Report on the Deliberation Results

March 10, 2022
Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Kerendia Tablets 10 mg Kerendia Tablets 20 mg
Non-proprietary Name	Finerenone (JAN*)
Applicant	Bayer Yakuhin, Ltd.
Date of Application	November 26, 2020

Results of Deliberation

In its meeting held on January 28, 2022, the First Committee on New Drugs concluded that the review of the present application should be continued for the following reason: Although global phase III studies of the product (Studies 16244 and 17530) achieved their objectives, the hazard ratio of the product to placebo for the "renal failure" event (one component of the primary endpoint in Study 16244) was greater than 1 in the Japanese subpopulation in both studies. In view of these results, precautions and a method of providing information should be further discussed to ensure that healthcare professionals can properly understand the efficacy of the product as demonstrated by the results of the clinical studies.

Subsequently, in its meeting held on February 25, 2022, the First Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council. Based on the following discussions, this conclusion was reached on the premise that a change is made to the Precautions Concerning Indication section of the package insert as shown in the table below and that a post-marketing surveillance is appropriately planned:

- The global phase III studies (Studies 16244 and 17530) were designed to give power to test the efficacy of the product in the overall population. The studies successfully demonstrated that the product was statistically significantly superior to placebo for efficacy measures in the overall population, as designed.
- In view of the objectives and designs of the global phase III studies (Studies 16244 and 17530), the effect of the product in delaying the occurrence of renal events should be evaluated mainly based on the results of the renal composite endpoint as the primary endpoint of Study 16244. In this study, the hazard ratio of the product to placebo was less than 1 in the Japanese population, as in the overall population. In addition, the global phase III studies (Studies 16244 and 17530) suggested that the incidence of the renal composite endpoint tended to decrease with a decrease in urine albumin-to-creatinine ratio (UACR), and not only estimated glomerular filtration rate (eGFR) data

but also UACR data from the Japanese population also supported the renoprotective effect of the product.

- However, the effect of the product in delaying progression to renal failure is possibly weaker in the Japanese population than in the overall population, given that the hazard ratio of the product to placebo for the "renal failure" event was greater than 1 in the Japanese population in both global phase III studies (Studies 16244 and 17530), and that the difference in annual changes in eGFR slope between the groups was smaller in the Japanese population than in the overall population.
- The post-marketing surveillance should be designed to ensure that the effect of the product in delaying the occurrence of renal events in Japanese patients is appropriately evaluated. In addition, an interim analysis should be performed to provide evaluation results to healthcare professionals in clinical practice as early as possible. Specific criteria for justification of continued use of the product in line with the current clinical positioning should be established before the start of each of the final and interim analyses.

The product is not classified as a biological product or a specified biological product. The re-examination period is 8 years. The drug substance is classified as a powerful drug. The drug product is not classified as a poisonous drug or a powerful drug.

Precautions Concerning Indication

New	Previous
5.1 (omitted) 5.2 (omitted) 5.3 In the Japanese subpopulation, the hazard ratio of Kerendia to placebo for the renal composite endpoint as the primary endpoint in the global phase III study (Study 16244) was 0.911, but the hazard ratios of Kerendia to placebo for renal failure as a component of the primary endpoint in the global phase III study (Study 16244), and the renal composite endpoint as the secondary endpoint in the global phase III study (Study 17530), were greater than 1. The effect of Kerendia to delay progression to renal failure is possibly weaker in the Japanese population than in the overall population of the study. [see Sections 17.1.1 and 17.1.2] 5.4 (omitted)	5.1 (omitted) 5.2 (omitted) 5.3 (omitted)

(Underline denotes changes.)

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

**Japanese Accepted Name (modified INN)*

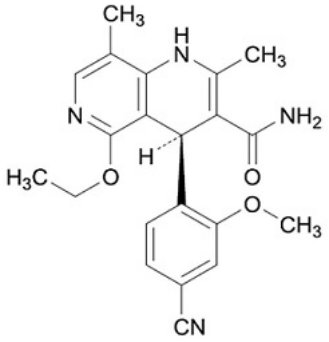
Review Report

January 19, 2022
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Kerendia Tablets 10 mg Kerendia Tablets 20 mg
Non-proprietary Name	Finerenone
Applicant	Bayer Yakuhin, Ltd.
Date of Application	November 26, 2020
Dosage Form/Strength	Tablets: Each tablet contains 10 or 20 mg of finerenone.
Application Classification	Prescription drug, (1) Drug with a new active ingredient

Chemical Structure



Molecular formula: $C_{21}H_{22}N_4O_3$

Molecular weight: 378.42

Chemical name: (4S)-4-(4-Cyano-2-methoxyphenyl)-5-ethoxy-2,8-dimethyl-1,4-dihydro-1,6-naphthyridine-3-carboxamide

Items Warranting Special Mention None

Reviewing Office Office of New Drug II

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of patients with chronic kidney disease associated with type 2 diabetes mellitus, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following approval condition. Adverse events of hyperkalaemia and function kidney decreased should be further evaluated.

Indication

Chronic kidney disease associated with type 2 diabetes mellitus (with exception of patients who have end-stage renal disease or are undergoing dialysis)

Dosage and Administration

The usual adult dosage is 20 mg of finerenone administered orally once daily. The starting dose should be determined as shown below:

eGFR ≥60 mL/min/1.73 m^2: 20 mg

eGFR <60 mL/min/1.73 m^2: 10 mg. The dose may be increased to 20 mg approximately 4 weeks after the start of treatment, based on serum potassium and estimated glomerular filtration rate (eGFR).

