy faiLure and dIsease prOgression in Diabetic Kidney Disease, FIGARO-DKD=**FI**nerenone in reducin**G** c**A**rdiovascular mo**R**tality and m**O**rbidity in Diabetic Kidney Disease, HF=heart failure, M=Male, LVEF=Left ventricular ejection fraction.

Source: Report B003525: Table 14.2/3.

Table SIII.4: Duration of exposure by dose (by indication and phase - Safety Analysis Set)

Chronic kidney disease and Type 2 Diabetes				
	Phase II studies (pooled Phase IIb studies ARTS-DN, #16243 and ARTS-DN Japan, #16816)		**Phase III studies (pooled Phase III studies FIGARO-DKD, #17530 and FIDELIO-DKD, #16244)**	
Dose exposure	**Patients**	**Person time (months)**	**Patients**	**Person time (months)**
1.25 mg od	108	316.57	-	-
2.5 mg od	104	302.53	-	-
5 mg od	112	316.93	-	-
7.5 mg od	109	319.33	-	-
10 mg od	110	309.80	998	21,869.77
15 mg od	137	386.73	-	-
20 mg od	131	379.93	1,284	47,145.73
10-20 mg od	-	-	4,207	138,934.10

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Table SIII.4: Duration of exposure by dose (by indication and phase - Safety Analysis Set)

Worsening of chronic heart failure (pooled Phase IIb studies ARTS-HF, #14564 and ARTS-HF Japan, #16815)		
Dose of exposure	**Patients**	**Person time (months)**
2.5 mg od	42	49.33
5 mg od	35	39.27
7.5 mg od	33	39.67
10 mg od	43	59.87
15 mg od	45	67.17
2.5-5 mg od	143	409.63
5-10 mg od	141	405.03
7.5-15 mg od	145	408.43
10-20 mg od	137	401.77
15-20 mg od	129	375.57
Stable chronic heart failure (Phase IIa study ARTS, #14563)		
Dose of exposure	**Patients**	**Person time (months)**
2.5 mg od	82	71.97
5 mg od	83	72.57
10 mg od	84	75.97
5 mg bid	64	55.13
Heart failure with LVEF ≥40% (Phase III study FINEARTS-HF, #20103)		
Dose of exposure[a]	**Patients**	**Person time (months)**
10 mg od	284	3,944.43
20 mg od	164	2,388.00
10-20 mg od	1,242	32,140.30
10-40 mg od	124	3,582.80
20-40 mg od	1,179	33,232.90

[a]Doses displayed as xx-yy mg include participants who have actually taken dosages (as per protocol) within the range displayed due to up- and down titration. For Phase III studies, categories are mutually exclusive, ie. subjects under 10 or 20 mg only took either dose, whereas subjects under 10-20 mg took both doses during the course of the study. Treatment duration is defined as time from start of study drug to permanent stop of study drug.30 days are considered as one month.

Abbreviations: ARTS=minerAlocorticoid-Receptor antagonist Tolerability Study, bid=twice daily, DKD=diabetic kidney disease, DN=diabetic nephropathy, FIDELIO-DKD=FInerenone in reducing kiDnEy faiLure and dIsease prOgression in Diabetic Kidney Disease, FIGARO-DKD=**FI**nerenone in reducin**G** c**A**rdiovascular mo**R**tality and m**O**rbidity in Diabetic Kidney Disease, HF=heart failure, LVEF=Left ventricular ejection fraction, od=once daily.

Source: Report B003525: Table 14.2/2.

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Table SIII.5: Duration of exposure by race origin (by indication and phase - Safety Analysis Set)

Chronic kidney disease and Type 2 Diabetes				
	Phase II studies (pooled Phase IIb studies ARTS-DN, #16243 and ARTS-DN Japan, #16816)		**Phase III studies (pooled Phase III studies FIGARO-DKD, #17530 and FIDELIO-DKD, #16244)**	
Race	**Patients**	**Person time (months)**	**Patients**	**Person time (months)**
White	608	1,746.80	4,441	142,419.23
Black or African American	25	70.87	250	7,195.87
Asian	160	466.50	1,414	47,590.73
American Indian or Alaska Native	-	-	150	4,087.17
Native Hawaiian or Other Pacific Islander	-	-	28	893.43
Not Reported	2	6.10	18	534.10
Multiple	16	41.57	188	5,229.07

Worsening of chronic heart failure (pooled Phase IIb studies ARTS-HF, #14564 and ARTS-HF Japan, #16815)		
Race	**Patients**	**Person time (months)**
White	766	1,934.67
Black or African American	20	57.13
Asian	96	234.10
American Indian or Alaska Native	1	3.00
Native Hawaiian or Other Pacific Islander	1	3.07
Not Reported	6	14.63
Multiple	3	9.13

Stable chronic heart failure (Phase IIa study ARTS, #14563)		
Race	**Patients**	**Person time (months)**
White	311	274.73
Black or African American	1	0.47
Asian	1	0.43

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Table SIII.5: Duration of exposure by race origin (by indication and phase - Safety Analysis Set)

Heart failure with LVEF ≥40% (Phase III study FINEARTS-HF, #20103)		
Race	**Patients**	**Person time (months)**
White	2,357	59,792.27
Black or African American	49	1,042.07
Asian	496	12,329.43
American Indian or Alaska Native	75	1,819.40
Native Hawaiian or Other Pacific Islander	1	37.37
Not Reported	8	200.90
Multiple	7	67.00

Treatment duration is defined as time from start of study drug to permanent stop of study drug.

30 days are considered as one month.

Abbreviations: ARTS=minerAlocorticoid-Receptor antagonist Tolerability Study, DKD=diabetic kidney disease, DN=diabetic nephropathy, FIDELIO-DKD=FInerenone in reducing kiDnEy faiLure and dIsease prOgression in Diabetic Kidney Disease, FIGARO-DKD=**FI**nerenone in reducin**G** c**A**rdiovascular mo**R**tality and m**O**rbidity in Diabetic Kidney Disease, HF=heart failure, LVEF=Left ventricular ejection fraction.

Source: Report B003525: Table 14.2/4.

Table SIII.6: Duration of exposure for special populations (by indication and phase – Safety Analysis Set)

Chronic kidney disease in Type 2 Diabetes				
	Phase II studies (pooled Phase IIb studies ARTS-DN, #16243 and ARTS-DN Japan, #16816)		**Phase III studies (pooled Phase III studies FIGARO-DKD, #17530 and FIDELIO-DKD, #16244)**	
Special population	**Patients**	**Person time (months)**	**Patients**	**Person time (months)**
Renal impairment				
≥60 mL/min/1.73 m^2	474	1,370.13	2,592	92,221.17
45 - <60 mL/min/1.73 m^2	190	549.90	1,709	54,025.73
25 - <45 mL/min/1.73 m^2	146	408.87	2,107	59,787.17
<25 mL/min/1.73 m^2	1	2.93	81	1,915.53
Hepatic impairment[a]				
Yes	103	290.40	1,086	34,940.97
No	708	2,041.43	5,403	173,008.63

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Table SIII.6: Duration of exposure for special populations (by indication and phase – Safety Analysis Set)

Pregnant women[b]				
No	-	-	86	2,854.47
Missing	811	2,331.83	6,403	205,095.13
Breastfeeding women				
Missing	811	2,331.83	6,489	207,949.60

Worsening of chronic heart failure (pooled Phase IIb studies ARTS-HF, #14564 and ARTS-HF Japan, #16815)

Special population	Patients	Person time (months)
Renal impairment		
≥60 mL/min/1.73 m^2	211	557.03
45 - <60 mL/min/1.73 m^2	249	655.73
25 - <45 mL/min/1.73 m^2	387	945.90
<25 mL/min/1.73 m^2	13	24.03
Missing	33	73.03
Hepatic impairment[a]		
Yes	62	157.90
No	831	2,097.83
Pregnant women[b]		
Missing	893	2,255.73
Breastfeeding women		
Missing	893	2,255.73

Stable chronic heart failure (Phase IIa study ARTS, #14563)

Special population	Patients	Person time (months)
Renal impairment		
≥60 mL/min/1.73 m^2	72	65.10
45 - <60 mL/min/1.73 m^2	128	112.40
25 - <45 mL/min/1.73 m^2	110	97.00
<25 mL/min/1.73 m^2	3	1.13
Hepatic impairment[a]		
Yes	7	6.63
No	306	269.00
Pregnant women[b]		
Missing	313	275.63
Breastfeeding women		
Missing	313	275.63

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Table SIII.6: Duration of exposure for special populations (by indication and phase – Safety Analysis Set)

Heart failure with LVEF ≥40% (Phase III study FINEARTS-HF, #20103)		
Special population	**Patients**	**Person time (months)**
Renal impairment		
≥60 mL/min/1.73 m^2	1,547	41,608.40
45 - <60 mL/min/1.73 m^2	800	20,245.10
25 - <45 mL/min/1.73 m^2	627	13,096.87
<25 mL/min/1.73 m^2	19	338.07
Hepatic impairment[a]		
Yes	304	7,908.00
No	2,689	67,380.43
Pregnant women[b]		
No	25	585.23
Missing	2,968	74,703.20
Breastfeeding women		
Missing	2,993	75,288.43

[a]Hepatic impairment is defined via SMQ hepatic disorders (excl. sub-SMQs liver related investigations, signs and symptoms and liver-related coagulation and bleeding disturbances).

Treatment duration is defined as time from start of study drug to permanent stop of study drug.

[b]Post baseline information on pregnancy in the laboratory data is considered to identify pregnant women.

30 days are considered as one month.

Abbreviations: ARTS=miner**A**locorticoid-**R**eceptor antagonist **T**olerability **S**tudy, DKD=diabetic kidney disease, DN=diabetic nephropathy, FIDELIO-DKD=**FI**nerenone in reducing ki**D**n**E**y fai**L**ure and d**I**sease pr**O**gression in **D**iabetic **K**idney **D**isease, FIGARO-DKD=**FI**nerenone in reducin**G** c**A**rdiovascular mo**R**tality and m**O**rbidity in Diabetic Kidney Disease, HF=heart failure, LVEF=Left ventricular ejection fraction, MedDRA=Medical Dictionary for Regulatory Activities, SMQ=standardised MedDRA query.

Source: Report B003525: Table 14.2/5.

