1. NAME OF THE MEDICINAL PRODUCT

Kerendia 10 mg film-coated tablets
Kerendia 20 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Kerendia 10 mg film-coated tablet
Each film-coated tablet contains 10 mg finerenone.

Kerendia 20 mg film-coated tablet
Each film-coated tablet contains 20 mg finerenone.

3. PHARMACEUTICAL FORM

Film-coated tablet

Kerendia 10 mg film-coated tablet
Pink, oval-oblong 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 tablet
Pale-yellow, oval-oblong tablet with a length of 10 mm and a width of 5 mm, marked ´20´ on one side and ´FI´ on the other side

4. CLINICAL PARTICULARS

4.1 Indication(s)

Kerendia, in addition to standard of care, is indicated to reduce the risk of sustained eGFR decline, end-stage kidney disease, cardiovascular death, non-fatal myocardial infarction and hospitalization for heart failure in adults with chronic kidney disease and albuminuria associated with type 2 diabetes.

4.2 Dosage and method of administration

4.2.1 Method of administration

Oral use

Tablets may be taken with a glass of water and with or without food *(see section 'Pharmacokinetic properties')*.

Avoid taking Kerendia with grapefruit or grapefruit juice *(see section ´*Special warnings and precautions for use*´and '*4.5 Interaction with other medicinal products and other forms of interaction*')*.

For patients who are unable to swallow whole tablets, Kerendia tablet may be crushed and mixed with water or soft foods, such as applesauce, immediately prior to use and administered orally *(see section 'Pharmacokinetic properties')*.

4.2.2 Dosage regimen

The recommended target dose of Kerendia is 20 mg once daily.

4.2.2.1 Initiation of treatment

Initiation of Kerendia treatment is recommended when serum potassium ≤ 4.8 mmol/L.

For monitoring of serum potassium, see 'Continuation of treatment.'

If serum potassium > 4.8 to 5.0 mmol/L, initiation of Kerendia treatment may be considered with additional serum potassium monitoring within the first 4 weeks based on patient characteristics and serum potassium levels *(see section ´*Special warnings and precautions for use*´)*.

If serum potassium > 5.0 mmol/L, initiation of Kerendia treatment is not recommended *(see section ´*Special warnings and precautions for use*´)*.

Measure estimated glomerular filtration rate (eGFR) to determine the starting dose.
The starting dose of Kerendia is:
- 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

Initiation of Kerendia treatment is not recommended in patients with eGFR < 25 mL/min/1.73 m^2 as clinical experience is limited.

4.2.2.2 Continuation of treatment
Four weeks after initiation or re-start or up-titration of Kerendia treatment, remeasure serum potassium and eGFR. See Table 1 to determine continuation of Kerendia treatment and dose adjustment.

Thereafter, remeasure serum potassium periodically and as needed based on patient characteristics and serum potassium levels *(see section '*Special warnings and precautions for use*' and '*4.5 Interaction with other medicinal products and other forms of interaction*').*

Table 1: Continuation of Kerendia treatment and dose adjustment

Serum potassium (mmol/L)	**Kerendia dose (after 4 weeks and thereafter)**
≤ 4.8	Maintain 20 mg once daily. For patients on 10 mg once daily, increase the dose to 20 mg once daily if eGFR has not decreased > 30% compared to the prior measurement.
> 4.8 – 5.5	Maintain dose.
> 5.5	Withhold Kerendia. Restart at 10 mg once daily if serum potassium ≤ 5.0 mmol/L.

4.2.2.3 Missed doses
A missed dose should be taken as soon as possible after it is noticed, but only on the same day. If this is not possible, the dose should be skipped, and the next dose taken as prescribed. Two doses should not be taken to make up for a missed dose.

The maximum daily dose of Kerendia is 20 mg.

4.2.3 Additional information on special populations
4.2.3.1 Patients with renal impairment
Initiation of Kerendia treatment
In patients with eGFR ≥ 25 to < 60 mL/min/1.73 m^2, the starting dose of Kerendia is 10 mg once daily. See section 'Initiation of treatment.'

In patients with eGFR < 25 mL/min/1.73m^2, initiation of Kerendia treatment is not recommended as clinical experience is limited *(see section '*Special warnings and precautions for use*' and section 'Pharmacokinetic properties')*.

Continuation of Kerendia treatment

In patients with mild, moderate or severe renal impairment, continue Kerendia treatment and adjust dose based on serum potassium. Measure eGFR 4 weeks after initiation to determine up-titration. See Table 1 and section 'Continuation of treatment.'
In patients with end-stage renal disease (eGFR < 15 mL/min/1.73 m^2), continue Kerendia treatment with caution regarding serum potassium levels as clinical experience is limited *(see section 'Special warnings and precautions for use').*

4.2.3.2 Patients with hepatic impairment

In patients with severe hepatic impairment (Child Pugh C), avoid treatment with Kerendia *(see section 'Special warnings and precautions for use' and section 'Pharmacokinetic properties')*. In patients with mild or moderate hepatic impairment, no initial dose adjustment is required (Child Pugh A or B) *(see section 'Pharmacokinetic properties')*.

In patients with moderate hepatic impairment (Child Pugh B), consider additional serum potassium monitoring and adapt monitoring according to patient characteristics *(see section 'Special warnings and precautions for use' and section 'Pharmacokinetic properties')*.

4.2.3.3 Patients taking concomitant medications
In patients taking Kerendia concomitantly with moderate or weak CYP3A4 inhibitors, potassium supplements, trimethoprim, or trimethoprim-sulfamethoxazole, consider additional serum potassium monitoring and adapt monitoring according to patient characteristics and make Kerendia treatment decisions as directed in Table 1. Temporary discontinuation of Kerendia when taking trimethoprim, or trimethoprim-sulfamethoxazole, may be necessary *(see sections 'Special warnings and precautions for use' and 'Interaction with other medicinal products and other forms of interaction').*

4.2.3.4 Pediatric patients
The safety and efficacy of Kerendia have not been established in patients under 18 years of age. Therefore, Kerendia is not recommended for use in pediatric patients.

4.2.3.5 Geriatric patients
No dose adjustment is required in the elderly *(see section 'Pharmacokinetic properties')*.

4.2.3.6 Gender
No dose adjustment is required based on gender *(see section 'Pharmacokinetic properties')*.

4.2.3.7 Body weight
No dose adjustment is required based on body weight *(see section 'Pharmacokinetic properties')*.

4.2.3.8 Ethnic differences
No dose adjustment is required based on ethnic differences *(see section 'Pharmacokinetic properties').*

4.2.3.9 Smoking status
No dose adjustment is required based on smoking status *(see section 'Pharmacokinetic properties').*

4.3 Contraindications

Kerendia is contraindicated in patients:
- taking concomitant medications that are strong CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, ritonavir, nelfinavir, cobicistat, clarithromycin, telithromycin and nefazodone) *(see section 'Interaction with other medicinal products and other forms of interaction').*
- with Addison's disease.

4.4 Special warnings and precautions for use

4.4.1 Hyperkalemia
Hyperkalemia has been observed in patients treated with Kerendia.

Some patients are at a higher risk to develop hyperkalemia. Risk factors include low eGFR, higher serum potassium and previous episodes of hyperkalemia. Consider more frequent monitoring in these patients.

Initiation of Kerendia treatment is not recommended if serum potassium > 5.0 mmol/L. If serum potassium > 4.8 to 5.0 mmol/L, initiation of Kerendia treatment may be considered with additional serum potassium monitoring within the first 4 weeks based on patient characteristics and serum potassium levels *(see section* 'Dosage and method of administration').

Withhold Kerendia in treated patients if serum potassium > 5.5 mmol/L. Follow local guidelines for the management of hyperkalemia. Restart Kerendia at 10 mg once daily if serum potassium ≤ 5.0 mmol/L *(see section* 'Dosage and method of administration').

Remeasure serum potassium and eGFR in all patients 4 weeks after initiation or re-start or up-titration of Kerendia treatment. Thereafter, remeasure serum potassium periodically and as needed based on patient characteristics and serum potassium levels *(see section* 'Dosage and method of administration').

Concomitant medications
The risk of hyperkalemia also may increase with the intake of concomitant medications that may increase serum potassium *(see section 'Interaction with other medicinal products and other forms of interaction')*. See also 'Concomitant use of substances that affect finerenone exposure.'