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

Attachment

Review Report (1)

December 17, 2021

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval

Brand Name	Kerendia Tablets 10 mg Kerendia Tablets 20 mg
Non-proprietary Name	Finerenone
Applicant	Bayer Yakuhin, Ltd.
Date of Application	November 26, 2020
Dosage Form/Strength	Tablets: Each tablet contains 10 or 20 mg of finerenone.

Proposed Indication

To delay progression of kidney diseases and to reduce the risk of cardiovascular diseases in patients with chronic kidney disease associated with type 2 diabetes mellitus

Proposed Dosage and Administration

The usual adult dosage is 20 mg of finerenone administered orally once daily.

Table of Contents

List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

Finerenone is a non-steroidal, mineralocorticoid receptor (MR) antagonist discovered by Bayer. Because of its high selectivity for MR, finerenone does not clearly antagonize other steroid hormone receptors (glucocorticoid receptor [GR], androgen receptor [AR], progesterone receptor [PR], and estrogen receptor [ER]). Finerenone, by binding to MR, inhibits aldosterone-induced activation of MR and thereby suppresses tissue inflammation and fibrosis, potentially leading to cardiorenal protection.

The clinical development of finerenone was initiated in 20[redacted]. The marketing application for finerenone was approved for the indication of chronic kidney disease associated with type 2 diabetes mellitus in the US in July 2021. The marketing application was submitted in Europe in November 2020 and has been under review as of December 2021.

In Japan, the applicant initiated the clinical development of finerenone in 20[redacted] and has submitted the marketing application with the proposed indication, i.e., “to delay progression of kidney diseases and to reduce the risk of cardiovascular diseases in patients with chronic kidney disease associated with type 2 diabetes mellitus,” based mainly on results from a global phase III study in patients with type 2 diabetes mellitus who received a diagnosis of diabetic kidney disease.

2. Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

2.1.1 Characterization

The drug substance occurs as a white to yellow powder. Its properties, including description, specific rotation, ultraviolet-visible spectroscopy (UV/VIS), pH, dissociation constant, partition coefficient, density, hygroscopicity, crystalline polymorphism, and solubility, have been determined. The drug substance was found to exist in 1 crystal form ([redacted]), an amorphous form, and 3 solvates ([redacted], [redacted], and [redacted]). The commercial manufacturing process is demonstrated to produce only [redacted], which is stable at room temperature.

The chemical structure of the drug substance has been elucidated by infrared absorption spectroscopy (IR), Raman spectroscopy, UV/VIS, nuclear magnetic resonance (NMR) spectroscopy (^{1}H-NMR, ^{13}C-NMR), mass spectrometry (MS), elemental analysis, and X ray crystallography.

2.1.2 Manufacturing process

The drug substance is synthesized using [redacted], [redacted], [redacted], and [redacted] as starting materials, and this process is composed of [redacted] steps. Description, identification, related substances, residual solvents, water content, particle size, [redacted], and content were identified as critical quality attributes (CQAs) (Table 1).

Table 1. Outline of control strategy of drug substance

CQA	Control method
Description	Specifications
Identification	Manufacturing process and specifications
Related substances	Manufacturing process and specifications
Residual solvents	Manufacturing process and specifications
Water content	Manufacturing process and specifications
Particle size	Manufacturing process and specifications
[redacted]	Manufacturing process and specifications
Content	Manufacturing process and specifications

[redacted] and [redacted] and [redacted] steps have been defined as critical steps. In addition, [redacted], [redacted], [redacted], [redacted], and [redacted] are controlled as critical intermediates.

2.1.3 Control of drug substance

The proposed specifications for the drug substance include content, description (appearance), identification (IR, high performance liquid chromatography [HPLC]), purity (related substances [HPLC], residual solvents [gas chromatography (GC)]), water content, particle size, [redacted] ([redacted]), and assay (HPLC).

2.1.4 Stability of drug substance

Table 2 shows major stability studies conducted on the drug substance, in which neither changes nor variations over time were observed. Photostability testing showed that the drug substance was photostable.

Table 2. Major stability studies of drug substance

Study	Primary batches	Temperature	Humidity	Storage form	Storage period
Long-term testing	3 commercial scale[a] batches	25°C	60%RH	PE bag	24 months[b]
Accelerated testing		40°C	75%RH		6 months

a [redacted] step was at a pilot scale,
b Of 3 batches, 1 batch was studied for up to 12 months.

Based on the above, a retest period of 24 months has been proposed for the drug substance when stored in a polyethylene (PE) bag, in accordance with the “Guideline on Evaluation of Stability Data” (PFSB/ELD Notification No. 0603004 dated June 3, 2003) (ICH Q1E guideline). Long-term testing will be continued up to 60 months.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is a film-coated tablet each containing 10 or 20 mg of the drug substance. The drug product contains microcrystalline cellulose, croscarmellose sodium, hypromellose, lactose hydrate, magnesium stearate, sodium lauryl sulfate, and lacquer light pink (10 mg tablets) or lacquer light yellow (20 mg tablets) as excipients.