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SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Table SIV.1: Important exclusion criteria across pivotal Phase III studies

Exclusion criteria	Reason for exclusion	Missing Information Yes/No	Rationale for not including as missing information
Patients with estimated glomerular filtration rate (eGFR) <25 mL/min/1.73 m^2 or on dialysis	The pharmacokinetics and safety of finerenone had not been studied in patients with eGFR <25 ml/min/1.73 m^2 or those on dialysis. This exclusion criterion was applied to avoid factors that may confound the evaluation of safety and efficacy in the trial.	No	Adequately reflected in the SmPC (section 4.2 and 4.4). In patients with eGFR <25 mL/min/1.73 m^2, finerenone treatment should not be initiated due to limited clinical data.
Clinical diagnosis of chronic heart failure with reduced ejection fraction (HFrEF) and persistent symptoms New York Heart Association (NYHA Class II - IV) at run in visit (Class 1A recommendation for mineralocorticoid receptor antagonist [MRAs])	This exclusion criterion was applied in order not to deprive this patient population of the guideline-recommended treatment with other MRAs in a placebo-controlled long-term trial where use of other MRAs were prohibited.	No	Finerenone was safely administered to patients with HFrEF in the Phase 2b study ARTS-HF (N=1,066) and an early indication of efficacy was observed on CV mortality and morbidity vs the active comparator, eplerenone. Moreover, finerenone showed a positive benefit-risk profile in patients with a history of heart failure in the Phase 3 FIDELIO-DKD and FIGARO-DKD trials. Information that patients with diagnosed HFrEF and NYHA II-IV were excluded from FIDELIO-DKD and FIGARO-DKD studies due to the Class 1A recommendation for MRA therapy is adequately reflected in the SmPC (section 5.1). Concomitant use of finerenone with other MRAs (e.g., eplerenone, esaxerenone, spironolactone, canrenone) is not recommended, which is

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Table SIV.1: Important exclusion criteria across pivotal Phase III studies

Exclusion criteria	Reason for exclusion	Missing Information Yes/No	Rationale for not including as missing information
			adequately reflected in the SmPC (sections 4.4 and 4.5).
Concomitant use of strong CYP3A4 inhibitors	Simulations suggest that concomitant use of finerenone with strong CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, ritonavir, nelfinavir, cobicistat, clarithromycin, telithromycin, and nefazodone) significantly increases finerenone exposure.	No	Adequately reflected in the SmPC (sections 4.3 and 4.5): Use of strong CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, ritonavir, nelfinavir, cobicistat, clarithromycin, telithromycin and nefazodone) is contraindicated.
Severe hepatic impairment (Child Pugh C)	No clinical trials had been conducted in patients with severe hepatic impairment (Child Pugh C). This exclusion criterion was applied to avoid factors that may confound the evaluation of safety and efficacy in the trial.	No	Adequately reflected in the SmPC (sections 4.2 and 4.4): Treatment of finerenone in patients with severe hepatic impairment should be avoided.
Pregnancy, or plans to become pregnant during the course of the trial	Reproductive toxicity studies in animals with finerenone have shown reproductive toxicity. Therefore, this exclusion criterion was applied in order to avoid potential harm to the unborn foetus.	Yes	Not applicable

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Table SIV.1: Important exclusion criteria across pivotal Phase III studies

Exclusion criteria	Reason for exclusion	Missing Information Yes/No	Rationale for not including as missing information
Breastfeeding or plans to breastfeed during the course or the trial	Pharmacokinetic and toxicological data in animals have shown excretion of finerenone and its metabolites in milk and it is unknown whether finerenone or its metabolites are excreted in human breast milk. Therefore, this exclusion criterion was applied in order to avoid potential harm to the breastfed infant.	Yes	Not applicable

Abbreviations: CYP=cytochrome P450, eGFR=estimated glomerular filtration rate, FIDELIO-DKD=**FI**nerenone in reducing ki**D**n**E**y fai**L**ure and d**I**sease pr**O**gression in **D**iabetic **K**idney **D**isease, FIGARO-DKD=**FI**nerenone in reducin**G** c**A**rdiovascular mo**R**tality and m**O**rbidity in Diabetic Kidney Disease, HFrEF=heart failure with reduced ejection fraction, MRA= mineralocorticoid receptor antagonist, NYHA=New York Heart Association, SmPC=Summary of Product Characteristics.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table SIV.2: Exposure of special populations included or not in clinical trial development programme[a]

Type of special population	Exposure
Pregnant women	Not included in the clinical development programme
Breastfeeding women	Not included in the clinical development programme
Paediatric population	Not included in the clinical development programme

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Table SIV.2: Exposure of special populations included or not in clinical trial development programme[a]

Type of special population	Exposure
Patients with relevant comorbidities:	
Patients with renal impairment	
eGFR ≥60 mL/min/1.73 m^2	4,896 subjects
eGFR 45 - <60 mL/min/1.73 m^2	3,076 subjects
eGFR 25 - <45 mL/min/1.73 m^2	3,377 subjects
eGFR <25 mL/min/1.73 m^2	117 subjects[b]
Patients with hepatic impairment[c]	1,562 subjects
Population with relevant different ethnic origin	
White	8,483 subjects
Black or African America	345 subjects
Asian	2,167 subjects
American Indian or Alaska native	226 subjects
Native Hawaiian or other Pacific Islander	30 subjects

[a]Cumulative for all indications, pool of 20103 (FINEARTS-HF), 16244 (FIDELIO-DKD), 17530 (FIGARO-DKD), 16243 (ARTS-DN), 16816 (ARTS-DN Japan), 14564 (ARTS-HF), 16815 (ARTS-HF Japan) and 14563 (ARTS)

[b]In the Phase III study FIDELIO-DKD, the mean eGFR value at baseline was 44.34 mL/min/1.73 m^2 (SD 12.56 mL/min/1.73 m^2). In the FIGARO-DKD, the mean eGFR value at baseline was 67.80 mL/min/1.73 m^2 (SD 21.69 mL/min/1.73 m^2). In both studies, when comparing eGFR values between screening and baseline, due to the inherent intra-individual variability associated with eGFR, a number of subjects shifted from one eGFR category at screening to another at baseline, resulting in a different distribution of subjects across categories. In the FIDELIO-DKD study, fewer subjects were seen in the categories 25 to <45 and 45 to <60 mL/min/1.73 m^2 at baseline than at screening, resulting in more subjects in the category ≥60 mL/min/1.73 m^2 and in the category of eGFR <25 mL/min/1.73 m^2 at baseline. In FIGARO-DKD study, fewer subjects were seen in the categories 25 to <45 and ≥60 mL/min/1.73 m^2 at baseline than at screening, resulting in more subjects in the category 45 to <60 mL/min/1.73 m^2 and in the category of eGFR <25 mL/min/1.73 m^2 at baseline. In Phase III study FINEARTS-HF the mean eGFR value at baseline was 62.11 (19.73) mL/min/1.73 m^2; overall, for 48.1% of participants the eGFR at baseline was <60 mL/min/1.73 m^2.
In the Phase II studies, 17 subjects had a baseline eGFR value <25 mL/min/1.73 m^2. In these studies, inclusion criteria required an eGFR value ≥30 mL/min/1.73 m^2.

[c]Hepatic impairment is defined via SMQ hepatic disorders (excl. sub-SMQs liver related investigations, signs and symptoms and liver-related coagulation and bleeding disturbances).

Abbreviations: ARTS= minerAlocorticoid-Receptor antagonist Tolerability Study, DKD=diabetic kidney disease, DN=diabetic nephropathy, eGFR=estimated glomerular filtration rate**,** FIDELIO-DKD**=FI**nerenone in reducing ki**D**n**E**y failure and d**I**sease progression in **D**iabetic **K**idney **D**isease, FIGARO-DKD=**FI**nerenone in reducin**G** c**A**rdiovascular mo**R**tality and m**O**rbidity in Diabetic Kidney Disease, MedDRA=Medical Dictionary for Regulatory Activities, SD=Standard deviation, SMQ=Standardised MedDRA query.

Source: Report B003525: Table 14.2/4, Table 14.2/5.

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Part II: Module SV - Post-authorisation experience

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SV.1 Post-authorisation exposure

Kerendia® (finerenone film-coated tablets, 10 mg, 20 mg) is currently approved for the treatment of chronic kidney disease (with albuminuria) associated with type 2 diabetes in adults. The first marketing authorisation of Kerendia® (finerenone film-coated tablets, 10 mg, 20 mg) was granted in the United States (US) since 09 JUL 2021. In selected countries, finerenone is marketed under the trade name Firialta®. In addition, the trade name Lyvelsa® is used in India.

SV.1.1 Method used to calculate exposure

Patient exposure has been estimated by calculation based on the marketing authorisation holders (MAH's) wholesale data for finerenone.

In order to present an overall estimate of patient exposure to all approved finerenone dosages (10 mg and 20 mg), allowing for calculation of reporting rates, patient-years (PY) were calculated independent of the dose schedule, and maximal tolerated dosages. The method to estimate patient exposure is based on the assumption that every patient will take one tablet/day 365 days/year with 100% compliance (strength of the tablet consumed depends on when in the treatment schedule it is taken) and is reflected in the respective strength version (10 mg or 20 mg).

SV.1.2 Exposure

The distributed volume of finerenone since market launch 09 JUL 2021 until 08 JUL 2024 (this data lock point [DLP] is taken from the recent Finerenone Periodic Benefit-Risk Evaluation Report [PBRER]/Periodic Safety Update Report [PSUR] No 5.0) was 165,767,019 tablets (10 mg tablets) and 34,818,590 tablets (20 mg tablets). The estimated cumulative exposure to the marketed product since market launch until 08 JUL 2024 was 549,550 PY (number of tablets distributed/365), see Table SV.1.

Table SV.1: Finerenone –Cumulative worldwide sales exposure (tablets) and patient exposure in total number of PYs (09 JUL 2021 – 08 JUL 2024)

	Tablets	PYs
Finerenone Tablet 10 mg	**165,767,019**	**454,156**
EU	5,008,602	13,722
ROW	160,758,417	440,434
Finerenone Tablet 20 mg	**34,818,590**	**95,394**
EU	1,839,530	5,040
ROW	32,979,060	90,354
Total	**200,585,609**	**549,550**

Abbreviations: EU=European Union (27 countries), PY=Patient-Year, ROW=Rest of the World.

Part II: Module SVI - Additional EU requirements for the safety specification

SVI.1 Potential for misuse for illegal purposes

There is no potential for misuse for illegal purposes with the Kerendia® product.

Neither finerenone nor its components are known to possess addictive properties. The established pharmacological profile of the active ingredients in product Kerendia® does not give reason to assume any risk for misuse for illegal purposes.

Part II: Module SVII - Identified and potential risks

The CKD-T2D Phase III data (FIDELIO-DKD, FIGARO-DKD and pooled FIDELIO-DKD & FIGARO-DKD) presented in this RMP retrospectively excludes data from 34 participants due to a GCP violation identified in 2023 that affected the FIDELIO-DKD and FIGARO-DKD studies. This integrated analysis also excludes data from another 2 participants in FIDELIO-DKD who had been flagged for potential GCP violations after data release in 2020. Thus, a total of 36 participants have been retrospectively excluded and therefore all sections of the module regarding FIDELIO-DKD and FIGARO-DKD studies were updated.

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

All adverse reactions outlined in Table SVII.1 are reflected as adverse drug reactions (ADRs) in the Kerendia® Summary of Product Characteristics (SmPC). This list of ADRs is based on the Phase III study FIDELIO-DKD (16244).

Table SVII.1: Adverse reactions reported with Kerendia® in the Phase III study FIDELIO-DKD (16244)

System Organ Class Adverse Reaction	Finerenone N=2,818 (%)	Placebo N=2,828 (%)
Metabolism and nutrition disorders		
Hyperkalemia[1]	514 (18.2%)	255 (9.0%)
Hyponatremia[2]	40 (1.4%)	19 (0.7%)
Vascular disorders		
Hypotension[3]	135 (4.8%)	96 (3.4%)
Investigations		
Glomerular filtration rate decreased	179 (6.4%)	133 (4.7%)

[1]Hyperkalemia includes the following PTs: Blood potassium increased and Hyperkalaemia

[2]Hyponatremia includes the following PTs: Blood sodium decreased and Hyponatraemia

[3]Hypotension includes the following PTs: Blood pressure decreased, Blood pressure diastolic decreased, Diastolic hypotension and Hypotension

Abbreviations: DKD=diabetic kidney disease, FIDELIO-DKD=FInerenone in reducing kiDnEy failure and dIsease progression in Diabetic Kidney Disease, N=number, PT=preferred term.

Source: Report B003480: Table 14.3.1.1/1.