Avoid concomitant use of Kerendia with the following medications:
- potassium-sparing diuretics (e.g., amiloride, triamterene)
- other mineralocorticoid receptor antagonists (MRAs) (e.g., eplerenone, esaxerenone, spironolactone, canrenone)

Use Kerendia with caution and monitor serum potassium when taken concomitantly with the following medications:
- potassium supplements
- trimethoprim, or trimethoprim-sulfamethoxazole. Temporary discontinuation of Kerendia may be necessary.

4.4.2 Renal impairment

The risk of hyperkalemia increases with decreasing renal function. Ongoing monitoring of renal function should be performed as needed according to standard practice *(see section* 'Dosage and method of administration' *and section 'Pharmacokinetic properties')*.

Initiation of Kerendia treatment is not recommended in patients with eGFR < 25 mL/min/1.73 m^2 as clinical experience is limited *(see section 'Dosage and method of administration')*.

Continue Kerendia treatment with caution regarding serum potassium levels in patients with end-stage renal disease (eGFR < 15 mL/min/1.73 m^2) as clinical experience is limited *(see section 'Dosage and method of administration'*).

4.4.3 Hepatic impairment

Patients with severe hepatic impairment (Child Pugh C) have not been studied *(see section 'Pharmacokinetic properties'*). Due to an expected significant increase in finerenone exposure, avoid use of Kerendia in patients with severe hepatic impairment *(see section 'Dosage and method of administration'*).

Due to an increase in finerenone exposure, consider additional serum potassium monitoring and adapt monitoring according to patient characteristics in patients with moderate hepatic impairment (Child Pugh B) *(see section* 'Dosage and method of administration' and *section 'Pharmacokinetic properties'*)*)*.

4.4.4 Concomitant use of substances that affect finerenone exposure

Moderate and weak CYP3A4 inhibitors

The concomitant use of Kerendia with moderate CYP3A4 inhibitors (e.g., erythromycin and verapamil) and weak CYP3A4 inhibitors (e.g., amiodarone and fluvoxamine) is expected to increase finerenone exposure *(see section 'Interaction with other medicinal products and other forms of interaction')*. Monitor serum potassium especially during initiation of or changes to dosing of Kerendia or the CYP3A4 inhibitor *(see section* 'Dosage and method of administration'*)*.

Strong and moderate CYP3A4 inducers

Avoid concomitant use of Kerendia with strong CYP3A4 inducers (e.g., rifampicin, carbamazepine, phenytoin, phenobarbital, St John's Wort) or moderate CYP3A4 inducers (e.g., efavirenz), which are expected to markedly decrease finerenone plasma concentrations and result in reduced therapeutic effect (see section 'Interaction with other medicinal products and other forms of interaction'). Consider selection of an alternate concomitant medicinal product with no or weak potential to induce CYP3A4.

Grapefruit

Avoid concomitant intake of grapefruit or grapefruit juice as it is expected to increase the plasma concentration of finerenone *(see sections* 'Dosage and method of administration' *and 'Interaction with other medicinal products and other forms of interaction')*.

4.4.5 Embryo-fetal toxicity

Animal data have shown reproductive toxicity *(see section 'Preclinical safety data')*. The relevance for humans is unknown . Kerendia should not be used during pregnancy unless there has been careful consideration of the benefit for the mother and the risk to the fetus. If the patient becomes pregnant while taking Kerendia, the patient should be informed of potential risks to the fetus. Advise women of childbearing potential to use effective contraception during treatment with Kerendia. Advise women not to breastfeed during treatment with Kerendia *(see section* 'Fertility, pregnancy and lactation'*)*.

4.5 Interaction with other medicinal products and other forms of interaction

4.5.1 Effects of other substances on finerenone

Finerenone is cleared almost exclusively via cytochrome P450 (CYP)-mediated oxidative metabolism (mainly CYP3A4 [90%] with a small contribution of CYP2C8 [10%]).

4.5.1.1 Effect of CYP3A4 inhibitors on finerenone

Strong CYP3A4 inhibitors

Simulations suggest that concomitant use of Kerendia with itraconazole (200 mg BID), a strong CYP3A4 inhibitor, increases finerenone AUC (+531%) and C_{max} (+137%). Clarithromycin (500 mg BID), another strong inhibitor, also is predicted to increase finerenone AUC (+428%) and C_{max} (+125%). Due to an expected marked increase in finerenone exposure, concomitant use of Kerendia with itraconazole, clarithromycin and other strong CYP3A4 inhibitors (e.g., ketoconazole, ritonavir, nelfinavir, cobicistat, telithromycin or nefazodone) is contraindicated (*see section* 'Contraindications').

Moderate CYP3A4 inhibitors

Concomitant use of erythromycin (500 mg thrice daily), a moderate CYP3A4 inhibitor, increased finerenone mean AUC and Cmax by 248% and 88%, respectively. Another moderate CYP3A4 inhibitor, verapamil (240 mg controlled-release tablet once daily), increased finerenone mean AUC and Cmax by 170% and 122%, respectively. Serum potassium may increase, and therefore, monitoring of serum potassium is recommended *(see sections 'Dosage and method of administration' and 'Special warnings and precautions for use')*.

Weak CYP3A4 inhibitors

In an analysis of Kerendia in patients, the use of amiodarone, a weak CYP3A4 inhibitor, was estimated to result in a 21% increase of finerenone AUC. Simulations suggest that fluvoxamine

(100 mg BID), another weak inhibitor, increases finerenone AUC (+57%) and C_{max} (+38%). Serum potassium may increase, and therefore, monitoring of serum potassium is recommended *(see sections* *'*Dosage and method of administration' *and '* Special warnings and precautions for use*')*.

Grapefruit
Concomitant intake of grapefruit or grapefruit juice is expected to increase the plasma concentration of finerenone and should be avoided *(see sections* *'*Dosage and method of administration' *and* *'*Special warnings and precautions for use*')*.

4.5.1.2 Effect of strong and moderate CYP3A4 inducers on finerenone
Simulations suggest that rifampicin (600 mg OD), a strong CYP3A4 inducer, decreases finerenone AUC (-93%) and C_{max} (-86%). Efavirenz (600 mg OD), a moderate CYP3A4 inducer, is predicted to decrease finerenone AUC (-81%) and C_{max} (-68%).

Concomitant use of Kerendia with rifampicin and other strong CYP3A4 inducers (e.g., carbamazepine, phenytoin, phenobarbital, St John's Wort) or with efavirenz and other moderate CYP3A4 inducers, markedly decreases finerenone plasma concentration and results in reduced therapeutic effect and should be avoided *(see section* *'*Special warnings and precautions for use*').*

4.5.1.3 Lack of clinically relevant drug-drug interaction
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.

Pre- and co-treatment with the proton pump inhibitor omeprazole (40 mg once daily) had no effect on finerenone mean AUC and mean C_{max}.

Concomitant use of antacid aluminum hydroxide and magnesium hydroxide (70 mVal) had no effect on finerenone mean AUC and reduced its mean C_{max} by 19%. This is not clinically relevant.

4.5.2 Effect of finerenone on other substances
In vivo a multiple-dose regimen of 20 mg finerenone once-daily had no effect on the AUC of the CYP3A4 probe substrate midazolam. Finerenone neither inhibits nor induces CYP3A4.

A single dose of 20 mg finerenone also had no effect on AUC and Cmax of the CYP2C8 probe substrate repaglinide. Finerenone does not inhibit CYP2C8.

Lack of mutual pharmacokinetic interaction was demonstrated between finerenone and the CYP2C9 substrate warfarin. Finerenone had no effect on AUC and Ctrough of the P-gp substrate digoxin at steady-state (90% CI of ratio (digoxin + finerenone / digoxin alone) within 90-111%). The ratio of digoxin Cmax at steady-state (digoxin + finerenone / digoxin alone) was 105.3% with a 90% CI of 94.65-117.16 %.

Multiple doses of 40 mg finerenone once daily had no clinically relevant effect on AUC or Cmax of the BCRP and OATP substrate rosuvastatin.