2.2.2 Manufacturing process

The drug product is manufactured through the process consisting of mixing, granulation, [redacted] mixing, tableting, coating, packaging, testing, packaging and labeling, and testing. Description, identification,

strength, related substances, dissolution, uniformity of dosage units, and microbial limit were identified as CQAs (Table 3).

Table 3. Outline of control strategy of drug product

CQA	Control method
Description	Manufacturing process and specifications
Identification	Specifications
Strength	Manufacturing process and specifications
Related substances	Manufacturing process and specifications
Dissolution	Manufacturing process and specifications
Uniformity of dosage units	Manufacturing process and specifications
Microbial limit	Specifications

2.2.3 Control of drug product

The proposed specifications for the drug product consist of strength, description (appearance), identification (HPLC, UV/VIS), purity (related substances [HPLC]), uniformity of dosage units (content uniformity), microbial limit, dissolution (HPLC), and assay (HPLC).

2.2.4 Stability of drug product

Table 4 shows major stability studies conducted on the drug product. Under the long-term condition, while the 10 mg tablets were stable, the 20 mg tablets were stable at all time points except for Month 18, at which the content of a related substance ([redacted]) in 1 batch exceeded the upper limit of the proposed specification. The applicant conducted a detailed investigation, revealed that the peak causing the result out of the proposed specifications was not derived from the test sample but was identified as an impurity derived from a contaminated glass apparatus, and took measures to prevent similar events from occurring in the subsequent analyses. Under the accelerated condition, the drug product was stable. Photostability testing showed that the drug product was photostable.

Table 4. Major stability studies of drug product

Study	Primary batches	Temperature	Humidity	Storage form	Storage period
Long-term testing	3 pilot-scale batches for each strength	25°C	60%RH	[redacted] film/aluminum blister package	24 months
Accelerated testing		40°C	75%RH		6 months

Based on the above, a shelf life of 36 months has been proposed for the drug product when stored in a [redacted] film/aluminum blister package, in accordance with the ICH Q1E guideline. Long-term testing will be continued up to 60 months.

2.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA concluded that the quality of the drug substance and drug product is appropriately controlled.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

In this section, unless otherwise specified, exposure to finerenone is expressed as an amount of the unbound (free) form.

3.1 Primary pharmacodynamics

3.1.1 *In vitro* studies

3.1.1.1 Binding affinity to MR (CTD 4.2.1.1.1)

Using human embryonic kidney (HEK) 293 cells stably expressing human MR, inhibitory effect of finerenone (1 nmol/L-3 μmol/L) and spironolactone (0.3 nmol/L-1 μmol/L) against the binding of ^{3}H-aldosterone to human MR was investigated. The results showed that 50% inhibitory concentrations (IC_{50}) of finerenone and spironolactone (individual values) was 23.9 and 16.0 nmol/L, respectively.

3.1.1.2 Effect on transcriptional activities of steroid hormone receptors (CTD 4.2.1.1.1)

Finerenone (0.3 nmol/L-10 μmol/L), spironolactone (0.3 nmol/L-10 μmol/L), or eplerenone (3 nmol/L-30 μmol/L) was added to CHO-K1 cells stably expressing a fusion protein of human MR, GR, AR, PR, ERα, ERβ, rat MR, or canine MR ligand-binding domain and GAL4 DNA-binding domain in the presence of ligand for each receptor. By measuring luciferase activities, inhibitory effect of these investigational drugs against activation of each receptor was investigated. Table 5 shows IC_{50} of these investigational drugs against activation of each receptor. In addition, a similar investigation was conducted in the absence of ligand for each receptor to investigate the activating effect of finerenone on each receptor. Finerenone had no activating effect on any of the receptors.

Table 5. IC_{50} of investigational drugs against MR, GR, AR, PR, ERα, or ERβ (nmol/L)

	Human						Rat	Dog
	MR[a]	GR[a]	AR[a]	PR[a]	ERα[b]	ERβ[b]	MR[b]	MR[b]
Finerenone	17	~10000	~10000	~10000	~10000	~10000	19.7	9.26
Spironolactone[c]	28	2430	160	1500[d]	5970	4940	6.90	5.44
Eplerenone[c]	990	~21000	~22000	~31000	~30000	~30000	401	465

Ligands used are as follows: Aldosterone for MR, dexamethasone for GR, dihydrotestosterone for AR, progesterone for PR, and 17-β-estradiol for ERα and ERβ.

a Mean (n = 3-9 for finerenone, n = 2-156 for spironolactone, and n = 8-54 for eplerenone)

b Individual values

c Facility historical data

d For spironolactone, which acts as an agonist to PR, the 50% effective concentration (EC_{50}) is presented.

~ "Approximately"

In a similar test system, inhibitory effect of finerenone (1 nmol/L-10 μmol/L), spironolactone (1 nmol/L-10 μmol/L), and eplerenone (3 nmol/L-30 μmol/L) against human MR activating effect induced by cortisol, corticosterone, and desoxycorticosterone acetate (DOCA) was investigated. Table 6 shows IC_{50} (individual values) of these investigational drugs against human MR activation induced by each ligand.