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SVII.1.1.1 Reason for not including an identified or potential risk in the list of safety concerns in the RMP

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Table SVII.2: List of adverse reactions and the justification for non-inclusion in the list of safety concerns in the RMP

ADVERSE REACTIONS	Justification for non-inclusion
Metabolism and nutrition disorders	
Hyponatremia	Hyponatremia-related adverse events were retrieved using MedDRA Labelling Grouping (MLG) *Hyponatremia*. This MLG includes PTs *Hyponatraemia* and *Blood sodium decreased*. <u>Frequency/seriousness:</u> Hyponatremia treatment-emergent adverse events (TEAEs) were reported in 40 subjects (1.4%) on finerenone, compared to 19 subjects (0.7%) on placebo. Hyponatremia TEAEs were considered as study drug-related in 7 subjects (0.2%) on finerenone vs 3 subjects (0.1%) on placebo. Treatment-emergent serious adverse events (TESAEs) were reported in 8 subjects (0.3%) on finerenone vs one subject (<0.1%) on placebo. In all these subjects TESAE hyponatremia led to hospitalisation. In the finerenone arm, only one TESAE was considered as drug-related: in this subject, decrease in sodium (123 mmol/L) was detected 1 year and 3 months after start of treatment with finerenone. In further course and 5 weeks after discontinuation of finerenone, the subject developed a second episode of hyponatremia. Both hyponatremia episodes resolved after sodium chloride infusion. In only this subject finerenone was permanently discontinued. The majority of hyponatremia TEAEs in both treatment arms were of mild to moderate intensity and had resolved or being resolving. No fatal or life-threatening hyponatremia TEAEs occurred. An initial decrease in mean serum sodium of approximately 0.7 mmol/L was observed in the finerenone arm at Visit 2 (Month 1), followed thereafter by a progressive gradual increase over time in both treatment arms, although the increase observed was smaller in the finerenone arm. <u>Clinical and benefit/risk impact:</u> Consistent with the pharmacological mode of action, finerenone can lead to a decrease of serum sodium levels, which may result in hyponatremia. However, taking into account that the majority of hyponatremia TEAEs were non-serious, mild to moderate in intensity, and only one led to finerenone discontinuation, the risk of finerenone-associated hyponatremia is assessed as of minimal clinical impact on patients in relation to the severity of the indication treated. Hyponatremia is adequately reflected as common ADR in the SmPC.
Vascular disorders	

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Hypotension	Hypotension-related adverse events were retrieved using MLG *Hypotension*. This MLG includes PTs *Blood pressure ambulatory decreased, Blood pressure decreased, Blood pressure diastolic decreased, Blood pressure systolic decreased, Diastolic hypotension, Hypotension,* and *Mean arterial decreased.* Frequency/seriousness: Hypotension TEAEs were reported more frequently in the finerenone arm (135 subjects [4.8%]) compared to the placebo arm (96 subjects [3.4%]). Hypotension TESAEs were reported in 7 subjects (0.2%) on finerenone vs 5 subjects (0.2%) on placebo. While hypotension TEAEs were assessed to be drug-related more frequently in finerenone-treated patients (44 subjects [1.6%] vs 22 subjects [0.8%] for placebo), the proportion of drug-related hypotension TESAEs was balanced between treatment groups (3 subjects [0.1%] on finerenone vs 2 subjects [<0.1%] on placebo). Most hypotension TEAEs were of mild to moderate intensity and had resolved or being resolving. No fatal or life-threatening hypotension TESAEs occurred in the finerenone arm (one placebo-treated subject experienced a life-threatening TESAE of hypotension). In only one subject, finerenone treatment was permanently discontinued due to non-serious hypotension. In 6 subjects (0.2%) on finerenone and 5 subjects (0.2%) on placebo, hypotension TESAE led to hospitalisation. TEAEs which potentially may occur within the context of hypotension were balanced or less frequent in the finerenone arm as compared to placebo treatment. These included TEAEs reported in the MLG Syncope (39 subjects [1.4%] on finerenone vs 61 subjects [2.2%] on placebo), the MLG Fall (44 subjects [1.6%] on finerenone vs 56 subjects [2.0%] on placebo), or the MLG Dizziness (156 subjects [5.5%] on finerenone vs 157 subjects [5.6%] on placebo). In the finerenone arm, the mean systolic blood pressure (SBP) decreased by approximately 3-4 mmHg (SD approx. 15) compared with placebo in the first 12 months of treatment. The difference between the treatment arms became smaller over the course of the study. Subgroup analysis showed that in both treatment arms for subjects with a low SBP at baseline (<130 mmHg), an increase in SBP was observed in both treatment arms. However, mean SBP values were lower in finerenone-treated subjects with a difference to placebo of approximately 2-4 mmHg over the first 12 months of treatment. For finerenone-treated subjects with higher SBP at baseline (130 to <160 mmHg), a decrease in SBP was observed of approximately 3-4 mmHg compared to placebo. In the subgroup of subjects with a baseline SBP >160 mmHg, a more marked decrease in SBP was observed in both treatment groups that was greater in the finerenone arm by approximately 5-7 mmHg compared to placebo in the first 12 months of treatment. In the finerenone arm, mean diastolic blood pressure (DBP) decreased by approximately 1-2 mmHg (SD approx. 7 - 10) compared to baseline in the first 12 months of treatment compared to placebo-treated subjects. The difference between the treatment arms became smaller over the course of the study. Across the SBP at baseline subgroups (<130 mmHg; 130<160 mmHg; ≥160 mmHg) a difference between the treatment arms in DBP of approximately 1-2 mmHg was observed. Further subgroup analysis showed that in both treatment arms for subjects with a low DBP at baseline (<60 mmHg), an increase in DBP was observed in both treatment arms. Clinical and benefit/risk impact:

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Table SVII.2: List of adverse reactions and the justification for non-inclusion in the list of safety concerns in the RMP

ADVERSE REACTIONS	Justification for non-inclusion
	Consistent with its mode of action, finerenone can lead to decrease in blood pressure, which may result in hypotension. However, most hypotension TEAEs were non-serious and mild to moderate in intensity and resolved. In only one subject, hypotension TEAE led to study treatment discontinuation. Based on these results, the risk of finerenone-associated hypotension is assessed as of minimal clinical impact on patients in relation to the severity of the indication treated. Hypotension is adequately reflected as common ADR in the SmPC.
Investigations	
Glomerular filtration rate decreased	<u>Frequency/seriousness:</u> Glomerular filtration rate decreased TEAEs were reported in 179 subjects (6.4%) in the finerenone arm compared to 133 subjects (4.7%) in the placebo arm. Glomerular filtration rate decreased TEAEs were assessed to be drug-related in 39 subjects (1.4%) in the finerenone arm and in 15 subjects (0.5%) in the placebo arm. TESAEs were reported in 5 subjects (0.2%) on finerenone vs 4 subjects (0.1%) on placebo. In one subject on placebo, serious glomerular filtration rate decreased was judged to be related. In the finerenone arm, all TESAEs were considered unrelated. The majority of glomerular filtration rate decreased TEAEs were of mild or moderate intensity and were resolved or being resolved. No fatal or life-threatening TEAE of glomerular filtration rate decreased were reported in either treatment arm. The number of subjects with TEAEs leading to permanent drug discontinuation and with TESAEs leading to hospitalisation was balanced between the treatment arms (7 subjects [0.2%] on finerenone vs 8 subjects [0.3%] on placebo had to discontinue treatment, and 3 subjects [0.1%] in each treatment arm needed to be hospitalised). A progressive decline in eGFR over time was observed in both treatment arms, as expected based on the known course of the underlying disease. An initial decrease in eGFR between 2 and 3 mL/min/1.73 m^2 was observed for subjects on finerenone up to Month 4. Thereafter, an attenuated decline in eGFR was observed in the finerenone group compared to placebo which was more attenuated the larger the acute decline. For subjects on finerenone with a higher eGFR at screening (≥60 mL/min/1.73 m^2), the initial drop compared with placebo in eGFR was larger than for subjects in the categories of 45 to <60 or 25 to <45 mL/min/1.73 m^2. Most of the subjects had a relative eGFR decrease of ≥30% (finerenone: 45.5%, placebo: 43.3%) or ≥40% (finerenone: 24.7%, placebo: 24.9%). Fewer subjects in the finerenone group showed a decline in eGFR of ≥57% (6.0% on finerenone, 8.7% on placebo). A small increase in the frequency of subjects with eGFR decreases of ≥30% was observed in the finerenone arm compared to placebo up to Month 12. Thereafter, overall, a lower frequency was observed in finerenone-treated patients compared to placebo, with differences most marked for the larger eGFR decreases of ≥50% and ≥57%.

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Table SVII.2: List of adverse reactions and the justification for non-inclusion in the list of safety concerns in the RMP

ADVERSE REACTIONS	Justification for non-inclusion
	Clinical and benefit/risk impact: Consistent with its mode of action, finerenone can lead to an initial reduction in eGFR. However, the majority of treatment-emergent glomerular filtration rate decrease events were non-serious and mild to moderate in intensity, the rate of subjects with events leading to permanent study drug discontinuation was very low and balanced between treatment arms and mean long-term decrease in eGFR function at study end was smaller in the finerenone arm. Therefore, the risk of finerenone-associated eGFR decrease is assessed as of minimal clinical impact on patients in relation to the severity of the indication treated. Glomerular filtration rate decrease is adequately reflected as common ADR in the SmPC.

Abbreviations: ADR=adverse drug reaction, AE=adverse event, DBP=diastolic blood pressure, eGFR=estimated glomerular filtration rate, MedDRA=Medical Dictionary for Regulatory Activities, MLG=Medical Labelling Grouping; PT=preferred term, SBP=systolic blood pressure, SD=standard deviation, SmPC=Summary of Product Characteristics, TEAE=treatment-emergent adverse event, TESAE=treatment-emergent serious adverse event.

Source: Report B003480: Tables 14.3.1.1/1, 14.3.1.1/2, 14.3.1.1/3, 14.3.1.1/4, 14.3.1.1/5, 14.3.1.1/6, 14.3.1.1/7, 14.3.1.1/8, 14.3.1.1/ 9; Report 16244: Table 14.3.5/1, 14.3.5 / 2, 14.3.5/6, 14.3.5/7, 14.3.5/8, 14.3.5/9, 14.3.5/10, 14.3.5/11, 14.3.4.5.

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Table SVII.3: Risks considered important for inclusion in the list of safety concerns in the RMP and the reasons for risk classification

Safety Concern	Reason for risk classification
Important Identified Risks	
Hyperkalemia	Mode of action: As a non-steroidal mineralocorticoid receptor antagonist (MRA), finerenone decreases the aldosterone effect by binding to the mineralocorticoid receptor. The functional hypoaldosteronism induced by finerenone leads to a decreased reabsorption of sodium by epithelial sodium channels in the terminal portions of the nephron and consequently to a decreased secretion of potassium and protons into the urine. Due to the inherent mode of action as MRA, the use of finerenone cannot be devoid of a risk for hyperkalemia. Clinical data: In the pivotal Phase III study FIDELIO-DKD conducted in patients with advanced chronic kidney disease (CKD) and type 2 diabetes (T2D), the number of subjects with treatment-emergent hyperkalemia AEs (i.e., PT Hyperkalaemia and Blood potassium increased) was higher in the finerenone arm (18.2%) vs the placebo arm (9.0%). In the finerenone arm, the majority of these events were non-serious and mild or moderate in intensity. Moreover, hyperkalemia TEAEs leading to permanent discontinuation from study drug (2.3% of subjects) or hospitalisation (1.4% of subjects) constituted a small proportion of these events.