4.5.3 Pharmacodynamic interactions
Medications that increase serum potassium
It is anticipated that medications that increase serum potassium will increase the risk of hyperkalemia when used concomitantly with Kerendia.

Concomitant use of Kerendia with the following medications should be avoided:
- potassium-sparing diuretics (e.g., amiloride, triamterene)
- other mineralocorticoid receptor antagonists (MRAs) (e.g., eplerenone, esaxerenone, spironolactone, canrenone)

Kerendia should be used with caution and serum potassium monitored when taken concomitantly with the following medications:

- potassium supplements
- trimethoprim, or trimethoprim - sulfamethoxazole. Temporary discontinuation of Kerendia may be necessary.

(See section 'Special warnings and precautions for use*')*

4.6 Fertility, pregnancy and lactation

4.6.1 Pregnancy

There are no data on the use of Kerendia in pregnant women . Animal studies have shown embryo-fetal developmental toxicity at exposures in excess to the maximum human exposure. In the pre- and post-natal developmental toxicity study, slightly increased locomotor activity was found in the offspring, which may have been caused by exposure during pregnancy *(see section 'Preclinical safety data')*.

Kerendia should not be used during pregnancy unless there has been careful consideration of the benefit for the mother and the risk to the fetus *(see section* ´Special warnings and precautions for use´*)*.

4.6.2 Lactation

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 Kerendia is considered essential *(see section* ´Special warnings and precautions for use´*)*.

4.6.3 Fertility

No human data on the effect of Kerendia 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 *(see section 'Preclinical safety data')*.

4.6.4 Women of childbearing potential / Contraception

Kerendia may cause embryo-fetal harm when administered during pregnancy. Women of childbearing potential should use effective contraception during treatment with Kerendia *(see section* ´Special warnings and precautions for use´*)*.

4.7 Effects on ability to drive or use machines

No effects on ability to drive and use machines have been observed.

4.8 Undesirable effects

4.8.1 Summary of the safety profile

The safety of Kerendia in patients with chronic kidney disease associated with type 2 diabetes was evaluated in two pivotal phase III studies, FIDELIO-DKD and FIGARO-DKD. In the FIDELIO-DKD study, 2,827 patients received Kerendia (10 or 20 mg once daily) with a mean duration of treatment of 2.2 years. In the FIGARO-DKD study, 3683 patients received Kerendia (10 or 20 mg once daily) with a mean duration of treatment of 2.9 years.

The most frequently reported (≥ 10%) adverse reaction was hyperkalemia. See 'Description of selected adverse reactions' below *(see section* 'Special warnings and precautions for use*')*.

4.8.2 Tabulated list of adverse reactions

The adverse reactions reported with Kerendia are summarized in Table 2 below by MedDRA system organ class and by frequency.

Adverse reactions are ranked by System organ class and then by frequency with the most frequent first, using the following convention:
very common (≥1/10)
common (≥1/100 to <1/10)
uncommon (≥1/1,000 to <1/100)
rare (≥1/10,000 to <1/1,000)
very rare (<1/10,000)

Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

Table 2: Adverse reactions reported with Kerendia in phase III studies (pooled FIDELIO-DKD and FIGARO-DKD)

MedDRA System Organ Class	**Very common**	**Common**
Metabolism and nutrition disorders	Hyperkalemia[1]	Hyponatremia[2] Hyperuricemia[3,4]
Vascular disorders		Hypotension[5,6]
Investigations		Glomerular filtration rate decreased [7]

[1] includes Blood potassium increased and Hyperkalemia
[2] includes Blood sodium decreased and Hyponatremia
[3] includes Blood uric acid increased and Hyperuricemia
[4] Asymptomatic hyperuricemia was observed. In the FIGARO-DKD study, an increase from baseline in mean serum uric acid of up to 0.3 mg/dL was seen in the Kerendia group compared to placebo, which attenuated over time. No hyperuricemia related treatment discontinuations were reported.
[5] includes Blood pressure decreased, Blood pressure diastolic decreased, Diastolic hypotension and Hypotension
[6] In patients treated with Kerendia, the mean systolic blood pressure (SBP) decreased by 3 mmHg and the mean diastolic blood pressure (DBP) decreased by 1-2 mmHg at month 1, remaining stable thereafter. The majority of hypotension events were mild or moderate and resolved. Events associated with hypotension, e.g., dizziness, syncope, or fall, were not more frequent in patients using Kerendia in comparison to placebo.
[7] An initial decrease in eGFR (mean 2 mL/min/1.73m^2) attenuated over time compared to placebo. This decrease has been shown to be reversible after treatment discontinuation.

4.8.3 Description of selected adverse reactions
Hyperkalemia
In the FIDELIO-DKD study including patients with CKD (mean eGFR 44.3 mL/min/1.73 m^2) and T2D, hyperkalemia events were reported in 18.3% of Kerendia-treated patients compared with 9.0% of placebo-treated patients. An increase from baseline in mean serum potassium in the first month of treatment of approximately 0.2 mmol/L was observed in the Kerendia group compared to placebo, which remained stable thereafter. In the FIGARO-DKD study including patients with CKD (mean eGFR 67.8 mL/min/1.73 m^2) and T2D, hyperkalemia events were reported in 10.8% of Kerendia-treated patients compared with 5.3% of placebo-treated patients. An increase from baseline in mean serum potassium in the first month of treatment of approximately 0.15 mmol/L was observed in the Kerendia group compared to placebo, which remained stable thereafter. In both studies, the majority of hyperkalemia events were mild to moderate in patients treated with Kerendia. For specific recommendations, refer to sections 'Dosage and method of administration' and 'Special warnings and precautions for use.'

4.9 Overdose

No cases of adverse events associated with finerenone overdose in humans have been reported. The most likely manifestation of overdose is anticipated to be hyperkalemia. If hyperkalemia develops, standard treatment should be initiated.

Finerenone is unlikely to be efficiently removed by hemodialysis given its fraction bound to plasma proteins of about 90%.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: aldosterone antagonists

ATC Code: C03DA05

5.1.1 Mechanism of action

Finerenone is a nonsteroidal, selective antagonist of the mineralocorticoid receptor (MR) that potently attenuates inflammation and fibrosis mediated by MR overactivation. The MR is expressed in the kidneys, heart and blood vessels where finerenone also counteracts sodium retention and hypertrophic processes. Finerenone has a high potency and selectivity for the MR due to its nonsteroidal structure and bulky binding mode. Finerenone has no relevant affinity for androgen, progesterone, estrogen and glucocorticoid receptors and therefore does not cause sex hormone-related adverse events (e.g., gynecomastia). Its binding to the MR leads to a specific receptor ligand complex that blocks recruitment of transcriptional coactivators implicated in the expression of pro-inflammatory and pro-fibrotic mediators.

5.1.2 Pharmacodynamic properties

5.1.2.1 Effects in patients with CKD and T2D

In FIDELIO-DKD and FIGARO-DKD, randomized, double-blind, placebo-controlled, multicenter phase III studies in adults with CKD and T2D, the placebo-corrected relative reduction in urinary albumin-to-creatinine ratio (UACR) in patients randomized to finerenone at Month 4 was 31% and 32%, respectively and UACR remained reduced throughout both studies.

In ARTS DN, a randomized, double-blind, placebo-controlled, multicenter phase IIb dose-finding study in adults with CKD and T2D, the placebo-corrected relative reduction in UACR at Day 90 was 25% and 38% in patients treated with finerenone 10 mg and 20 mg once daily, respectively.

5.1.2.2 Cardiac electrophysiology

In a thorough QT study in 57 healthy participants, there was no indication of a QT/QTc prolonging effect of finerenone after single doses of 20 mg (therapeutic) or 80 mg (supratherapeutic), indicating that finerenone has no effect on cardiac repolarization.

5.1.3 Clinical efficacy and safety

5.1.3.1 Chronic kidney disease associated with type 2 diabetes

Kerendia was investigated in two randomized, double-blind, placebo-controlled, multicenter phase III studies, FIDELIO-DKD and FIGARO-DKD. In these studies, the effect of Kerendia on kidney and cardiovascular outcomes was evaluated in adults with CKD and T2D receiving either Kerendia 10 mg or 20 mg once daily, or placebo.