Table 6. IC_{50} of investigational drugs against human MR activation induced by each ligand (nmol/L)

	Cortisol	Corticosterone	DOCA
Finerenone	5	24	46
Spironolactone[a]	19	41	114
Eplerenone[a]	360	940	1970

a Facility historical data

3.1.1.3 Effect of metabolites on transcriptional activity of MR (CTD 4.2.1.1.3)

A human plasma metabolite of finerenone[1)] (M-1a, M-1b, M-2a, M-2b, M-3a, or M-3b[1)]) (3 nmol/L-10 μmol/L) was added to CHO-K1 cells stably expressing a fusion protein of human MR

1) For each of M-1, M-2, and M-3, which have axial chirality, "a" is affixed to a given atropisomer, and "b" is to the other.

ligand-binding domain and GAL4 DNA-binding domain in the presence of aldosterone. By measuring luciferase activities, inhibitory effect of these metabolites against human MR activation was investigated. None of the metabolites inhibited human MR activation (IC_{50} >9 μmol/L).

3.1.1.4 Effect on binding of coregulators to MR and gene expression (CTD 4.2.1.1.2, *Hypertension*. 2018;71:599-608, Reference data)

Effects of finerenone and eplerenone on the binding of coregulators to MR were investigated by a peptide array analysis using H9C2 cells stably expressing rat MR. In the presence of aldosterone, both investigational drugs inhibited the binding of coactivators (steroid receptor coactivator-1 [SRC1], RNA polymerase II transcription subunit 1 [TRAP220], transcriptional intermediary factor 1α [TIF1α], peroxisome proliferator-activated receptor γ coactivator 1α [PGC-1α], and activating signal co-integrator 2 [ASC2]) in a concentration-dependent manner and enhanced the binding of corepressor (nuclear receptor corepressor 1 [NCoR1]) in a concentration-dependent manner as well.

Finerenone (50 nmol/L-5 μmol/L), eplerenone (50 nmol/L-50 μmol/L), or spironolactone (50 nmol/L-5 μmol/L) was added to H9C2 cells stably expressing rat MR to incubate in the presence of aldosterone for 24 hours, and messenger ribonucleic acid (mRNA) expression of Teneicin-X (TNX) and a disintegrin and metallopeptidase with thrombospondin motif 1 (ADAMTS-1) genes, MR's target genes, was investigated by a quantitative polymerase chain reaction (PCR) method. All of the investigational drugs significantly reduced mRNA expression of TNX and ADAMTS-1 genes except for one condition where spironolactone did not change mRNA expression of TNX.

3.1.2 *In vivo* studies

3.1.2.1 Natriuretic effect in rats (CTD 4.2.1.1.4)

Male rats fed with a low-salt diet for 72 hours (n = 6-8/group) orally received a single dose of finerenone (0.3, 1, 3, 10, 30, or 100 mg/kg), eplerenone (3, 10, 30, or 100 mg/kg), or vehicle (85.8% polyethylene glycol [PEG] 400, 5.3% glycerin, and 8.9% water). After collection of urine for 8 hours, the urine volume and urinary Na^+ and K^+ concentrations were measured. Both finerenone and eplerenone increased the urinary Na^+/K^+ concentration ratio in a dose-dependent manner. The urine volume was significantly higher only in the finerenone 100 mg/kg group than in the vehicle group.

3.1.2.2 Anti-mineralocorticoid effect in dogs (CTD 4.2.1.1.5)

Male and female dogs (n = 6 males and 3 females) orally received a single dose of 9α-fluorohydrocortisone (0.3 mg) and, on the following day, a single dose of finerenone (0.001, 0.01, 0.1, or 1 mg/kg), spironolactone (0.3 mg/kg), or vehicle (empty capsule), followed by urine collection under anesthesia 5 hours later. Urine osmolality and urinary Na^+ and K^+ concentrations were measured. The urinary Na^+/K^+ concentration ratio was significantly higher in the finerenone ≥0.01 mg/kg groups and spironolactone group than in the vehicle group. Changes in urine osmolality in all investigational drug groups were not significantly different from that in the vehicle group.

3.1.2.3 Effect in DOCA-salt hypertensive rat (CTD 4.2.1.1.6)

Male rats (n = 6-11/group) underwent uninephrectomy and, 1 week later, started salt loading (with 1% NaCl in drinking water) and once-weekly subcutaneous administration of DOCA (30 mg/kg), which