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Table SVII.3: Risks considered important for inclusion in the list of safety concerns in the RMP and the reasons for risk classification

Safety Concern	Reason for risk classification
	There were no treatment-emergent fatal events of hyperkalemia observed. Further, there was no evidence for an increased incidence of any severe clinical cardiac manifestations of hyperkalemia (e.g., ventricular arrhythmia or sudden cardiac death). An increase from baseline in mean serum potassium in the first month of treatment of approximately 0.2 mmol/L was observed in the finerenone arm compared to placebo, with stable mean measurements from Month 4 onwards in the finerenone arm. The mean between-group difference in serum potassium of approximately 0.2 mmol/L was consistently observed across different subgroups, including baseline serum potassium and eGFR at screening. A change in potassium to >5.5 mmol/L at any time during treatment was reported for 21.4% of subjects on finerenone and 9.2% of subject on placebo. A change in potassium to >6.0 mmol/L at any time during treatment was reported for 4.5% of subjects on finerenone and 1.4% of subjects on placebo. The analysis of data collected in the context of dose titration and interruption indicates that hyperkalemia with finerenone treatment is manageable using a serum-potassium-guided dose titration regimen. This is supported by simulation of the exposure-serum potassium model, which demonstrated that even at higher exposures, no increased risk for hyperkalemia is observed when dose titration is applied. <u>Impact on benefit-risk:</u> The patient population in the Phase III study FIDELIO-DKD has an inherent risk of hyperkalemia due to the underlying CKD and T2D which are both known risk factors for hyperkalemia, as well as due to the background standard of care therapy (ACEis/ARBs). Current clinical data revealed a 2-fold increased incidence of hyperkalemia events with finerenone. However, the majority of hyperkalemia events were non-serious, mild to moderate and resolved. There was no evidence for an increased incidence of any severe clinical cardiac manifestations of hyperkalemia and there were no fatal hyperkalemia events. Addressing hyperkalemia as ADR together with dosing guidance, monitoring, and clinical action – if necessary – in the proposed Kerendia® SmPC is considered adequate. The current hyperkalemia data from the Phase II study FIDELIO-DKD together with clinically relevant beneficial effects of finerenone on kidney disease progression and cardiovascular mortality and morbidity indicate favourable benefit-risk balance in the target patient population with CKD and T2D. However, since severe elevation of potassium may lead to life-threatening cardiac arrhythmias and suden cardiac death, a potential future occurrence of these cardiovascular events may have an impact on the benefit-risk profile of finerenone. Therefore, hyperkalemia is regarded as an important identified risk.
Important Potential Risks	
Embryo-foetal toxicity	<u>Non-clinical data:</u> In studies on embryo-foetal development, effects in rats were observed at finerenone exposures considered sufficiently in excess to the maximum human exposure thereby not indicating an increased concern for foetal harm. When rats were exposed during pregnancy and lactation in the pre- and postnatal developmental toxicity study, increased pup mortality and other

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Table SVII.3: Risks considered important for inclusion in the list of safety concerns in the RMP and the reasons for risk classification

Safety Concern	Reason for risk classification
	adverse effects (lower pup weight, delayed pinna unfolding) were observed at about 4 times the $AUC_{unbound}$ expected in humans. In addition, the offspring showed slightly increased locomotor activity, but no other neurobehavioural changes starting at about 4 times the $AUC_{unbound}$ expected in humans. The increased locomotor activity in offspring may indicate a potential risk for the foetus, as these alterations in behaviour may be due to exposure during pregnancy when the blood-brain barrier is not yet fully formed. For more details on the non-clinical data, please refer to Part II: Module SII - Non-clinical part of the safety specification. Clinical data: There are no data on the use of finerenone in pregnant women. Impact on benefit-risk if confirmed: Increased risk of damage to the foetus.
Missing information	
Use in pregnancy and lactation	No human data available. Use in pregnancy and lactation is considered missing information.

Abbreviations: ACEi=angiotensin-converting-enzyme inhibitor, ADR=adverse drug reaction, AE=adverse event, ARB=angiotensin receptor blocker, AUC=Area under the plasma concentration vs time curve; CKD=chronic kidney disease, DKD=diabetic kidney disease, eGFR= estimated glomerular filtration rate, FIDELIO-DKD= FInerenone in reducing kiDnEy faiLure and dIsease prOgression in Diabetic Kidney Disease, MRA= mineralocorticoid receptor antagonist, PT=preferred term, T2D=type 2 diabetes, TEAE=treatment-emergent adverse event.

Source: Report B003480: Tables 14.3.1.1/1, 14.3.1.1/2, 14.3.1.1/3, 14.3.1.1/4, 14.3.1.1/5, 14.3.1.1/7, 14.3.1.1/8, 14.3.1.1/9; Report 16244: Table 14.3.4/49.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1 Presentation of important identified risks and important potential risks

SVII.3.1.1 Important identified risk: Hyperkalemia

Hyperkalemia is defined as a serum or plasma potassium level above the upper limits of normal, in general greater than 5.0 mmol/L to 5.5 mmol/L. While mild hyperkalemia is usually asymptomatic, high levels of potassium may cause life-threatening ventricular arrhythmias and cardiac arrest. Symptoms usually develop at higher levels (6.5 mmol/L to 7.0 mmol/L), but the rate of change is more important than the numerical value. Patients with

chronic hyperkalemia may be asymptomatic at increased levels, while patients with dramatic, acute potassium shifts may develop severe symptoms at lower levels (108-111).

The most common cause of hyperkalemia is pseudohyperkalemia, a false elevation in measured potassium, which is mainly caused by specimen collection and handling (108). True hyperkalemia mainly occurs in patients with either acute or CKD, in whom the reduced renal function interferes with potassium excretion. In clinical practice, the development of hyperkalemia is usually the result of a combination of factors superimposed on renal dysfunction, such as diabetes mellitus, hyporeninemic hypoaldosteronism, or advanced stages of HF with accompanying reductions in renal perfusion. In addition, concurrent high-potassium diet, use of potassium-based salt substitutes, and use of medications interfering with potassium homeostasis such as ACEis, ARBs, aldosterone receptor antagonists, and beta blockers may increase the risk of developing hyperkalemia (112).

Potential mechanisms

Finerenone is a non-steroidal, potent, and highly selective antagonist of the mineralocorticoid receptor. The functional hypoaldosteronism induced by finerenone leads to a decreased reabsorption of sodium by epithelial sodium channels in the terminal portions of the nephron and consequently to a decreased secretion of potassium and protons into the urine.

Evidence source(s) and strength of evidence

The evidence is based on three pivotal Phase III studies (FIDELIO-DKD (#16244) and FIGARO-DKD (#17530) conducted in patients with CKD and T2D, FINEARTS-HF conducted in patients with HF and LVEF ≥40%) and PBRERs/PSURs.

Characterisation of the risk

Clinical trials

Finerenone was investigated in three pivotal randomised, double-blind, placebo-controlled, multicentre Phase III studies, FIDELIO-DKD, FIGARO-DKD, and FINEARTS-HF.

In FIDELIO-DKD and FIGARO-DKD, the effect of finerenone on kidney and cardiovascular outcomes was evaluated in adults with CKD and T2D receiving either finerenone (10 mg or 20 mg once daily) or placebo.

FIDELIO-DKD study included patients with advanced CKD (mean eGFR 44.3 ml/min/1.73 m^2) and T2D, while FIGARO-DKD study included patients with less advanced CKD (mean eGFR 67.8 ml/min/1.73 m^2) and T2D.

In the FIDELIO-DKD study 2,818 patients received finerenone and 2,828 received placebo. Overall, the mean treatment duration was 2.2 years. In the FIGARO-DKD study 3,671 patients received finerenone and 3,646 received placebo. Overall, the mean treatment duration was 2.9 years.

In the FINEARTS-HF study, the effect of finerenone on cardiovascular outcomes was evaluated in adults with HF (NYHA Class II-IV) and LVEF ≥40% receiving either finerenone (10 mg, 20 mg, or 40 mg once daily) or placebo.

In the FINEARTS-HF study 2,993 patients received finerenone and 2,993 received placebo. Overall mean treatment duration was 2.1 years.

In FINEARTS-HF the mean (SD) LVEF at baseline was 52.56% (7.81) with 44.6% of the participants in the category of LVEF ≥50% to <60% or 36.2% in the category of LVEF <50%. 4.5% of all participants had a history LVEF <40% (i.e. participants with recovered HF or HF with improved ejection fraction). The largest proportion of participants had NYHA Class II (69.1%). The mean (SD) eGFR value at baseline was 62.11 (19.73) mL/min/1.73 m^2; overall, for 48.1% of participants the eGFR at baseline was <60 mL/min/1.73 m^2.

As hyperkalemia is a frequent event in subjects with advanced CKD as well as in subjects with HF and known risk associated with steroidal MRAs, potassium was closely monitored in all Phase III studies. The investigator was asked to adjust the dose of study drug intake based on serum potassium and eGFR. It was at the clinical discretion of the investigator to report any increase in laboratory potassium levels as an AE.

In order to retrieve all hyperkalemia-related events from all Phase III studies, the Medical Dictionary for Regulatory Activities (MedDRA) Labelling Grouping (MLG) Hyperkalemia was used. This MLG includes PTs: Hyperkalaemia and Blood potassium increased. In this and the following sections, the term hyperkalemia refers to the MLG Hyperkalemia.

Frequency/seriousness

Hyperkalemia-related adverse events

Phase III study FIDELIO-DKD (#16244)

In the FIDELIO-DKD study including patients with advanced CKD (mean eGFR 44.3 ml/min/1.73 m^2) and T2D, there was overall approximately a 2-fold increase in the proportion of subjects with any treatment-emergent hyperkalemia in the finerenone arm compared with placebo (514 subjects [18.2%] vs 255 subjects [9.0%]). Cumulative incidences based on Aalen-Johansen estimates for time to first event for treatment-emergent AEs are described in the following subsection. Study drug-related treatment-emergent hyperkalemia events were reported in 332 subjects (11.8%) on finerenone compared with 135 subjects (4.8%) on placebo (Table SVII.4).

The number of subjects with treatment-emergent adverse events (TEAEs) reported as serious (44 subjects [1.6%] on finerenone vs 12 subjects [0.4%] on placebo), TESAEs leading to hospitalisation (40 subjects [1.4%] on finerenone vs 8 subjects [0.3%] on placebo), and TEAEs leading to permanent discontinuation of study drug (64 subjects [2.3%] on finerenone vs 25 subjects [0.9%] on placebo) was small. Of note, most of the hyperkalemia TEAEs which led to permanent drug discontinuation were non-serious. In 5 subjects (0.2%) with treatment-emergent serious hyperkalemia, study drug was withdrawn permanently in the finerenone arm (and 1 subject [<0.1%] in the placebo arm, respectively). Furthermore, there was no evidence for an increased incidence of any severe clinical cardiac manifestations of hyperkalemia (e.g., ventricular arrhythmias, sudden cardiac death) (Table SVII.4).

In the finerenone arm, 791 treatment-emergent hyperkalemia events were reported in 514 subjects. In the placebo arm, 342 events were reported in 255 subjects. In both treatment

arms, most subjects reported one treatment-emergent hyperkalemia event (11.8% on finerenone, 6.6% on placebo. More recurrent events occurred on finerenone than on placebo (Report B003478, Table 14.3.2/7).

Life-threatening treatment-emergent hyperkalemia events were reported in 3 subjects (0.1%) in each treatment group. In the finerenone group, two life-threatening hyperkalemia TEAEs were assessed by the investigator as not related to study drug, while one life-threatening hyperkalemia TEAE was assessed as related. In all three cases, alternative explanations were provided (concomitant chemotherapy with Folfox; hypovolemia; concomitant use with trimethoprim). In the placebo group, 2 life-threatening hyperkalemia TEAEs were assessed by the investigator as not related to study drug, while one life-threatening hyperkalemia TEAE was assessed as related. In all 3 cases, alternative explanations were provided (worsening of CKD and *E. coli* urinary tract infection; haemorrhagic shock; cardiac hypoperfusion leading to stent insertion).

There were no treatment-emergent hyperkalemia events with a fatal outcome. One subject in the finerenone arm with concomitant lung carcinoma (unspecified cell type) died of hyperkalemia 11 days after stop of study drug intake. Two days after stop of finerenone, serum potassium as measured in the central laboratory was 4.7 mmol/L. Ten days after stop of finerenone, an unscheduled serum potassium measurement showed a value of 7.4 mmol/L.