In FIDELIO-DKD patients were eligible based on evidence of persistent albuminuria (≥30 mg/g to <300 mg/g) and eGFR ≥25 but <60 mL/min/1.73 m^2 and presence of diabetic retinopathy or persistent albuminuria (≥300 mg/g to 5,000 mg/g) and eGFR ≥25 to <75 mL/min/1.73 m^2, serum potassium ≤ 4.8 mmol/L at screening, and were required to be receiving standard of care, including a maximum

tolerated labeled dose of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB). The trial excluded patients with known significant non-diabetic kidney disease. Patients with a clinical diagnosis of chronic heart failure with reduced ejection fraction and persistent symptoms (New York Heart Association class II to IV) were excluded.

The primary endpoint in the FIDELIO-DKD study was a composite of time to first occurrence of kidney failure (defined as chronic dialysis or kidney transplantation, or a sustained decrease in eGFR to < 15 mL/min/1.73 m^2 over at least 4 weeks), a sustained decline in eGFR of 40% or more compared to baseline over at least 4 weeks, or renal death. The key secondary endpoint was a composite of time to first occurrence of cardiovascular (CV) death, non-fatal myocardial infarction (MI), non-fatal stroke or hospitalization for heart failure.

The trial analyzed 5,674 patients randomly assigned to receive either Kerendia (N=2833), or placebo (N=2841), with a median follow-up duration of 2.6 years. After the end of study notification, vital status was obtained for 99.7% of patients. The trial population was 63% White, 25% Asian and 5% Black. The mean age at enrollment was 66 years and 70% of patients were male. At baseline, the mean eGFR was 44.3 mL/min/1.73 m^2, with 55% of patients having an eGFR < 45 mL/min/1.73 m^2, median urine albumin-to-creatinine ratio (UACR) was 852 mg/g, and mean glycated hemoglobin A1c (HbA1c) was 7.7%, 46% had a history of atherosclerotic cardiovascular disease, 30% had history of coronary artery disease, 8% had a history of cardiac failure, and the mean blood pressure was 138/76 mmHg. The mean duration of type 2 diabetes at baseline was 16.6 years and a history of diabetic retinopathy and diabetic neuropathy was reported in 47% and 26% of patients, respectively. At baseline, almost all patients were on ACEi (34%) or ARB (66%), and 97% of patients used one or more antidiabetic medications (insulin [64%], biguanides [44%], glucagon-like peptide-1 [GLP-1] receptor agonists [7%], sodium-glucose cotransporter 2 [SGLT2] inhibitors [5%]). The other most frequent medications taken at baseline were statins (74%) and calcium channel blockers (63%).

Kerendia demonstrated superiority to placebo by significantly reducing the risk of the primary composite endpoint compared to placebo in a time-to-event analysis using the Cox proportional hazards model and log-rank test (HR 0.82, 95% CI 0.73-0.93, p=0.0014). See Figure 1/Table 3 below. Kerendia also significantly reduced the risk of the key secondary composite endpoint of time to first occurrence of CV death, non-fatal MI, non-fatal stroke or hospitalization for heart failure compared to placebo (HR 0.86, 95% CI 0.75-0.99, p=0.0339). See Figure 2. Prespecified secondary time-to-event endpoints are included in Table 3. The treatment effect for the primary and key secondary endpoints was generally consistent across subgroups, including region, eGFR, UACR, systolic blood pressure (SBP) and HbA1c at baseline.

In the FIDELIO-DKD study, hyperkalemia events were reported in 18.3% of Kerendia-treated patients compared with 9.0% of placebo-treated patients. Hospitalization due to hyperkalemia for the Kerendia group was 1.4% versus 0.3% in the placebo group. Hyperkalemia leading to permanent discontinuation in patients who received Kerendia was 2.3% versus 0.9% in the placebo group.

In the FIDELIO-DKD study, Glomerular filtration rate decreased events were reported in 6.3% of Kerendia-treated patients compared with 4.7% of placebo-treated patients, and those leading to permanent discontinuation in patients receiving Kerendia were 0.2% versus 0.3% in the placebo group. Patients on Kerendia experienced an initial decrease in eGFR (mean 2 mL/min/1.73m^2) that attenuated over time compared to placebo. This decrease was reversible after treatment discontinuation. The initial decrease in eGFR was associated with long term preservation of kidney function.

The FIGARO-DKD study included adults with CKD and T2D, based on having a UACR of ≥ 30 mg/g to <300 mg/g and an eGFR of 25 to 90 mL/min/1.73m2, or a UACR ≥ 300 mg/g and an eGFR ≥ 60 mL/min/1.73m2 at screening. Patients were required to have a serum potassium of ≤ 4.8 mmol/L at

screening and received standard of care, including a maximum tolerated labeled dose of a RAS inhibitor (either an ACEi or ARB).

The primary endpoint in the FIGARO-DKD study was a composite of time to first occurrence of CV death, non-fatal MI, non-fatal stroke or hospitalization for heart failure. Secondary endpoints included a composite of time to kidney failure, a sustained decline in eGFR of 40% or more compared to baseline over at least 4 weeks, or renal death and a composite of time to kidney failure, a sustained decline in eGFR of 57% or more compared to baseline, or renal death.

The trial analyzed 7,352 patients randomly assigned to receive either Kerendia (N=3686), or placebo (N=3666) that were followed for a median duration of 3.4 years. After the end of study notification, vital status was obtained for 99.8% of patients. The trial population was 72% White, 20% Asian and 4% Black. The mean age at enrollment was 64 years and 69% of patients were male. At baseline, the mean eGFR was 67.8 mL/min/1.73 m2, with 62% of patients having an eGFR ≥ 60 mL/min/1.73 m2, median UACR was 308 mg/g, and mean glycated HbA1c was 7.7%, 45% of patients had a history of atherosclerotic cardiovascular disease, 8% had a history of cardiac failure, and the mean blood pressure was 136/77 mmHg. The mean duration of type 2 diabetes at baseline was 14.5 years and a history of diabetic retinopathy and diabetic neuropathy was reported in 31% and 28% of patients, respectively. At baseline, almost all patients were on a RAS-inhibitor and 98% of patients used one or more antidiabetic medications (insulin [54%], biguanides [69%], GLP-1 receptor agonists [7%], SGLT2 inhibitors [8%]). The other most frequent medication class taken at baseline was statins (71 %).

Kerendia significantly reduced the risk of the primary composite endpoint compared to placebo in a time to event analysis using the Cox proportional hazards model and log rank test (HR 0.87, 95% CI 0.76-0.98, p=0.0264). See Figure 5/Table 4 below. The treatment effect for the primary endpoint was consistent across subgroups, including region, eGFR, UACR, SBP and HbA1c at baseline. A lower incidence rate of the secondary composite outcome of kidney failure, sustained eGFR decline of 40% or more or renal death was observed in the Kerendia group compared to placebo, however this difference did not achieve statistical significance (HR 0.87, 95% CI 0.76-1.01, p=0.0689). See Figure 6/Table 4 below. A lower risk of the secondary outcome of kidney failure, sustained eGFR decline of 57% or more or renal death was observed in the Kerendia group compared to placebo (HR 0.77, 95% CI 0.60-0.99). Prespecified secondary time-to-event endpoints are included in Table 4.

In the FIGARO-DKD study, hyperkalemia events were reported in 10.8% of Kerendia-treated patients compared with 5.3% of placebo-treated patients. Hospitalization due to hyperkalemia for the Kerendia group was 0.6% versus <0.1% in the placebo group. Hyperkalemia leading to permanent discontinuation in patients who received Kerendia was 1.2% versus 0.4% in the placebo group.

In the FIGARO-DKD study, Glomerular filtration rate decreased events were reported in 4.6% of Kerendia-treated patients compared with 3.9% of placebo-treated patients, and those leading to permanent discontinuation in patients receiving Kerendia were 0.2% versus 0.1% in the placebo group. Patients on Kerendia experienced an initial decrease in eGFR of around 2 mL/min/1.73m2 that attenuated over time compared to placebo. This decrease was reversible after treatment discontinuation. The initial decrease in eGFR was associated with long term preservation of kidney function.