were continued for 10 weeks. The resultant rats served as a hypertensive rat model with peripheral organ disorders. In addition, rats that underwent the same surgery without removal of the kidney were included in the sham surgery group. From the day when administration of DOCA was started, finerenone (0.1, 1, or 10 mg/kg) or vehicle (10% ethanol, 40% solutol, and 50% water) was orally administered once daily for 77 days. At Week 10, systolic blood pressure and urinary concentration of plasminogen activator inhibitor-1 (PAI-1) were measured. At the time of the last dose, cardiorenal weight, plasma N-terminal pro-B type natriuretic peptide (NT-proBNP),[2)] urine protein, urine creatinine, and left ventricular hemodynamic parameters were measured, and a histological approach and quantitative PCR method were applied to investigate morphological changes in the heart and kidney as well as gene expression in the kidney. The cardiorenal weight/body weight ratio, urinary PAI-1 concentration, and plasma NT-proBNP concentration were significantly higher in the vehicle group than in the sham surgery group and significantly lower in the finerenone 1 and 10 mg/kg groups than in the vehicle group. The systolic blood pressure and urine protein/urine creatinine ratio were significantly higher in the vehicle group than in the sham surgery group and significantly lower in the finerenone 10 mg/kg group than in the vehicle group. Maximum rate of pressure rise (dp/dt_{max}), the parameter indicative of myocardial contraction function, was significantly higher in the vehicle group, which was accompanied by cardiac hypertrophy, than in the sham surgery group and significantly lower in the finerenone 1 and 10 mg/kg groups than in the vehicle group. In addition, relaxation time, the parameter indicative of myocardial dilation function, was significantly longer in the vehicle group than in the sham surgery group and significantly shorter in the finerenone 10 mg/kg group than in the vehicle group. Both heart and kidney injury severity scores[3)] were significantly higher in the vehicle group than in the sham surgery group and significantly lower in the finerenone 10 mg/kg group than in the vehicle group. Expressions of marker genes indicative of inflammation, fibrosis, and remodeling (PAI-1, osteopontin [OPN], kidney injury molecule-1 [KIM-1], monocyte chemoattractant protein-1 [MCP-1], tissue inhibitor of matrixmetalloproteinase-1 [TIMP-1], and matrix metalloproteinase-2 [MMP-2]) were all significantly higher in the vehicle group than in the sham surgery group and significantly lower in the finerenone 1 or 10 mg/kg group than in the vehicle group.

3.1.2.4 Effect in stroke-prone spontaneous hypertensive rat (SHRSP) model (CTD 4.2.1.1.8)

Male SHRSP (10-week-old, n = 12/group), high-renin hypertensive and peripheral organ disorder model, were loaded with salt (2% NaCl in drinking water) and orally received finerenone (10 mg/kg) or vehicle (10% ethanol, 40% solutol, and 50% water) once daily for 45 days. Of animals in the vehicle group and finerenone group, 42% and 92% survived. On Day 44, urine protein, urine creatinine as well as urinary and serum OPN concentrations were measured. The urine protein/urine creatinine ratio as well as urinary and serum OPN concentrations were significantly lower in the finerenone group than in the vehicle group. On Day 45, morphological changes in the heart and kidney

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2) The measured value might have reflected a sum of prohormone of brain natriuretic peptide (proBNP) and NT-proBNP concentrations because the measurement kit used responded to not only NT-proBNP but also proBNP (1-45), but the ratio of proBNP relative to NT-proBNP in rat plasma was limited (*Am J Physiol Regul Integr Comp Physiol.* 2015;309:R639-49), and thus it is considered to reflect the NT-proBNP concentration practically.

3) The cardiorenal injury severity score was calculated by semiquantitatively grading cardiorenal lesions such as vascular, myocardial, glomerular, and tubular lesions according to the criteria (Grade 0, no findings; Grade 1, Minimal/very few/very small; Grade 2, Slight/few/small; Grade 3, Moderate/moderate number/moderate size; and Grade 4, Marked/many/large).

were histologically examined. The heart and kidney injury severity scores[3)] were significantly lower in the finerenone group than in the vehicle group.

3.1.2.5 Effect in type-2 diabetes mellitus rat model (CTD 4.2.1.1.10, *Diabetes Obes Metab.* 2018;20:2399-407, Reference data)

Male Zucker fatty fa/fa rats (12-week-old, n = 10-12/group), model of type-2 diabetes mellitus, were allocated to either finerenone or non-treatment group. Rats in the finerenone group were further allocated to either a short-term or long-term treatment group which received finerenone (2 mg/kg/day) in the diet for 7 or 90 days, respectively. In the short-term treatment group, urine protein was measured in urine collected for 24 hours on Day 7, and in the long-term treatment group, urine protein was measured in the same manner on Day 90. Gene expression in the kidney was investigated by a quantitative PCR method. In addition, male Zucker fa/+ rats (12-week-old, n = 9) were included in the respective control groups for comparison with the short-term treatment group and long-term treatment group. The urine protein was significantly higher in the non-treatment group than in the control group for both short-term and long-term treatment groups, and in the long-term treatment group, it was significantly lower in the finerenone group than in the non-treatment group. Of neutrophil gelatinase-associated lipocalin (NGAL) gene, a marker of renal disorder, mRNA expression was significantly higher in the non-treatment group than in the control group and significantly lower in the finerenone group than in the non-treatment group.

3.1.2.6 Effect in ischemia/reperfusion-induced chronic kidney disease (CKD) rat model (CTD 4.2.1.1.12, *Hypertension.* 2017;69:870-8, Reference data)

Male rats (n = 7-9/group) orally received finerenone (10 mg/kg) or vehicle (40% kolliphor, 10% ethanol, and 50% water) 48, 24, and 1 hour before bilateral renal ischemia/reperfusion. In addition, rats not subjected to ischemia/reperfusion were included in the sham surgery group. At 4 months after the bilateral renal ischemia/reperfusion, plasma creatinine and urea concentrations, urine protein as well as renal hemodynamic parameters were measured, and a histological approach and quantitative PCR method were applied to investigate morphological changes and gene expression in the kidney. The plasma creatinine and urea concentrations as well as urine protein were significantly higher in the vehicle group than in the sham surgery group and significantly lower in the finerenone group than in the vehicle group. The renal vascular resistance was significantly higher in the vehicle group than in the sham surgery group and significantly lower in the finerenone group than in the vehicle group. The renal blood flow did not differ significantly between the vehicle group and sham surgery group, but it was significantly higher in the finerenone group than in the vehicle group. The renal disorder severity score was significantly higher in the vehicle group, which showed progression of tubular dilation, presence of tubular casts, and glomerular sclerosis, than in the sham surgery group, while the score in the finerenone group, in which development of these lesions was suppressed, was significantly lower than that in the vehicle group. The renal fibrosis severity score[4)] was significantly higher in the vehicle group than in the sham surgery group and significantly lower in the finerenone group than in the vehicle group. Of NGAL and KIM-1, markers of renal disorder, mRNA expression was significantly higher in the vehicle group than in the sham surgery group. Of NGAL, mRNA expression was