Phase III study FIGARO-DKD (#17530)

In the FIGARO-DKD study including patients with less advanced CKD (mean eGFR 67.8 ml/min/1.73 m^2) and T2D, there was overall approximately a 2-fold increase in the proportion of subjects with any treatment-emergent hyperkalemia in the finerenone arm compared with placebo (394 subjects [10.7%] vs 193 subjects [5.3%]). Cumulative incidences based on Aalen-Johansen estimates for time to first event for treatment-emergent AEs are described in the following subsection. Study drug-related treatment-emergent hyperkalemia events were reported in 239 subjects (6.5%) on finerenone compared with 114 subjects (3.1%) on placebo (Table SVII.4).

The number of subjects with TEAEs reported as serious (25 subjects [0.7%] on finerenone vs 4 subjects [0.1%] on placebo), TESAEs leading to hospitalisation (21 subjects [0.6%] on finerenone vs 2 subjects [<0.1%] on placebo), and TEAEs leading to permanent discontinuation of study drug (46 subjects [1.3%] on finerenone vs 13 subjects [0.4%] on placebo) was small. Of note, most of the hyperkalemia TEAEs which led to permanent drug discontinuation were non-serious. In 5 subjects (0.1%) with treatment-emergent serious hyperkalemia, study drug was withdrawn permanently in the finerenone arm (and in 1 subject [<0.1%] in the placebo arm). Furthermore, there was no evidence for an increased incidence of any severe clinical cardiac manifestations of hyperkalemia (e.g., ventricular arrhythmias, sudden cardiac death) (Table SVII.4).

While in FIGARO-DKD and FIDELIO-DKD an approximate 2-fold increase of the percentage of subjects with events was seen, the overall percentage of subjects with treatment-emergent hyperkalemia events was generally lower in FIGARO-DKD compared

with FIDELIO-DKD. This applies also to all AE subcategories, such as drug-related TEAEs, serious TEAEs, and TEAEs leading to permanent discontinuation of study drug.

In the finerenone arm, 578 treatment-emergent hyperkalemia events were reported in 394 subjects. In the placebo arm, 262 events were reported in 193 subjects. In both treatment arms, most subjects reported one treatment-emergent hyperkalemia event (7.6% on finerenone, 3.9% on placebo). More recurrent events occurred on finerenone than on placebo (Report B003478, Table 14.3.2/7).

Life-threatening treatment-emergent hyperkalemia events were reported in 1 subject (<0.1%) in the finerenone arm and in 2 subjects (<0.1%) in the placebo arm. In the finerenone group, life-threatening hyperkalemia TEAE was assessed by the investigator as related to study drug for which an alternative explanation was provided (diarrhoea that led to dehydration). In the placebo group, 2 life-threatening hyperkalemia TEAEs were assessed by the investigator as related to study drug. In both cases, alternative explanations were provided (dehydration; underlying CKD and T2D).

There were no treatment-emergent hyperkalemia events with a fatal outcome (Table SVII.4).

Table SVII.4: Frequency of treatment-emergent adverse events in MLG Hyperkalemia in Phase III studies (FIDELIO-DKD, FIGARO-DKD and pooled FIDELIO-DKD & FIGARO-DKD) (SAF)

	FIDELIO-DKD		FIGARO-DKD		FIDELIO-DKD & FIGARO-DKD (POOLED)	
Number (%) of subjects with TEAE in MLG Hyperkalemia	**Finerenone N=2,818 (100%)**	**Placebo N=2,828 (100%)**	**Finerenone N=3,671 (100%)**	**Placebo N=3,646 (100%)**	**Finerenone N=6,489 (100%)**	**Placebo N=6,474 (100%)**
TEAEs	514 (18.2%)	255 (9.0%)	394 (10.7%)	193 (5.3%)	908 (14.0%)	448 (6.9%)
TEAEs drug-related	332 (11.8%)	135 (4.8%)	239 (6.5%)	114 (3.1%)	571 (8.8%)	249 (3.8%)
TEAEs leading to permanent discontinuation of study drug	64 (2.3%)	25 (0.9%)	46 (1.3%)	13 (0.4%)	110 (1.7%)	38 (0.6%)
TESAEs	44 (1.6%)	12 (0.4%)	25 (0.7%)	4 (0.1%)	69 (1.1%)	16 (0.2%)
TESAEs drug-related	26 (0.9%)	5 (0.2%)	17 (0.5%)	3 (<0.1%)	43 (0.7%)	8 (0.1%)
TESAEs leading to hospitalisation	40 (1.4%)	8 (0.3%)	21 (0.6%)	2 (<0.1%)	61 (0.9%)	10 (0.2%)
TESAEs leading to permanent discontinuation of study drug	5 (0.2%)	1 (<0.1%)	5 (0.1%)	1 (<0.1%)	10 (0.2%)	2 (<0.1%)
TESAEs reported as life-threatening	3 (0.1%)	3 (0.1%)	1 (<0.1%)	2 (<0.1%)	4 (<0.1%)	5 (<0.1%)
TESAEs with outcome death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

A subject is counted only once within each PT or any associated MedDRA labelling grouping.

All interruptions are excluded from the person time at risk, i.e., for subjects with an interruption, events in the period from interruption start + 3 days until end of interruption are not considered. Pre-defined disease-related efficacy events are not documented as (S)AE. MedDRA version 23.0 is used.

Abbreviations: DKD=diabetic kidney disease, FIDELIO-DKD=FInerenone in reducing kiDnEy failure and dIsease progression in Diabetic Kidney Disease, FIGARO-DKD=FInerenone in reducinG cArdiovascular moRtality and mOrbidity in Diabetic Kidney Disease, MedDRA=Medical Dictionary for Regulatory Activities, MLG=MedDRA labelling grouping, N=number of subjects, PT=preferred term, (S)AE=(serious) adverse events, SAF=safety analysis set, TEAE=treatment-emergent adverse event, TESAE=treatment-emergent serious adverse event.

Source: Report B003480: Tables 14.3.1.1/1, 14.3.1.1/2, 14.3.1.1/3, 14.3.1.1/4, 14.3.1.1/5, 14.3.1.1/7, 14.3.1.1/8, 14.3.1.1/9.

Phase III study FINEARTS-HF (#20103)

In FINEARTS-HF, overall, there was approximately a 2-fold increase in the proportion of participants with any treatment-emergent hyperkalemia (289 subjects [9.7%] vs 125 subjects [4.2%]) and about a 3-fold increase in treatment-related hyperkalemia events (197 subjects [6.6%] vs 63 subjects [2.1%]) in the finerenone arm compared with placebo (Table SVII.5).

The number of participants with TEAEs reported as serious (20 subjects [0.7%] on finerenone vs 6 subjects [0.2%] on placebo), TESAEs leading to hospitalisation (16 subjects [0.5%] on finerenone vs 6 subjects [0.2%] on placebo), was small in both treatment groups but numerically larger in the finerenone group compared with placebo. While the overall number of participants with treatment-emergent hyperkalemia requiring hospitalisation was low, in all participants, the events were reported as resolved.

Permanent discontinuation of study intervention due to treatment-emergent hyperkalemia was low and reported more frequently in the finerenone group compared with placebo:
13 participants (0.4%) vs 5 participants (0.2%, Table SVII.5).

Life-threatening treatment-emergent hyperkalemia events were reported in 3 subjects (0.1%) in the finerenone group. There were no life-threatening treatment-emergent hyperkalemia events reported in the placebo arm. Out of three (3) cases in the finerenone arm, two life-threatening hyperkalemia TEAE were assessed by the investigator as related to study drug. In both cases no clinical symptoms were observed. In the remaining one case the investigator provided alternative explanation (stomach flu) for life-threatening hyperkalemia TEAE and assessed event as not related to study drug.

There were no TEAEs leading to permanent discontinuation and no treatment-emergent hyperkalemia events with a fatal outcome (Table SVII.5).

Table SVII.5: Frequency of treatment-emergent adverse events in MLG Hyperkalemia in Phase III study FINEARTS-HF

	FINEARTS-HF	
Number (%) of subjects with TEAE in MLG Hyperkalemia	**Finerenone N=2,993 (100%)**	**Placebo N=2,993 (100%)**
TEAEs	289 (9.7%)	125 (4.2%)
TEAEs drug-related	197 (6.6%)	63 (2.1%)
TEAEs leading to permanent discontinuation of study drug	13 (0.4%)	5 (0.2%)
TESAEs	20 (0.7%)	6 (0.2%)
TESAEs drug-related	16 (0.5%)	4 (0.1%)
TESAEs leading to hospitalisation	16 (0.5%)	6 (0.2%)
TESAEs leading to permanent discontinuation of study drug	0 (0.0%)	0 (0.0%)

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Table SVII.5: Frequency of treatment-emergent adverse events in MLG Hyperkalemia in Phase III study FINEARTS-HF

	FINEARTS-HF	
Number (%) of subjects with TEAE in MLG Hyperkalemia	**Finerenone N=2,993 (100%)**	**Placebo N=2,993 (100%)**
TESAEs reported as life-threatening	3 (0.1%)	0 (0.0%)
TESAEs with outcome death	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.

Pre-defined disease-related efficacy events are not documented as (S)AE. For Japanese and Indian participants pre-defined disease-related cardiovascular outcome events are documented as (S)AE, but are not shown in this table.

MedDRA version 27.0 was used.

Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, MLG=MedDRA labelling grouping, N=number of subjects, PT=preferred term, (S)AE=(serious) adverse events, SAF=safety analysis set, TEAE=treatment-emergent adverse event, TESAE=treatment-emergent serious adverse event.

Source: Report B003525: Table 14.3.2.1/1.

In accordance with the dosing scheme in FINEARTS-HF (Module 2.5 Clinical Overview: Table 12-1), participants in the subgroup with eGFR ≥60 mL/min/1.73 m^2 would have had a maintenance dose of 40 mg, whereas the maintenance dose for participants in the subgroup with eGFR<60 mL/min/1.7 m^2 at baseline was 20 mg. Consequently, the participants in the subgroup with eGFR ≥60 mL/min/1.7 m^2 at baseline were observed to be treated with a higher dose on average (overall mean exposure of about 33 mg) compared to participants in the subgroup with eGFR <60 mL/min/1.7 m^2 at baseline (about 16 mg).

The subgroup with eGFR ≥60 mL/min/1.73 m^2 (maintenance dose 40 mg) did not have higher frequencies of TEAEs of hyperkalemia in either of the treatment groups when compared with the subgroup with eGFR <60 mL/min/1.73 m^2 (maintenance dose 20 mg) (see Table SVII.6). While there is an exposure-response relationship for serum potassium, this is adequately managed by the provided titration guidance and allows to safely increase the dose to maximize efficacy.

Table SVII.6: Frequency of treatment-emergent adverse events in MLG Hyperkalemia by eGFR at baseline in Phase III study FINEARTS-HF

Any treatment-emergent in MLG Hyperkalemia	**Finerenone N=2,993 (100%) n/Ns (%)**	**Placebo N=2,993 (100%) n/Ns (%)**
Overall	289/2,993 (9.7%)	125/2,993 (4 2%)
<60 mL/min/1.73 m^2 at baseline	192/1,446 (13.3%)	96/1,436 (6.7%)
≥60 mL/min/1.73 m^2 at baseline	97/1,547 (6.3%)	29/1,557 (1.9%)

Abbreviations: AE= Adverse event, eGFR=estimated glomerular filtration rate, N=Number.
Source: Report B003525: Table 14.3.2.3/1.

Cumulative incidences for hyperkalemia-related adverse events

Phase III study FIDELIO-DKD (#16244)

In the FIDELIO-DKD study, cumulative incidences based on Aalen-Johansen estimates for time to first event for treatment-emergent hyperkalemia revealed a steep increase in hyperkalemia event onset during the first 3 months of finerenone treatment, with subsequent continuous, but less steep increase. While the cumulative incidence comparing finerenone vs placebo is up to 3 times higher in the first year, it is about two times higher after three years. The differences between cumulative incidences of finerenone and placebo are slowly but constantly increasing over time (Report PH-41745: Table 1.3.2/1; Figure 1.3.2/1).