Table 3: Analysis of the Primary and Secondary Time-to-Event Endpoints (and their Individual Components) in Phase III Study FIDELIO-DKD

	Subjects with Chronic Kidney Disease and Type 2 Diabetes					
	Kerendia* 10 or 20 mg OD N=2833		**Placebo* N=2841**		**Treatment Effect Kerendia / Placebo**	
Primary and Secondary Time-to-event Endpoints:	**n (%)**	**Event Rate (100 pt–yr)**	**n (%)**	**Event Rate (100 pt–yr)**	**Hazard Ratio (95% CI)**	**p-value**
Primary composite of kidney failure, sustained eGFR decline ≥40% or renal death	504 (17.8%)	7.59	600 (21.1%)	9.08	0.82 [0.73; 0.93]	0.0014
Kidney failure	208 (7.3%)	2.99	235 (8.3%)	3.39	0.87 [0.72; 1.05]	-
Sustained eGFR decline ≥40%	479 (16.9%)	7.21	577 (20.3%)	8.73	0.81 [0.72; 0.92]	-
Renal death	2 (<0.1%)	-	2 (<0.1%)	-	-	-
Secondary composite of CV death, non-fatal MI, non-fatal stroke or hospitalization for heart failure	367 (13.0%)	5.11	420 (14.8%)	5.92	0.86 [0.75; 0.99]	0.0339
CV death	128 (4.5%)	1.69	150 (5.3%)	1.99	0.86 [0.68;1.08]	-
Non-fatal MI	70 (2.5%)	0.94	87 (3.1%)	1.17	0.80 [0.58;1.09]	-
Non-Fatal stroke	90 (3.2%)	1.21	87 (3.1%)	1.18	1.03 [0.76;1.38]	-
Hospitalization for heart failure	139 (4.9%)	1.89	162 (5.7%)	2.21	0.86 [0.68;1.08]	-
All-cause mortality	219 (7.7%)	2.90	244 (8.6%)	3.23	0.90 [0.75; 1.07]	0.2348**
All-cause hospitalization	1263 (44.6%)	22.56	1321 (46.5%)	23.87	0.95 [0.88; 1.02]	-
Kidney failure, sustained eGFR decline ≥ 57% or renal death	252 (8.9%)	3.64	326 (11.5%)	4.74	0.76 [0.65; 0.90]	-

* Treatment in addition to maximum tolerated labeled doses of ACEi or ARB.

** Not significant

Figure 1: Time to first occurrence of kidney failure, sustained decline in eGFR ≥40% from baseline, or renal death in the FIDELIO-DKD study

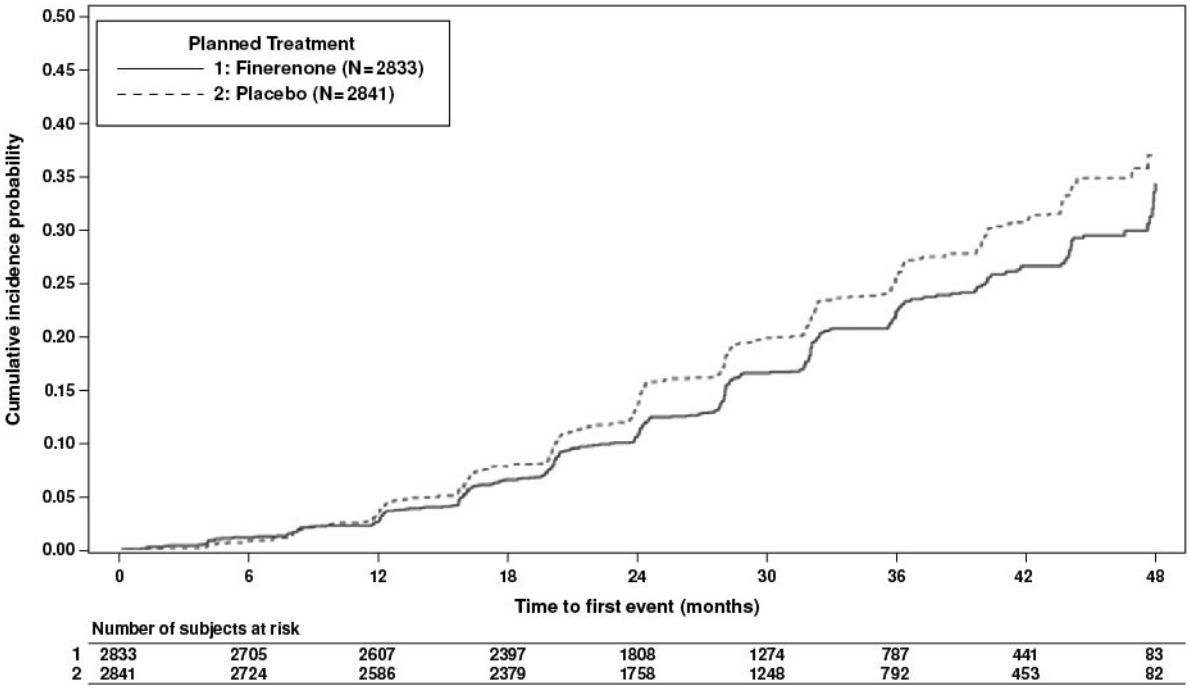


Figure 2: Time to first occurrence of CV death, non-fatal myocardial infarction, non-fatal stroke or hospitalization for heart failure in the FIDELIO-DKD study