[4)] The renal fibrosis severity score was calculated on the basis of the proportion of tissue with collagen deposition, which is indicative of fibrosis, as follows: 1, <25%; 2, 26% to 50%; 3, 51% to 75%; and 4, 76% to 100%.

significantly lower in the finerenone group than in the vehicle group. Of KIM-1, mRNA expression was lower in the finerenone group than in the vehicle group, but the difference was not significant.

3.1.2.7 Effect in genetic CKD rat model accompanied by albuminuria (CTD 4.2.1.1.13, *Front Pharmacol.* 2018;9:1131, Reference data)

Male Munich Wistar Frömter (MWF) rats (12-week-old, n = 10/group), a CKD model exhibiting endothelial dysfunction associated with low nitric oxide (NO) availability, orally received finerenone (10 mg/kg) or vehicle (10% ethanol, 40% PEG 400, and 50% water) once daily for 4 weeks. At 24 hours after the last dose, urinary albumin was measured. In addition, male normal rats (12-week-old, n = 10) were included in the control group. The urinary albumin was higher in the vehicle group than in the control group and significantly lower in the finerenone group than in the vehicle group.

3.1.2.8 Effect in chronic myocardial infarction rat model (CTD 4.2.1.1.7)

Male rats (8-10-week-old, n = 10-14/group) underwent ligation of left anterior descending coronary artery and 1 week later started once-daily oral administration of finerenone (0.1, 0.3, or 1 mg/kg) or vehicle (10% ethanol, 40% solutol, and 50% water), which was continued for 8 weeks. In addition, rats not subjected to ligation of the coronary artery were included in the sham surgery group. At Week 8, hemodynamics was examined through catheterization into the left ventricle. The dp/dt_{max} was significantly lower in the vehicle group than in the sham surgery group and significantly higher in the finerenone 1 mg/kg group than in the vehicle group. In addition, minimum rate of pressure drop (dp/dt_{min}), the parameter indicative of myocardial dilation function, was significantly higher in the vehicle group than in the sham surgery group and significantly lower in the finerenone 1 mg/kg group than in the vehicle group. At Week 8, plasma NT-proBNP concentrations[2)] were measured by radioimmunoassay. The plasma NT-proBNP concentrations were significantly higher in the vehicle group than in the sham surgery group and significantly lower in the finerenone 1 mg/kg group than in the vehicle group.

3.2 Secondary pharmacodynamics

3.2.1 Effect on molecular targets (CTD 4.2.1.2.1 to 4.2.1.2.5)

The effect of finerenone and its human plasma metabolites (M-1a, M-1b, M-2a, and M-3a[1)]) (10 µmol/L for each) on 56 to 57 receptors, 4 transporters, and 6 ion channels were investigated by radioactive ligand binding assay. Neither finerenone nor its metabolites inhibited or enhanced binding of any ligand by ≥50%.

3.2.2 Effect on human myocardial ion channels (CTD 4.2.1.2.6 to 4.2.1.2.10)

Finerenone or its human plasma metabolite (M-1a, M-1b, M-2a, or M-3a[1)]) (10 µmol/L for each) was added to HEK293 cells expressing human sodium channel/current isoform 1.5 (hNav1.5) or CHO cells expressing human voltage-gated (L-type) calcium channel/current isoform 1.2 (hCav1.2) to investigate the effects on these ion channels. Neither finerenone nor its metabolites inhibited or activated these ion channels.

A human plasma metabolite of finerenone (M-1a, M-1b, M-2a, or M-3a) (0.1-10 μmol/L for each) was added to HEK293 cells expressing human ether-a-go-go related gene (hERG) channel to investigate their inhibition effect against hERG channel. None of the metabolites inhibited the channel.

3.3 Safety pharmacology

Table 7 shows results from safety pharmacology studies.