While the overall incidence proportion of treatment-emergent hyperkalemia leading to hospitalisation in both treatment arms was low following an early separation in the curves, there is a gradual and even increase over time in the incidence of treatment-emergent hyperkalemia leading to hospitalisation, with a higher incidence seen in the finerenone arm (cumulative incidence of 0.021 after 3.5 years, Report PH-41745: Table 1.3.2/3, Figure 1.3.2/3).

Phase III study FIGARO-DKD (#17530)

In the FIGARO-DKD study, cumulative incidences based on Aalen-Johansen estimates for time to first treatment-emergent hyperkalemia revealed that the overall incidence rate of events in both treatment arms was low (cumulative incidence up to 0.137 after 5 years in the finerenone arm; Report PH-39747: Table 14.3.1.1/2, Figure 14.3.1.1/1). After an early separation of the curves, there was a gradual and even increase over time in the cumulative incidence of treatment-emergent hyperkalemia with a 2-fold higher cumulative incidence in the finerenone arm.

The overall incidence of treatment-emergent hyperkalemia leading to hospitalisation was overall low, but slightly higher in the finerenone arm when compared to the placebo (cumulative incidence after 5 years was up to 0.006 versus 0.001; Report PH-39747: Table 14.3.1.1/3, Figure 14.3.1.1/2).

Phase III study FINEARTS-HF (#20103)

In the FINEARTS-HF study, cumulative incidences based on Aalen-Johansen estimates for time to first treatment-emergent hyperkalemia revealed that the overall incidence rate of events in both treatment arms was low (cumulative incidence up to 12.6% in the finerenone group and up to 5.1% in the placebo group, Module 5.3.5.3, Report B003523, Table 2.4.1/2). After an early separation of the curves, there was a gradual and consistent increase over time in the incidence of first TEAE hyperkalemia in the finerenone group versus placebo, which is in line with the approximate 2-fold increase.

Serum potassium (central laboratory)

Phase III study FIDELIO-DKD (#16244)

In the FIDELIO-DKD study, an increase from baseline in mean serum potassium in the first month of treatment of approximately 0.2 mmol/L was observed in the finerenone arm compared to placebo, remaining stable thereafter (Report PH-39746: Tables 14.3.4/49 and 14.3.4/68-70).

A change in serum potassium to values >5.5 mmol/L at any time during treatment was reported for 595 subjects (21.4%) on finerenone and 256 subjects (9.2%) on placebo (Table SVII.7). A change in serum potassium to values >6.0 mmol/L at any time during treatment was reported for 126 subjects (4.5%) on finerenone and 38 subjects (1.4%) on placebo. Treatment-emergent lab abnormalities of serum potassium >5.5 mmol/L in the finerenone and placebo arms were most commonly limited to the 5.5-6.0 mmol/L range (Report PH-41710: Table 14.3.4.1/2, Figure 14.3.4.1/1).

Phase III study FIGARO-DKD (#17530)

In the FIGARO-DKD study, an increase from baseline in mean serum potassium in the first month of treatment of approximately 0.15 mmol/L was observed in the finerenone group compared to placebo, which remained stable thereafter (Report PH-39747: Table 14.3.4/57).

A change in serum potassium to values >5.5 mmol/L at any time during treatment was reported for 477 subjects (13.2%) on finerenone and 214 subjects (6.0%) on placebo (Table SVII.7). A change in serum potassium to values >6.0 mmol/L at any time during treatment was reported for 85 subjects (2.3%) on finerenone and 42 subjects (1.2%) on placebo (Report PH-39747: Table 14.3.4/4). Treatment-emergent lab abnormalities of serum potassium >5.5 mmol/L in the finerenone and placebo arms were mostly limited to the 5.5-6.0 mmol/L range (Report PH-42131: Table 14.3.2/8).

In the FIGARO-DKD study, the overall percentages of subjects with serum potassium values >5.5 mmol/L and >6.0 mmol/L at any time during treatment were generally lower in both treatment groups when compared with the FIDELIO-DKD study.

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Table SVII.7: Frequency of treatment-emergent serum potassium values >5.5 and >6.0 mmol/L as reported in Phase III studies (FIDELIO-DKD, FIGARO-DKD and pooled FIDELIO-DKD & FIGARO-DKD) (SAF) (central laboratory)

	FIDELIO-DKD		FIGARO-DKD		FIDELIO-DKD & FIGARO-DKD (POOLED)	
Serum potassium	Finerenone N=2,818 (100%) Num/Den (%)	Placebo N=2,828 (100%) Num/Den (%)	Finerenone N=3,671 (100%) Num/Den (%)	Placebo N=3,646 (100%) Num/Den (%)	Finerenone N=6,489 (100%) Num/Den (%)	Placebo N=6,474 (100%) Num/Den (%)
>5.5 mmol/L	595/2,776 (21.4%)	256/2,772 (9.2%)	477/3,605 (13.2%)	214/3,583 (6.0%)	1,072/6,381 (16.8%)	470/6,355 (7.4%)
>6.0 mmol/L	126/2,793 (4.5%)	38/2,793 (1.4%)	85/3,625 (2.3%)	42/3,605 (1.2%)	211/6,418 (3.3%)	80/6,398 (1.3%)

The denominator (Den) represents all subjects at risk for a treatment-emergent laboratory abnormality. Subjects must have both a baseline and post-baseline treatment-emergent value and the baseline value must be as follows:

In the analysis of values >5.5 mmol/l, subjects with potassium baseline values of >5.5 mmol/L were excluded.

In the analysis of values >6.0 mmol/l, subjects with potassium baseline values of >6.0 mmol/L were excluded.

The numerator (Num) represents the number of subjects at risk with at least one treatment-emergent laboratory assessment meeting the criterion.

Due to the inherent intra-individual variability associated with potassium, a number of subjects shifted from a value below the threshold as defined in the inclusion criteria (≤4.8 mmol/L) at screening to a value above this threshold at baseline.

Only assessments from start of treatment until 3 days after any temporary or permanent interruption of study drug are considered.

Abbreviations: DKD=diabetic kidney disease, FIDELIO-DKD=FInerenone in reducing kiDnEy failure and dIsease progression in Diabetic Kidney Disease, FIGARO-DKD=FInerenone in reducinG cArdiovascular moRtality and mOrbidity in Diabetic Kidney Disease, Den=denominator, Num=numerator, SAF=safety analysis set.

Source: Report B003480: Table 14.3.2/8, Figure 14.3.2/1.

Phase III study FINEARTS-HF (#20103)

As anticipated based on its mode of action, in FINEARTS-HF, participants in the finerenone group had higher serum potassium values than participants in the placebo group during the entire study. The mean increase from baseline (SD) was 0.212 mmol/L (0.499) at Month 1 and 0.246 mmol/L (0.530) at Month 6 under finerenone and remained generally stable thereafter (Module 5.3.5.1, Report B002803, Table 8.3.3/17).

In all categories of change in laboratory serum potassium (Table SVII.8), an increase above the cut-off was more frequently reported in the finerenone group compared with placebo, with approximately a 2-fold increase in the proportion of participants in the finerenone group.

These results are consistent with the results seen in FIDELITY-DKD, although the overall percentage of participants with treatment-emergent hyperkalemia events or increases in serum

potassium was higher in FIDELITY-DKD (Table SVII.7) than in FINEARTS-HF (Table SVII.8).

The subgroup with eGFR ≥60 mL/min/1.7 m^2 (maintenance dose 40 mg) did not have higher frequencies of TE serum potassium >5.5 mmol/L or >6.0 mmol/L in either of the treatment groups when compared to the subgroup with eGFR <60 mL/min/1.7 m^2 (Table SVII.8). These results together with results of hyperkalemia TEAEs (see Table SVII.6) indicate that no increased risk for hyperkalemia was observed by the use of higher 40 mg dose; rather, the expected and main risk of hyperkalemia is well-manageable by using the dose titration scheme.

Table SVII.8: Frequency of treatment-emergent serum potassium values >5.5 and >6.0 mmol/L as reported in Phase III study FINEARTS-HF (SAF) - overall and by baseline eGFR (central laboratory)

	FINEARTS-HF	
Serum potassium	**Finerenone N=2,993 (100%) Num/Den (%)**	**Placebo N=2,993 (100%) Num/Den (%)**
>5.5 mmol/L		
Overall	401/2,866 (14.0%)	190/2,868 (6.6%)
<60 mL/min/1.73 m^2 at baseline	231/1,369 (16.9%)	108/1,360 (7.9%)
≥60 mL/min/1.73 m^2 at baseline	170/1,497 (11.4%)	82/1,508 (5.4%)
> 6.0 mmol/L		
Overall	85/2,891 (2.9%)	41/2,885 (1.4%)
<60 mL/min/1.73 m^2 at baseline	49/1,385 (3.5%)	25/1,371 (1.8%)
≥60 mL/min/1.73 m^2 at baseline	36/1,506 (2.4%)	16/1,514 (1.1%)

The denominator (Den) represents all participants at risk for a treatment-emergent laboratory abnormality. Participants must have both a baseline and post-baseline treatment-emergent value and the baseline value must not exceed the displayed threshold. The numerator (Num) represents the number of participants at risk with at least one treatment-emergent laboratory assessment meeting the criterion.

Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, MLG=MedDRA labelling grouping.

Source: Report B003523: Table 2.4.2/1; Report B003525: Table 14.3.2.4/4.

Severity/outcomes

Severity

Phase III study FIDELIO-DKD (#16244)

In the FIDELIO-DKD study, overall, the majority of hyperkalemia TEAEs in both treatment arms were mild to moderate in intensity (Annex 7.2).

Phase III study FIGARO-DKD (#17530)

In the FIGARO-DKD study, overall, the majority of hyperkalemia TEAEs in both treatment arms were mild to moderate in intensity (Annex 7.2).

Phase III study FINEARTS-HF (#20103)

In the FINEARTS-HF study, overall, the majority of hyperkalemia TEAEs in both treatment arms were mild to moderate in intensity (please see Annex 7.2).

Outcomes

Phase III study FIDELIO-DKD (#16244)

In the FIDELIO-DKD study, the majority of hyperkalemia TEAEs in both treatment arms had resolved (Annex 7.3). There were no treatment-emergent hyperkalemia events with a fatal outcome (Table SVII.4).

Hyperkalemia TEAEs leading to permanent study drug discontinuation had resolved in 53/64 subjects in the finerenone arm and in 13/25 subjects in the placebo arm. Hyperkalemia TESAEs leading to hospitalisation had resolved in 37/40 subjects in the finerenone arm and in 7/8 subjects in the placebo arm (Annex 7.3).

Hyperkalemia TEAEs led to permanent study drug discontinuation in 64/514 subjects in the finerenone arm and in 25/255 subjects in the placebo arm. As described above, in the majority of subjects with such events, these had resolved ore were resolving in both treatment arms. Overall, in the majority of subjects with hyperkalemia TEAEs, study drug was interrupted, but could be resumed (309/514 subjects in the finerenone and 146/255 subjects in the placebo arm, respectively) (Annex 7.4). Study drug dose was reduced in 9/514 subjects in the finerenone arm and 6/255 subjects in the placebo arm. Study drug dose was not changed in about 26% of subjects experiencing hyperkalemia in both treatment groups (126/514 for subjects treated with finerenone and 75/255 subjects receiving placebo).

Phase III study FIGARO-DKD (#17530)

In the FIGARO-DKD study, the majority of hyperkalemia TEAEs in both treatment arms had resolved (Annex 7.3). There were no treatment-emergent hyperkalemia events with a fatal outcome (Table SVII.4).