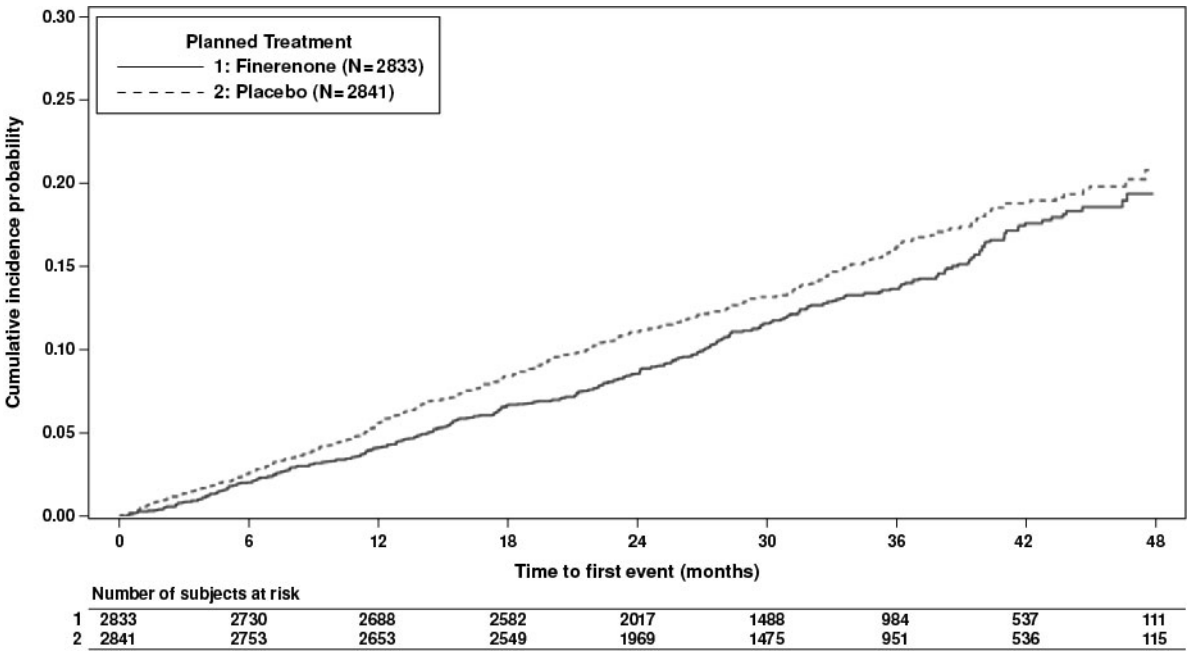


Figure 3: Primary renal composite outcomes according to subgroups

Primary Renal Composite Outcome	Finerenone (n=2833)		Placebo (n=2841)		Hazard ratio (95% CI)	*P*-value for interaction
	Number of patients with event	Number of patients with event per 100 patient-years	Number of patients with event	Number of patients with event per 100 patient-years		
Screening Albuminuria						
UACR 30 to < 300 mg/g	11/210	1.62	15/213	2.27	0.70 (0.32–1.52)	0.6708
UACR ≥ 300 mg/g	493/2623	8.27	585/2628	9.84	0.83 (0.73–0.93)	
History of Cardiovascular Disease						
Present	200/1303	6.60	267/1302	9.06	0.70 (0.58-0.84)	0.0160
Absent	304/1530	8.42	333/1539	9.10	0.94 (0.80–1.09)	
Body Mass Index at Baseline						
< 30 kg/m2	235/1320	7.62	321/1342	10.52	0.68 (0.58-0.81)	0.0028
≥ 30 kg/m2	266/1501	7.53	279/1494	7.86	0.98 (0.83-1.17)	
Baseline use of SGLT-2 inhibitor						
No	490/2709	7.73	590/2706	9.39	0.82 (0.72-0.92)	0.2114
Yes	14/124	4.66	10/135	3.07	1.38 (0.61-3.10)	
Baseline use of GLP-1 receptor agonist						
No	472/2644	7.63	568/2636	9.32	0.80 (0.71-0.91)	0.1502
Yes	32/189	7.03	32.205	6.29	1.17 (0.71-1.90)	
Baseline use of DPP4-inhibitor						
No	345/2069	7.19	445/2083	9.29	0.77 (0.67-0.88)	0.0680
Yes	159/764	8.62	155/758	8.54	0.98 (0.79-1.23)	

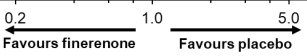


Figure 4: Secondary cardiovascular composite outcome according to subgroups

Key Secondary Cardiovascular Composite Outcome	Finerenone (n=2833)		Placebo (n=2841)		Hazard ratio (95% CI)	*P*-value for interaction
	Number of patients with event	Number of patients with event per 100 patient-years	Number of patients with event	Number of patients with event per 100 patient-years		
Screening Albuminuria						
UACR 30 to < 300 mg/g	23/210	3.32	27/213	3.94	0.83 (0.48-1.45)	0.8958
UACR ≥ 300 mg/g	344/2623	5.30	393/2628	6.13	0.86 (0.75-1.00)	
History of Cardiovascular Disease						
Present	231/1303	7.18	263/1302	8.50	0.85 (0.71-1.01)	0.8535
Absent	136/1530	3.43	157.1539	3.92	0.87 (0.69-1.09)	
Body Mass Index at Baseline						
< 30 kg/m2	142/1320	4.20	176/1342	5.28	0.79 (0.64-0.99)	0.4051
≥ 30 kg/m2	220/1501	5.83	243/1494	6.48	0.90 (0.75-1.07)	
Baseline use of SGLT-2 inhibitor						
No	352/2709	5.12	405/2706	5.99	0.85 (0.74-0.98)	0.4553
Yes	15/124	4.90	15/135	4.44	1.12 (0.55-2.30)	
Baseline use of GLP-1 receptor agonist						
No	340/2644	5.07	392/2636	5.98	0.85 (0.73-0.98)	0.5072
Yes	27/189	5.54	28/205	5.20	1.02 (0.60-1.74)	
Baseline use of DPP4-inhibitor						
No	275/2069	5.28	321/2083	6.23	0.85 (0.72-0.99)	0.6794
Yes	92/764	4.64	99/758	5.10	0.91 (0.68-1.20)	

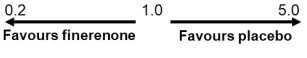


Table 4: Analysis of the Primary and Secondary Time-to-Event Endpoints (and their Individual Components) in Phase III Study FIGARO-DKD

	Subjects with Chronic Kidney Disease and Type 2 Diabetes					
	Kerendia* 10 or 20 mg OD N=3686		**Placebo* N=3666**		**Treatment Effect Kerendia / Placebo**	
Primary and Secondary Time-to-event Endpoints:	**n (%)**	**Event Rate (100 pt–yr)**	**n (%)**	**Event Rate (100 pt–yr)**	**Hazard Ratio (95% CI)**	**p-value**
Primary composite of CV death, non-fatal MI, non-fatal stroke or hospitalization for heart failure	458 (12.4%)	3.87	519 (14.2%)	4.45	0.87 [0.76; 0.98]	0.0264
CV death	194 (5.3%)	1.56	214 (5.8%)	1.74	0.90 [0.74; 1.09]	-
Non-fatal MI	103 (2.8%)	0.85	102 (2.8%)	0.85	0.99 [0.76; 1.31]	-
Non-fatal stroke	108 (2.9%)	0.89	111 (3.0%)	0.92	0.97 [0.74; 1.26]	-
Hospitalization for heart failure	117 (3.2%)	0.96	163 (4.4%)	1.36	0.71[0.56; 0.90]	-
Composite of kidney failure, sustained eGFR decline ≥40% or renal death	350 (9.5%)	3.15	395 (10.8%)	3.58	0.87 [0.76; 1.01]	0.0689**
Kidney failure	46 (1.2%)	0.40	62 (1.7%)	0.54	0.72 [0.49; 1.05]	-

Sustained eGFR decline ≥ 40%	338 (9.2%)	3.04	385 (10.5%)	3.49	0.87 [0.75; <1.00]	-
Renal death	0	-	2 (<0.1%)	-	-	-
All-cause hospitalization	1573 (42.7%)	16.91	1605 (43.8%)	17.52	0.97 [0.90; 1.04]	-
All-cause mortality	333 (9.0%)	2.68	370 (10.1%)	3.01	0.89 [0.77; 1.04]	-
Composite of kidney failure, sustained eGFR decline ≥ 57% or renal death	108 (2.9%)	0.95	139 (3.8%)	1.23	0.77 [0.60; 0.99]	-

* Treatment in addition to maximum tolerated labeled doses of ACEi or ARB.

** Not significant

Figure 5: Time to first occurrence of CV death, non-fatal myocardial infarction, non-fatal stroke or hospitalization for heart failure in the FIGARO-DKD study