Table 7. Outline of safety pharmacology studies

Organ	Test system	Parameters and methods	Dose	Route of administration	Findings	CTD
Central nervous system	Wistar rat (6 males/group)	General behavior (modified Irwin method), locomotor activity, and body temperature	Finerenone 0,[a] 3, 10, 30 mg/kg Single dose	Oral	No effects	4.2.1.3.2
	Wistar rat (12 males/group)	Motor coordination (rotarod test)	Finerenone 0,[a] 3, 10, 30 mg/kg Single dose	Oral	No effects	4.2.1.3.8
	Wistar rat (7 males/group)	Effect on PTZ-induced seizure threshold	Finerenone 0,[a] 3, 10, 30 mg/kg Single dose	Oral	No effects	4.2.1.3.7
	Wistar rat (7-8 males/group)		Finerenone 0,[b] 30, 60, 100 mg/kg Single dose	Oral	No effects	4.2.1.3.3 (Reference data)
Cardiovascular system	HEK293 cells stably expressing hERG channel	hERG current	Finerenone 0,[c] 1, 10, 100 μmol/L	*In vitro*	Finerenone at 10 and 100 μmol/L inhibited hERG current by 10.0% and 53.9% compared with the control.	4.2.1.3.5
			M-1a[d]: 0,[c] 0.1, 1, 10 μmol/L M-2a or M-3a[d]: 0,[c] 1, 10, 100 μmol/L	*In vitro*	M-2a at 100 μmol/L inhibited hERG current by 15.2% compared with the control. M-1a and M-3a: No effect	4.2.1.3.1 (Reference data)
	Beagle dog (a total of 5 males and females/group)	Blood pressure, heart rate, and electrocardiogram (telemetry method)	Finerenone 0,[e] 1, 3, 10 mg/kg Single dose	Oral	≥3 mg/kg: Shortened PQ interval	4.2.1.3.4
Respiratory system	SD rat (8 males/group)	Respiratory rate, tidal volume, and minute ventilation volume (plethysmograph method)	Finerenone 0,[a] 3, 10, 30 mg/kg Single dose	Oral	No effects	4.2.1.3.6

a Mixture of ethanol, solutol, and water (10:40:50)
b Mixture of PEG400, glycerin, and water (96.9 g:6 g:10 g)
c Solution containing 146 mmol/L sodium chloride, 4 mmol/L potassium chloride, 2 mmol/L calcium chloride dihydrate, 2 mmol/L magnesium chloride hexahydrate, and 10 mmol/L hydroxyethylpiperazine ethane sulfonic acid
d For each of M-1, M-2, and M-3, which have axial chirality, "a" is affixed to a given atropisomer, and "b" to the other.
e Mixture of ethanol and PEG400 (10:90)

3.R Outline of the review conducted by PMDA

3.R.1 Primary pharmacodynamics

The applicant's explanation about pharmacological actions of finerenone:

MR hyperactivation caused by hypersecretion of aldosterone and cortisol, hormones activating MR, enhances inflammation and fibrosis in various tissues, which lead to a glomerular lesion, podocytopathy, tubulointerstitial fibrosis, endothelial dysfunction, and extracellular collagen deposition in the kidney, potentially contributing to development of function kidney decreased and end-stage renal disease (*J Endocrinol.* 2017;234:T125-40, *Nat Rev Nephrol.* 2013;9:86-98, etc.). Pathological MR hyperactivation associated with CKD potentially causes organ dysfunction and thereby increases morbidity and mortality of cardiorenal diseases (*Hypertension.* 2018;71:599-608). In addition, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) recommended for treatment of CKD, when used for a long time, may induce aldosterone breakthrough, which is characterized by elevated aldosterone concentrations in circulating blood (*Nat Clin Pract Nephrol.* 2007;3:486-92).

In *in vitro* studies, nonsteroidal finerenone was shown to bind to human MR and thereby inhibit MR activation in response to aldosterone and glucocorticoid. In addition, finerenone inhibited the other steroid hormone receptors without the activation of them, and its inhibitory concentrations against them were ≥500 times higher than those against MR. Spironolactone, an approved MR antagonist which also acts as an AR antagonist and PR agonist, has raised a concern of adverse drug reactions such as gynaecomastia (*Mol Cell Endcrinol.* 2004;217:27-31, *J Endocrinol.* 2017;234:T125-40), but the above *in vitro* study results give an expectation that finerenone is unlikely to raise clinical problems owing to its actions on the other steroid hormone receptors. In *in vivo* studies, finerenone increased urinary Na^+/K^+ ratio in a dose-dependent manner in rats and dogs and increased urine volume in rats at 100 mg/kg. In studies in DOCA-salt hypertensive rats or SHRSP model, finerenone when orally administered at 1 or 10 mg/kg suppressed inflammation and fibrosis in the kidney, prevented kidney injury and renal hypertrophy as well as reduced urine protein. In the heart, finerenone improved hemodynamics, prevented cardiac hypertrophy, myocardial fibrosis, and heart injury as well as reduced plasma NT-proBNP. In a myocardial infarction rat model, finerenone when orally administered at 1 mg/kg improved hemodynamics and reduced plasma NT-proBNP concentrations. In addition, published literature [see Sections “3.1.2.5 Effect in type-2 diabetes mellitus rat model” and “3.1.2.7 Effect in genetic CKD rat model accompanied by albuminuria”] suggested that finerenone would protect the kidney in type-2 diabetes mellitus rat model treated with finerenone at 2 mg/kg in the diet and in CKD rat model orally treated with finerenone at 10 mg/kg. The inhibitory effect of finerenone against MR transcriptional activities did not differ between human and rat receptors, it is considered acceptable to infer the clinical effect of finerenone from the submitted non-clinical data. Exposure to finerenone in rats after administration at 10 mg/kg at which cardiorenal protection was observed in various animal models was slightly higher than that in humans after administration at the recommended clinical dose of 20 mg; more specifically, C_{max} and AUC in rats at 10 mg/kg (18.9 µg/L and 273 µg·h/L, respectively) were 1.4 and 5.0 times the corresponding exposures in humans at 20 mg (13.4 µg/L and 55 µg·h/L, respectively). The minimum effective dose, however, is not necessarily deemed to be 10 mg/kg because all the studies did not cover multiple doses. In DOCA-salt hypertensive rats, finerenone at 1 mg/kg, which led to exposure (0.2 times for C_{max} and 0.88 times for AUC) lower than that in humans at the recommended clinical dose, prevented renal hypertrophy and cardiac hypertrophy as well as reduced urinary PAI-1 and plasma NT-proBNP; and exposure to finerenone at the recommended clinical dose exceeded the IC_{50} (6.4 µg/L) of finerenone