Hyperkalemia TEAEs leading to permanent study drug discontinuation had resolved in 39/46 subjects in the finerenone arm and in 9/13 subjects in the placebo arm. Hyperkalemia TESAEs leading to hospitalisation had resolved in 21/21 subjects in the finerenone arm and in 1/2 subjects in the placebo arm (Annex 7.3).

Hyperkalemia TEAEs led to permanent study drug discontinuation in 46/394 subjects in the finerenone arm and in 13/193 subjects in the placebo arm. As described above, in the majority of subjects with such events, these had resolved or were resolving in both treatment arms. Overall, in the majority of subjects with hyperkalemia TEAEs, study drug was interrupted, but could be resumed (221/394 subjects in the finerenone and 102/193 subjects in the placebo arm (Annex 7.4). Study drug dose was reduced in 5/394 subjects in the finerenone arm and 3/193 subjects in the placebo arm.

Phase III study FINEARTS-HF (#20103)

In the FINEARTS-HF study, the majority of hyperkalemia TEAEs in both treatment arms had resolved (Annex 7.3). There were no treatment-emergent hyperkalemia events with a fatal outcome (Table SVII.5).

Hyperkalemia TEAEs led to permanent study drug discontinuation in 13/289 subjects in the finerenone arm and in 5/125 subjects in the placebo arm. These TEAEs leading to permanent study drug discontinuation had resolved in 8/13 subjects in the finerenone arm and in 3/5 subjects in the placebo arm.

Hyperkalemia TESAEs leading to hospitalisation had resolved in 16/16 subjects in the finerenone arm and in 5/6 subjects in the placebo arm (please see Annex 7.3). There were no TESAEs leading to permanent study drug discontinuation.

Overall, in the majority of subjects with hyperkalemia TEAEs, study drug was interrupted but could be resumed (143/289 subjects in the finerenone and 50/125 subjects in the placebo arm, respectively (please see Annex 7.4). Study drug dose was reduced in 58/289 subjects in the finerenone arm and 28/125 subjects in the placebo arm. Study drug dose was not changed in about 1.8% of subjects experiencing hyperkalemia in both treatment groups (70/289 for subjects treated with finerenone and 40/125 subjects receiving placebo).

Similar results were seen in FIDELITY-DKD, with a generally higher percentage of participants with interruptions of study intervention. However, depending on potassium measurements, the dose was to be down-titrated or interrupted in FINEARTS-HF, while in the FIDELITY-DKD studies, the dose was to be interrupted with no option to down-titrate.

Remedial therapy for treatment-emergent hyperkalemia

Phase III study FIDELIO-DKD (#16244)

In the FIDELIO-DKD study, in both treatment groups, approx. half of patients who were reported with treatment-emergent hyperkalemia, received treatment for hyperkalemia (247/514 [48.1%]) in the finerenone arm and 121/255 [47.5%] in the placebo arm) (Report B003862: Table 1/1). In the majority of cases in both treatment arms, potassium binders (e.g., calcium or sodium polystyrene sulfonate) were used, followed by diuretics (e. g. furosemide), insulin, glucose, and calcium gluconate. In the finerenone arm, 3/514 subjects (0.6%) underwent haemodialysis for treatment of hyperkalemia versus 3/255 subjects in the placebo arm (1.2%) (Report B003480: Table 14.3.2/12).

The analysis of data collected in the context of dose titration and interruption (PH-39746) indicates that hyperkalemia with finerenone treatment is manageable using a serum-potassium-guided dose titration regimen (Report PH-39746: Table7-2). This is supported by simulation of the exposure-serum potassium model (Report PH-41204), which demonstrated that even at higher exposures, no increased risk for hyperkalemia is observed when dose titration is applied (Report R-13543).

Phase III study FIGARO-DKD (#17530)

In the FIGARO-DKD study, the proportion of subjects who received remedial therapy for treatment-emergent hyperkalemia was comparable in finerenone and placebo arm (157/394 subjects with hyperkalemia, [38.8%]) versus (69/193 subjects, 35.8%]). The most frequently reported remedial therapy for treatment-emergent hyperkalemia was sodium polystyrene sulfonate, followed by calcium polystyrene sulfonate and furosemide (Report B003862: Table 1/1). In the finerenone arm, 3/394 subjects (0.8%) underwent haemodialysis for treatment of hyperkalemia, with no haemodialysis events reported in the placebo arm (Report B003480: Table 14.3.2/12).

There were no relevant differences in remedial therapy between FIGARO-DKD and FIDELIO-DKD studies except for the generally observed higher percentage of subjects with event and remedial therapy for the events in FIDELIO-DKD.

The finerenone exposure-serum potassium model for FIGARO-DKD confirmed the utility of dose titration in managing serum potassium and preventing increased hyperkalemia at higher finerenone exposure levels and doses, as was demonstrated for FIDELIO-DKD (Reports: PH-39747, R-13322).

Phase III study FINEARTS-HF (#20103)

In the FINEARTS-HF study, the number of subjects who received remedial therapy for treatment-emergent hyperkalemia was higher in finerenone (74/289 subjects, [25.6%]) compared with placebo (26/125 subjects, 20.8%]). The most frequently reported remedial therapy for treatment-emergent hyperkalemia was calcium polystyrene sulfonate, followed by sodium polystyrene sulfonate and furosemide (Report B003525: Table 14.3.2.1/30). There were no subjects that underwent haemodialysis treatment due to treatment-emergent hyperkalemia events (Report B003525: Table 14.3.2.1/29).

The finerenone exposure-serum potassium model for FINEARTS-HF (CPMX50156), demonstrated that even at higher exposures including those resulting from 40 mg, no increased risk for hyperkalemia is observed when dose titration is applied (for details, see B002565).

Post-marketing data

Hyperkalemia cases from post-marketing surveillance (spontaneous reports, non-interventional studies, and literature reports) were retrieved from the Bayer safety database using the MLG *Hyperkalemia*. This MLG includes the PTs *Hyperkalaemia* and *Blood potassium increased*. In the section below, the term “hyperkalemia” refers to the MLG *Hyperkalemia*.

The below text provides a cumulative review of the hyperkalemia cases from post-marketing surveillance that were received since finerenone launch on 09 JUL 2021 until 08 JUL 2024 (this DLP is taken from the recent Finerenone PBRER/PSUR No 5.0).

Cumulatively a total of 619 cases with hyperkalemia events (544 spontaneous reports, 74 non-interventional studies, one literature case) were retrieved from the Bayer safety database. Of these 619 cases:

- 564 cases were medically confirmed, and 55 were not medically confirmed.
- In 458 cases, hyperkalemia was reported as serious adverse event (SAE) (in 92 cases, hyperkalemia led to hospitalisation; in 356 cases, hyperkalemia was classified as medically significant; in 10 cases as life-threatening and no fatal hyperkalemia events were reported), while in 161 cases hyperkalemia was reported as a non-serious event.

A detailed review of these cases, as presented in the consecutive finerenone PBRERs/PSURs, revealed no new safety findings for the *Important identified risk* "Hyperkalemia".

Risk factors and risk groups

Hyperkalemia is a known complication of reduced renal function in patients with CKD. Besides CKD, the most common risk factors for hyperkalemia include cardiovascular disease, diabetes mellitus and concomitant use of drugs which raise the potassium concentration (e.g., ACEis, ARBs, potassium-sparing diuretics, and beta blockers) (113).

Based on the analyses in three pivotal the Phase III studies FIDELIO-DKD, FIGARO-DKD, and FINEARTS-HF, risk factors for hyperkalemia include low eGFR, higher serum potassium at baseline, and previous episodes of hyperkalemia. Concomitant use of finerenone with CYP3A4 inhibitors may be associated with a higher risk of developing hyperkalemia due to an increase in finerenone exposure.

Preventability

Appropriate treatment of risk factors for hyperkalemia as applied to the general population as well as careful choice of co-medications may reduce the risk of developing hyperkalemia while receiving finerenone. If hyperkalemia develops, standard management of hyperkalemia should be applied.

In the Kerendia® SmPC, detailed guidance is provided on the initiation of therapy based on serum potassium and eGFR, frequency of potassium monitoring during treatment, as well as dose adjustment/withdrawal based on potassium levels.

Impact on the risk-benefit balance of the product

Two pivotal Phase III studies FIDELIO-DKD and FIGARO-DKD have demonstrated clinically relevant beneficial effects of finerenone on kidney disease progression and cardiovascular mortality and morbidity in patients with CKD and T2D.

The pivotal Phase III study FINEARTS-HF demonstrated clinically relevant beneficial effects of finerenone in reducing the rate of the primary composite CV endpoint (CV death and total HF events) in patients with HF with LVEF ≥40%.

Although an increased risk of hyperkalemia is noted, this risk is considered manageable and is, together with precautionary measures, appropriately addressed in the Kerendia® SmPC. Therefore, the beneficial effects of finerenone are considered to outweigh the risk in patients with CKD and T2D, and patients with HF with LVEF ≥40%. However, since severe elevation of potassium may lead to life-threatening cardiac arrhythmias and fatal cardiac arrest, a potential future occurrence of these cardiovascular events may have an impact on the benefit-risk profile of finerenone. Therefore, hyperkalemia is regarded as an important identified risk.

Routine pharmacovigilance activities will further characterise the risk of hyperkalemia with respect to number of reports, seriousness, outcome, and risk factors. The risk will be mitigated by routine risk minimisation measures (Kerendia® SmPC) such that the benefit-risk for the product will remain positive.

Public health impact

In all three pivotal Phase III studies, the studied population has an inherent risk of hyperkalemia due to the underlying CKD and T2D (FIDELIO-DKD and FIGARO-DKD studies) or underlying HF with LVEF ≥40% (FINEARTS-HF) which are known risk factors for hyperkalemia, as well as due to the background standard of care therapy (ACEis/ARBs) (114).

Hyperkalemia was very common in the finerenone clinical trial population with CKD and T2D and common in the finerenone clinical trial population with HF with LVEF ≥40%, however, most of the events were non-serious and resolved. For both indications, in the finerenone arm, the frequencies of treatment-emergent serious hyperkalemia events with clinical consequence, i.e., leading to hospitalisation (CKD and T2D indication: 1.4% (FIDELIO-DKD) and 0.6% (FIGARO-DKD), HF with LVEF ≥40% indication: 0.5% (FINEARTS-HF) or permanent discontinuation of study drug (CKD and T2D indication: 0.1% (FIDELIO-DKD) and 0.1% (FIGARO-DKD), HF with LVEF ≥40% indication: 0.0% (FINEARTS-HF) were low.

The impact of hyperkalemia on the individual patient is dependent on the severity of hyperkalemia. Hyperkalemia can be easily managed with standard medical treatment on an outpatient basis; however, severe hyperkalemia may be life-threatening and potentially fatal. Quality of life of the individual patient may be affected by emergency treatment, admission to intensive care units, or invasive procedures (e.g., haemodialysis) leading to significant restrictions in daily life.

No public health impact of hyperkalemia was identified.

SVII.3.1.2 Important potential risk: Embryo-foetal toxicity

Potential mechanisms

In the embryo-foetal toxicity study in rats, finerenone resulted in reduced placental weights and signs of foetal toxicity, including reduced foetal weights and retarded ossification at the maternal toxic dose of 10 mg/kg/day corresponding to an $AUC_{unbound}$ of 19 times that in humans in CKD and 7 times in HF. At 30 mg/kg/day, the incidence of visceral and skeletal variations was increased (slight oedema, shortened umbilical cord, slightly enlarged fontanelle) and one foetus showed complex malformations including a rare malformation (double aortic arch) at an $AUC_{unbound}$ of about 25 times that in humans in CKD and about 10 times in HF. The doses free of any findings (low dose in rats, high dose in rabbits) provided safety margins of 10 to 13 times for $AUC_{unbound}$ in CKD and 4 to 5 times in HF. Therefore, the findings in rats do not indicate an increased concern for teratogenicity or embryolethality.