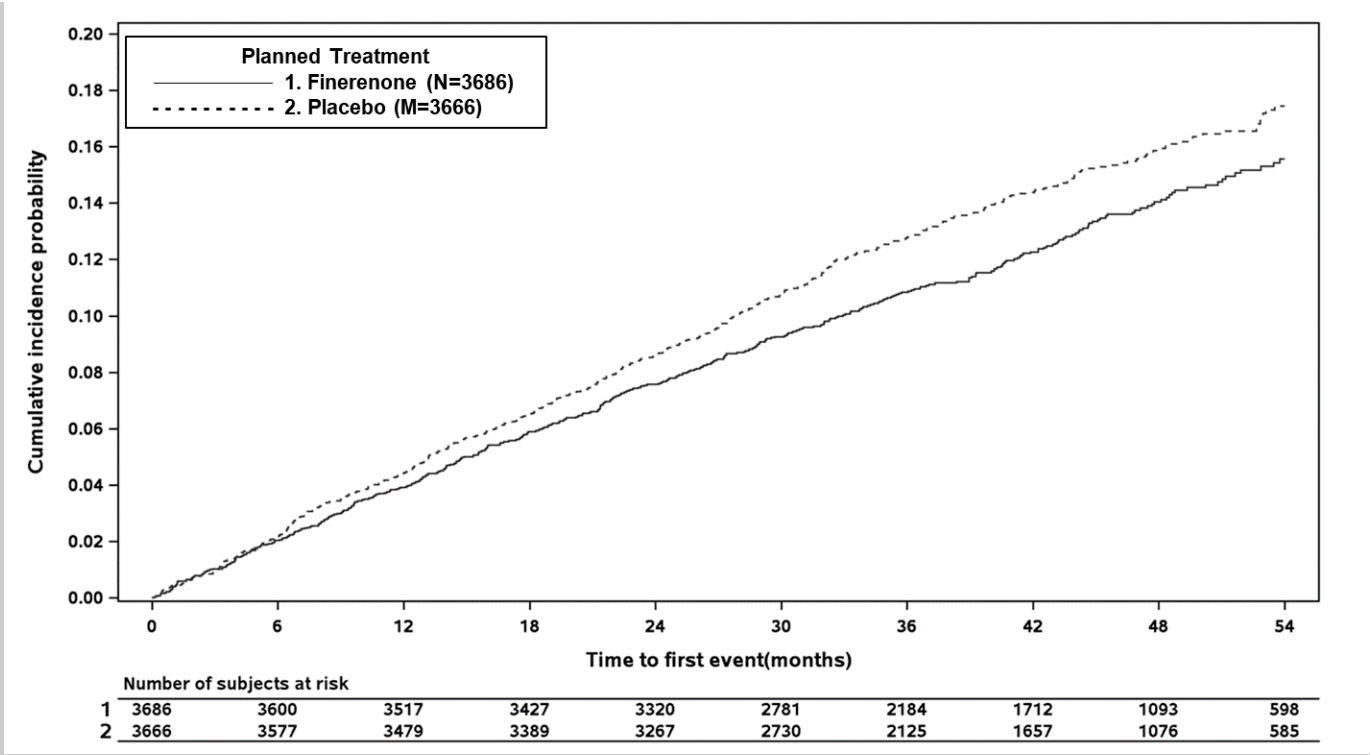
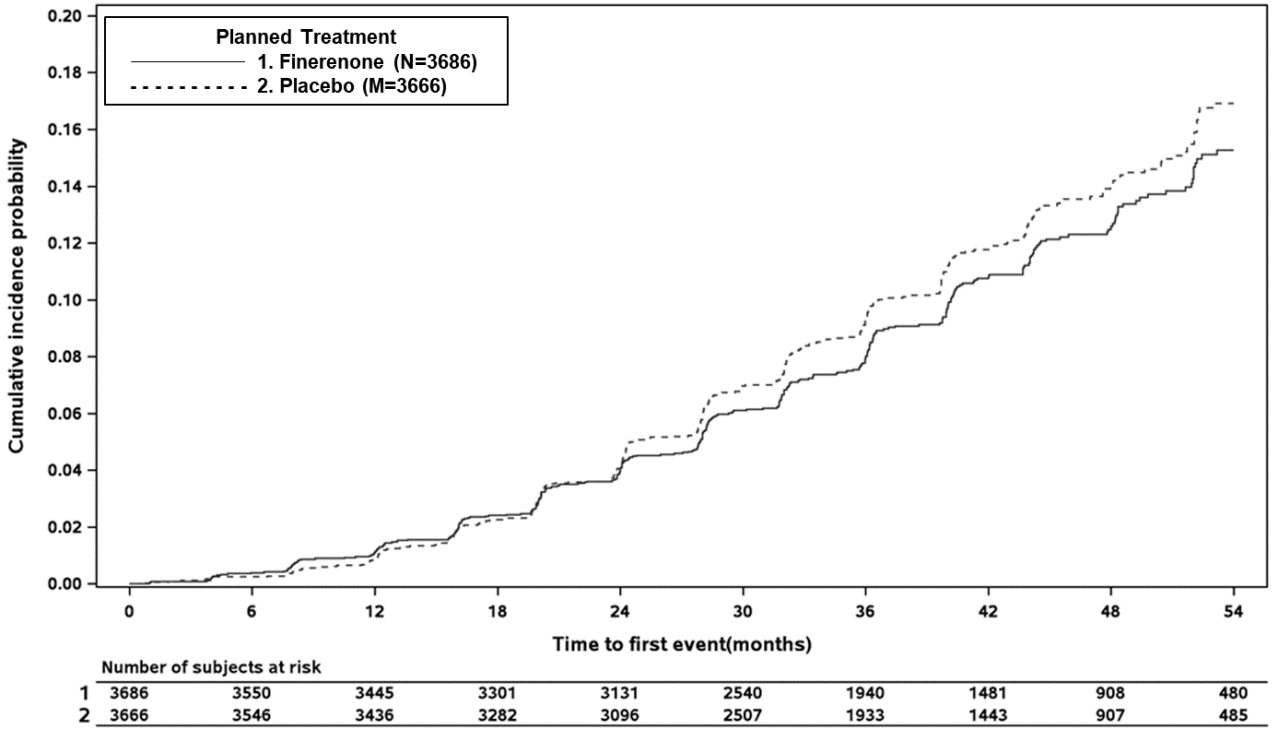


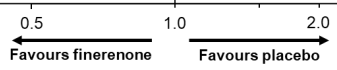
Figure 6: Time to first occurrence of kidney failure, sustained decline in eGFR ≥40% from baseline, or renal death in the FIGARO-DKD study



In a pre-specified pooled analysis of the FIDELIO-DKD and FIGARO-DKD studies, finerenone reduced the risk of the CV composite endpoint of time to CV death, non-fatal MI, non-fatal stroke or hospitalization for heart failure compared to placebo (HR 0.86 [95% CI 0.78; 0.95]). See Figure 7. The risk of the kidney composite endpoint of time to kidney failure, a sustained decrease in eGFR of 40% or more compared to baseline or renal death was also reduced with finerenone compared to placebo (HR 0.85 [95% CI 0.77; 0.93]), as was the composite endpoint of time to kidney failure, a sustained decrease in eGFR of 57% or more compared to baseline or renal death (HR 0.77 [95% CI 0.67; 0.88]). See Figure 7.

Figure 7: Cardiovascular and kidney composite outcomes in the pooled analysis of FIDELIO-DKD and FIGARO-DKD

Outcome	Finerenone (n=6519)		Placebo (n=6507)		Hazard ratio (95% CI)
	Number of patients with event (%)	Number of patients with event per 100 patient-years	Number of patients with event (%)	Number of patients with event per 100 patient-years	
Composite cardiovascular outcome	825 (12.7)	4.34	939 (14.4)	5.01	0.86 (0.78–0.95)
Death from cardiovascular causes	322 (4.9)	1.61	364 (5.6)	1.84	0.88 (0.76–1.02)
Non-fatal myocardial infarction	173 (2.7)	0.88	189 (2.9)	0.97	0.91 (0.74–1.12)
Non-fatal stroke	198 (3.0)	1.01	198 (3.0)	1.02	0.99 (0.82–1.21)
Hospitalisation for heart failure	256 (3.9)	1.31	325 (5.0)	1.68	0.78 (0.66–0.92)
eGFR 40% composite kidney outcome	854 (13.1)	4.81	995 (15.3)	5.64	0.85 (0.77–0.93)
Kidney failure	254 (3.9)	1.38	297 (4.6)	1.62	0.84 (0.71–0.99)
End-stage kidney disease	151 (2.3)	0.76	188 (2.9)	0.96	0.80 (0.64–0.99)
Sustained decrease in eGFR to <15 mL/min/1.73 m^2	195 (3.0)	1.06	237 (3.6)	1.29	0.81 (0.67–0.98)
Sustained ≥40% decrease in eGFR from baseline	817 (12.5)	4.60	962 (14.8)	5.45	0.84 (0.76–0.92)
Renal death	2 (<0.1)	0.01	4 (<0.1)	0.02	0.53 (0.10–2.91)
eGFR 57% composite kidney outcome	360 (5.5)	1.96	465 (7.1)	2.55	0.77 (0.67–0.88)
Sustained ≥57% decrease in eGFR from baseline	257 (3.9)	1.40	361 (5.5)	4.03	0.70 (0.60–0.83)



5.2 Pharmacokinetic properties

5.2.1 Pharmacokinetic / Pharmacodynamic relationships

The concentration-effect relationship over time for UACR was characterized by a maximum effect model indicating saturation at high exposures. The model-predicted time to reach the full (99%) steady-state drug effect on UACR was 138 days. The pharmacokinetic (PK) half-life was 2-3 hours and PK steady state was achieved after 2 days, indicating timescale separation.

5.2.2 Absorption

Finerenone is almost completely absorbed after oral administration. Absorption is rapid with maximum plasma concentrations (C_{max}) appearing between 0.5 and 1.25 hours after tablet intake in the fasted state. The absolute bioavailability of finerenone is 43.5% due to first-pass metabolism in the gut-wall and liver. Finerenone is not a substrate of the efflux transporter P-gp in vivo. Intake with ≥high fat, high calorie food increased finerenone AUC by 21%, reduced C_{max} by 19% and prolonged the time to reach C_{max} to 2.5 hours. This is not clinically relevant. Therefore, finerenone can be taken with or without food *(see section* 'Dosage and method of administration*')*.

5.2.3 Distribution

The volume of distribution at steady state (Vss) of finerenone is 52.6 L. The human plasma protein binding of finerenone *in vitro* is 91.7%, with serum albumin being the main binding protein.