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When rats were exposed during pregnancy and lactation in the pre- and postnatal developmental toxicity study, the offspring showed slightly increased locomotor activity after weaning, but no other neurobehavioural changes starting at about 2 or 4 times the $AUC_{unbound}$ expected in humans. The dose free of findings provided a safety margin of about 2 for $AUC_{unbound}$ in CKD and was in the range of human exposure in HF. As finerenone shows a very low penetration of blood-brain-barrier, the increased locomotor activity in offspring may indicate a potential risk for the foetus, as the behavioural changes may be due to exposure of the foetus during pregnancy, when the blood-brain-barrier is not yet fully formed. Finerenone was shown in pregnant rats to cross the placenta with foetal exposure also in the brain. Mineralocorticoid receptors (MRs) are broadly expressed in the brain and MRAs were shown to modulate anxiety-like behaviour, and to result in anti-depressant-like effects. Some investigations indicate that foetal exposure e.g., to stress may impact MR expression in adulthood, which may give some hint why effects may still be present after the end of exposure.

Evidence source(s) and strength of evidence

The evidence is based on non-clinical data in the developmental toxicity studies in the rat. The overall experience on the use of finerenone in pregnant women is very limited.

Characterisation of the risk

Clinical trials

Frequency/seriousness

There are no clinical data on the use of finerenone in pregnant women.

Severity/outcomes

There are no clinical data on the use of finerenone in pregnant women.

Post-marketing data

Cumulatively since finerenone launch on 09 JUL 2021 until 08 JUL 2024 (this DLP is taken from the recent Finerenone PBRER/PSUR No 5.0), two spontaneous case reports of finerenone exposure during pregnancy were reported from post-marketing surveillance (one case with maternal exposure to finerenone during pregnancy with no abnormal offspring finding, and one case with exposure to finerenone during pregnancy via father).

Based on the review of currently available human data from post-marketing surveillance, there is no evidence of embryo-foetal toxicity when finerenone is taken in therapeutic doses by pregnant women.

Risk factors and risk groups

Women of childbearing potential.

Preventability

SmPC states that finerenone should not be used during pregnancy unless there has been careful consideration of the benefit for the mother and the risk to the foetus. Women of childbearing potential should use effective contraception during treatment with finerenone.

Impact on the risk-benefit balance of the product

Considering the risks associated with pregnancy and the fact that current treatment guidelines advise against pregnancy, as well as minimisation of the risk by correct use of contraception, the impact on the benefit-risk balance is likely to be low.

Public health impact

Current treatment guidelines advise against pregnancy. The public health impact is therefore considered to be low.

SVII.3.2 Presentation of the missing information

SVII.3.2.1 Use in Pregnancy and Lactation

Evidence source:

The evidence is based on non-clinical data in the developmental toxicity studies in the rat. The overall experience on the use of finerenone in pregnant women is very limited and there are no data in lactating women.

Clinical data:

There are no clinical data on the use of finerenone in pregnant and lactating women.

Post-marketing data:

Cumulatively since finerenone launch on 09 JUL 2021 until 08 JUL 2024 (this DLP is taken from the recent Finerenone PBRER/PSUR No 5.0), two spontaneous case reports of finerenone exposure during pregnancy were reported from post-marketing surveillance (one case with maternal exposure to finerenone during pregnancy with no abnormal offspring finding, and one case with exposure to finerenone during pregnancy via father).

Cumulatively since finerenone launch on 09 JUL 2021 until 08 JUL 2024, no cases concerning drug exposure during breast feeding were received.

From the currently available human data from post-marketing surveillance regarding pregnancy and breast feeding, no new safety findings can be derived for the Missing information “Pregnancy and lactation”.

Anticipated risk / consequence of the missing information:

Increased risk of damage to the foetus and breastfed infants.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of the Safety Concerns

Important identified risks	Hyperkalemia
Important potential risks	Embryo-foetal toxicity
Missing information	Use in pregnancy and lactation

Part III: Pharmacovigilance plan (including post-authorisation safety studies)

SIII.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities are in place for the *important identified risk* "Hyperkalemia", *important potential risk* "Embryo-foetal toxicity" and *missing information* "Use in pregnancy and lactation", and they will be conducted as detailed in corresponding pharmacovigilance procedures that are in place at Bayer AG. These routine activities include collection, follow-up, evaluation, and expedited reporting of individual case reports, ongoing monitoring and signal investigation, as well as preparation of PBRER/PSUR.

SIII.1.1 Specific adverse reaction follow-up questionnaires for safety concerns

No specific adverse reaction follow-up questionnaires are in place for Kerendia®.

SIII.1.2 Other forms of routine pharmacovigilance activities for safety concerns

Not applicable.

SIII.2 Additional pharmacovigilance activities

No additional pharmacovigilance activities are in place for Kerendia®.

SIII.3 Summary table of additional pharmacovigilance activities

Not applicable.

Part IV: Plans for post-authorisation efficacy studies

No post-authorisation efficacy studies with Kerendia® are planned.

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Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk minimisation plan

"Hyperkalemia" has been identified as an *important identified risk* of Kerendia®. The risk minimisation measures for "Hyperkalemia" comprise the routine risk minimisation measures detailed in Section V.1. No additional risk minimisation measures beyond routine are considered necessary for Kerendia®.

"Embryo-foetal toxicity" has been identified as an *important potential risk* of Kerendia®. The risk minimisation measures for "Embryo-foetal toxicity" comprise the routine risk minimisation measures detailed in Section V.1. No additional risk minimisation measures beyond routine are considered necessary for Kerendia®.

"Use in pregnancy and lactation" has been identified as *missing information* of Kerendia®. The risk minimisation measures for "Use in pregnancy and lacation" comprise the routine risk minimisation measures detailed in Section V.1. No additional risk minimisation measures beyond routine are considered necessary for Kerendia®.

V.1 Routine risk minimisation measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important identified risk	
Hyperkalemia	**Routine risk communication:** • SmPC section 4.2 Posology and method of administration • SmPC section 4.4 Special warnings and precautions for use • SmPC section 4.5 Interaction with other medicinal products and other forms of interaction • SmPC section 4.8 Undesirable effects **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • SmPC section 4.2 Posology and method of administration • SmPC section 4.4 Special warnings and precautions for use • SmPC section 4.5 Interaction with other medicinal products and other forms of interaction **Other routine risk minimisation measures beyond the Product Information:** • Kerendia® is a prescription-only medicine

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Table Part V.1: Description of routine risk minimisation measures by safety concern

Important potential risk	
Embryo-foetal toxicity	**Routine risk communication** • SmPC section 4.4 Special warnings and precautions for use • SmPC section 4.6 Fertility, pregnancy and lactation • SmPC section 5.3 Preclinical safety data **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • SmPC section 4.4 Special warnings and precautions for use • SmPC section 4.6 Fertility, pregnancy and lactation • SmPC section 5.3 Preclinical safety data **Other routine risk minimisation measures beyond the Product Information:** • Kerendia® is a prescription-only medicine
Missing information	
Use in pregnancy and lactation	**Routine risk communication** • SmPC section 4.4 Special warnings and precautions for use • SmPC section 4.6 Fertility, pregnancy and lactation • SmPC section 5.3 Preclinical safety data **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • SmPC section 4.4 Special warnings and precautions for use • SmPC section 4.6 Fertility, pregnancy and lactation • SmPC section 5.3 Preclinical safety data **Other routine risk minimisation measures beyond the Product Information:** • Kerendia® is a prescription-only medicine

Abbreviations: SmPC=Summary of Product Characteristics.

V.2 Additional risk minimisation measures

Routine risk minimisation activities as described in Section V.1 are sufficient to manage the *important identified risk* "Hyperkalemia", *important potential risk* "Embryo-foetal toxicity", and *missing information* "Use in pregnancy and lactation".

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V.3 Summary of risk minimisation measures

Table Part V.2: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risk		
Hyperkalemia	**Routine risk minimisation measures:** • SmPC sections 4.2, 4.4, 4.5, and 4.8 • Kerendia® is a prescription-only medicine **Additional risk minimisation measures**: • None	**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.

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Part VI: Summary of the risk management plan

Summary of risk management plan for Kerendia® (Finerenone)

This is a summary of the risk management plan (RMP) for Kerendia®. The RMP details important risks of Kerendia®, how these risks can be minimised, and how more information will be obtained about Kerendia®'s risks and uncertainties (missing information).

Kerendia®'s Summary of Product Characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Kerendia® should be used.

This summary of the RMP for Kerendia® should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Kerendia®'s RMP.

I. The medicine and what it is used for

Kerendia® is authorised

- 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". It contains finerenone as the active substance and it is given by oral administration.

  Further information about the evaluation of Kerendia®'s benefits can be found in Kerendia®'s EPAR, including in its plain-language summary, available on the EMA website: https://www.ema.europa.eu/en/medicines/human/EPAR/kerendia
- for "the treatment of symptomatic chronic heart failure with left ventricular ejection fraction ≥40% in adults". It contains finerenone as the active substance and it is given by oral administration.

  Further information about the evaluation of Kerendia®'s benefits can be found in Kerendia®'s EPAR, including in its plain-language summary, available on the EMA website: <*Pre-authorisation RMP (this line should be only edited by EMA)*: link to the EPAR summary landing page>.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Kerendia®, together with measures to minimise such risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;

- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Kerendia® is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Kerendia® are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Kerendia®. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

Table Part VI.1: Summary of safety concerns

List of important risks and missing information	
Important identified risks	Hyperkalemia
Important potential risks	Embryo-foetal toxicity
Missing information	Use in pregnancy and lactation

II.B Summary of important risks

Important identified risk – Hyperkalemia	
Evidence for linking the risk to the medicine	The evidence is based on three pivotal Phase III studies (FIDELIO-DKD, FIGARO-DKD, FINEARTS-HF) and PBRERs/PSURs.
Risk factors and risk groups	The most common risk factors for hyperkalemia include chronic kidney disease, cardiovascular disease, diabetes mellitus and concomitant use of drugs which raise the potassium concentration (e.g., ACEis, ARBs, potassium-sparing diuretics, and beta blockers). Based on the analyses of three pivotal Phase III studies, risk factors for hyperkalemia include low eGFR, higher baseline serum potassium and previous episodes of hyperkalemia. Concomitant use of finerenone with CYP3A4 inhibitors may be associated with a

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Important identified risk – Hyperkalemia	
	higher risk of developing hyperkalemia due to an increase in finerenone exposure.
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC sections: 4.2, 4.4, 4.5 and 4.8 • Kerendia® is a prescription-only medicine **Additional risk minimisation measures:** • None
Important potential risk – Embryo-foetal toxicity	
Evidence for linking the risk to the medicine	The evidence is based on non-clinical data in the developmental toxicity studies in the rat. The overall experience on the use of finerenone in pregnant women is very limited.
Risk factors and risk groups	Women of childbearing potential
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC section 4.4 Special warnings and precautions for use • SmPC section 4.6 Fertility, pregnancy and lactation • SmPC section 5.3 Preclinical safety data • Kerendia® is a prescription-only medicine **Additional risk minimisation measures:** • None
Missing information – Use in pregnancy and lactation	
Risk minimisation measures	**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

II.C Post-authorisation development plan

There are no studies that are conditions of the marketing authorisation or specific obligation of Kerendia®.

II.C.1 Studies which are conditions of the marketing authorisation

Not applicable.

II.C.2 Other studies in post-authorisation development plan

Not applicable.

Part VII: Annexes

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Annex 4 - Specific adverse drug reaction follow-up forms

Not applicable.

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Not applicable.