5.2.4 Metabolism / Biotransformation

Approximately 90% of finerenone metabolism is mediated by CYP3A4 and 10% by CYP2C8. Four major metabolites were found in plasma, resulting from oxidation of the dihydropyridine moiety to a pyridine (M1a, M1b), subsequent hydroxylation of a methyl group (M2a) and formation of a carboxyl function (M3a). All metabolites are pharmacologically inactive.

5.2.5 Elimination / Excretion

The elimination of finerenone from plasma is rapid with an elimination half-life ($t_{1/2}$) of about 2 to 3 hours. Excretion of unchanged finerenone represents a minor route (<1% of dose in the urine due to glomerular filtration, < 0.2% in the feces). About 80% of the administered dose was excreted via urine and approximately 20% of the dose was excreted via feces, almost exclusively in the form of metabolites. With a systemic blood clearance of about 25 L/h, finerenone can be classified as a low clearance drug.

5.2.6 Linearity / Non-linearity

Finerenone pharmacokinetics are linear across the investigated dose range from 1.25 to 80 mg.

5.2.7 Additional information on special populations

5.2.7.1 Patients with renal impairment

Mild renal impairment (CL_{CR} 60 - < 90 mL/min) did not affect finerenone AUC and C_{max}. Compared to subjects with normal renal function (CLCR ≥ 90 mL/min), the effect of moderate (CL_{CR} 30 - < 60 mL/min) or severe (CL_{CR} < 30 mL/min) renal impairment on AUC of finerenone was

similar with increases by 34-36%. Moderate or severe renal impairment had no effect on C_{max} *(see section* 'Dosage and method of administration*)*.

Due to the high plasma protein binding, finerenone is not expected to be dialyzable.

5.2.7.2 Patients with hepatic impairment

There was no change in finerenone exposure in cirrhotic subjects with mild hepatic impairment (Child Pugh A) *(see section* 'Dosage and method of administration'*)*.

In cirrhotic subjects with moderate hepatic impairment (Child Pugh B), finerenone mean AUC was increased by 38% and C_{max} was unchanged compared to healthy control subjects *(see section* 'Dosage and method of administration*)*.

There are no data in patients with severe hepatic impairment (Child Pugh C) *(see section* 'Dosage and method of administration' *and* 'Special warnings and precautions for use'*)*.

5.2.7.3 Geriatric patients

Of the 2827 patients who received Kerendia in the FIDELIO-DKD study, 58% of patients were 65 years and older, and 15% were 75 years and older. No overall differences in safety or efficacy were observed between these patients and younger patients.

Of the 3683 patients who received Kerendia in the FIGARO-DKD study, 52% of patients were 65 years and older, and 13% were 75 years and older. No overall differences in safety or efficacy were observed between these patients and younger patients.

Elderly subjects (≥ 65 years of age) exhibited higher finerenone plasma concentrations than younger subjects (≤ 45 years of age), with mean AUC and C_{max} values being 34% and 51% higher in the elderly *(see section* 'Dosage and method of administration*')*. [13]

Population-pharmacokinetic analyses did not identify age as a covariate for finerenone AUC or C_{max}.

5.2.7.4 Gender

Gender had no effect on the pharmacokinetics of finerenone *(see section* 'Dosage and method of administration'*)*.

5.2.7.5 Body Weight

Population-pharmacokinetic analyses identified body weight as a covariate for finerenone C_{max}. The C_{max} of a subject with a body weight of 50 kg was estimated to be 38% to 51% higher compared to a

subject of 100 kg. Dose adaptation based on body weight is not warranted *(see section* 'Dosage and method of administration'*)*.

5.2.7.6 Ethnic differences

Population-pharmacokinetic analyses in patients demonstrated no clinically relevant difference in finerenone exposure between Asian and Caucasian patients *(see section* 'Dosage and method of administration'*)*.

5.2.7.7 Smoking status

Finerenone is not metabolized by an enzyme that is inducible by tobacco smoke *(see section* 'Dosage and method of administration*)*.

5.3 Preclinical safety data

5.3.1 Embryotoxicity / Teratogenicity

In the embryo-fetal toxicity in rats, finerenone resulted in reduced placental weights and signs of fetal toxicity including reduced fetal 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. At 30 mg/kg/day, the incidence of visceral and skeletal variations was increased (slight edema, shortened umbilical cord, slightly enlarged fontanelle) and one fetus showed complex malformations including a rare malformation (double aortic arch) at an $AUC_{unbound}$ of about 25 times that in humans. The doses free of any findings (low dose in rats, high dose in rabbits) provided safety margins of 10 to 13 times for AUCunbound. Therefore, the findings in rats do not indicate an increased concern for fetal harm *(see section* `Fertility, pregnancy and lactation'*)*.

When rats were exposed during pregnancy and lactation in the pre- and postnatal developmental toxicity study, increased pup mortality and other 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 neurobehavioral changes starting at about 4 times the $AUC_{unbound}$ expected in humans. The dose free of findings provided a safety margin of about 2 for $AUC_{unbound}$. The increased locomotor activity in offspring may indicate a potential risk for the fetus. In addition, because of the findings in pups, a risk for the nursing infant cannot be excluded *(see section* 'Special warnings and precautions for use' *and* `Fertility, pregnancy and lactation'*)*.

5.3.2 Reproduction toxicity

Male fertility was not affected by Kerendia *(see section* `Fertility, pregnancy and lactation'*)*.

Finerenone caused reduced female fertility (decreased number of corpora lutea and implantation sites) as well as signs of early embryonic toxicity (increased post-implantational loss and decreased number of viable fetuses) at about 21 times the human $AUC_{unbound}$. In addition, reduced ovarian weights were found at about 17 times the human $AUC_{unbound}$. No effects on female fertility and early embryonic development were found at 10 times the human $AUC_{unbound}$. Therefore, the findings in female rats are of little clinical relevance *(see section* `Fertility, pregnancy and lactation'*)*.

5.3.3 Genotoxicity and carcinogenicity

Finerenone was non-genotoxic in an in vitro bacterial reverse mutation (Ames assay), the in vitro chromosomal aberration assay and the in vivo micronucleus assay.

In 2-year carcinogenicity studies, finerenone did not show a carcinogenic potential in Wistar rats as well as CD1 mice. In male mice, finerenone resulted in an increase in Leydig cell adenoma at doses

representing 26 times the $AUC_{unbound}$ in humans. A dose representing 17 times the $AUC_{unbound}$ in humans did not cause any tumors. Based on the known sensitivity of rodents to develop these tumors and the pharmacology-based mechanism at supratherapeutic doses as well as adequate safety margins, the increase in Leydig cell tumors in male mice is not clinically relevant.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Cellulose microcrystalline (E 460)
Croscarmellose sodium
Hypromellose 5 cP (E 464)
Lactose monohydrate
Magnesium stearate (E 470b)
Sodium laurilsulfate (E 487)

Tablet coating:
Ferric oxide red (E 172) (Kerendia 10 mg film-coated tablet)
Ferric oxide yellow (E 172) (Kerendia 20 mg film-coated tablet)
Hypromellose 5 cP (E 464)
Talc (E 553 b)
Titanium dioxide (E 171)

6.2 Incompatibilities

N/A

6.3 Shelf life

Please refer to labels

6.4 Special precautions for storage

Store below 30 °C

6.5 Nature and contents of container

PVC/PVDC-Aluminium transparent calendarised blisters with 14 film-coated tablets. Pack sizes of 14, 28 or 98 film-coated tablets

PVC/PVDC-Aluminium transparent perforated unit dose blisters with 10 x 1 film-coated tablets. Pack size of 10 × 10 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Instructions for use / handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 PRODUCT REGISTRANT

Bayer (South East Asia Pte Ltd)
2 Tanjong Katong Road #07-01, Paya Lebar Quarter 3 Singapore 437161

8 DATE OF LAST REVISION

September 2022

If you would like to report a side effect for any Bayer Pharmaceutical or Consumer Health product, you can do it easily using our online reporting portal: https://safetrack-public.bayer.com/ or scan the QR code available below. Please also remember to seek medical advice directly from your doctor or pharmacist.

SafeTrack