against MR determined in *in vitro* studies. Taking account of the above, the applicant considers that finerenone when administered to humans at the recommended clinical dose can exert cardiorenal protection by competitively binding to MR and thereby inhibiting MR activation

PMDA's view:
CKD is accompanied by chronic MR hyperactivation, and subsequent inflammation and fibrosis lead to organ dysfunction, which then potentially contributes to development of heart diseases and end-stage renal disease. The *in vitro* studies showed that finerenone selectively bound to MR and thereby inhibited MR activation in response to aldosterone and glucocorticoid. The *in vivo* studies in multiple organ dysfunction animal models including ones potentially accompanied by MR hyperactivation showed that finerenone prevented renal hypertrophy and kidney injury by suppressing inflammation and fibrosis in the kidney as well as improved hemodynamics in the heart and prevented myocardial fibrosis, cardiac hypertrophy, and heart injury. The exposure after administration at the main test dose (10 mg/kg) at which cardiorenal protection was observed in *in vivo* studies exceeded that after administration at the recommended clinical dose of 20 mg, but at another test dose (1 mg/kg) leading to smaller exposure, the test result also suggested the cardiorenal protection of finerenone [see Section "3.1.2.3 Effect in DOCA-salt hypertensive rat"]. The non-clinical pharmacology studies did not elucidate how finerenone's antagonism against MR prevents renal impairment attributable to type 2 diabetes mellitus. Finerenone can be expected to exert cardiorenal protection in patients with CKD because studies in various disease models including CKD model suggested that finerenone would protect the heart and kidney; and the applicant's explanation about involvement of MR activation in pathogenesis of CKD is convincing.

3.R.2 Safety pharmacology

The applicant's explanation about findings in safety pharmacology studies of finerenone:
The effect of finerenone on the cardiovascular system is considered unlikely to raise clinical problems because in HEK293 cells stably expressing hERG channel, finerenone inhibited hERG current in its concentration-dependent manner, but the 20% inhibition concentration (IC_{20}) of finerenone (8325 μg/L) against hERG current was approximately 621 times the exposure to finerenone at the maximum recommended clinical dose (C_{max} = 13.4 μg/L), and in dogs, Fridericia-corrected QT interval (QTcF) was not affected by finerenone at up to 10 mg/kg (approximately 57 times the exposure to finerenone in humans after administration at the maximum recommended clinical dose). In addition, in secondary pharmacodynamics studies, off-target binding test showed that finerenone, which is a compound with dihydropyridine-based structure, did not act on either L- or N-type calcium channel at up to 10 μmol/L, and an electrophysiologic test showed that neither finerenone nor its metabolites (M-1a, M-1b, M-2a, and M-3a,[1)] 10 μmol/L for each) acted on myocardial ion channels (hERG K^+ current, hNav1.5 Na^+ current, and hCav1.2 Ca^{2+} current). The concentration of finerenone or its metabolite tested is 10 μmol/L, which is approximately 282 times the exposure to finerenone after administration at the maximum recommended clinical dose. In dogs, PQ interval was shortened after administration of finerenone at 3 and 10 mg/kg, but the concerned finding is considered unlikely to raise clinical problems because the exposure to finerenone after administration at 3 mg/kg (219.6 μg/L) is approximately 16 times that after administration at the maximum recommended clinical dose.

PMDA concludes that the effect on hERG current observed in the study using cells expressing hERG channel is unlikely to raise clinical problems in view of the relationship between IC_{20} of finerenone against hERG current and exposure to finerenone after administration at the maximum recommended clinical dose and results from the *in vivo* safety pharmacology studies.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

Plasma concentrations of finerenone were determined by liquid chromatography and tandem mass spectrometry (LC-MS/MS), and the lower limit of quantitation was 0.50 or 100 µg/L. Radioactivity of ^{14}C or ^{3}H-labeled compound of finerenone or its major metabolite (M-1a, M-1b, M-2a, or M-3a[1)]) was determined by a liquid scintillation counter or quantitative whole-body autoradiography.

Unless otherwise specified, pharmacokinetics (PK) parameters are expressed as the mean or mean ± standard deviation (SD).

4.1 Absorption

4.1.1 Single-dose studies (CTD 4.2.2.2.1, 4.2.2.2.2, 4.2.2.2.3, and 4.2.2.2.4)

Table 8 shows PK parameters after a single administration of finerenone or ^{14}C-finerenone to male mice, male rats, female dogs, and female monkeys.

Table 8. PK parameters after single administration of finerenone or ^{14}C-finerenone

Animal species	Dose (mg/kg)	Route of administration	n	C_{max} (µg/L)	t_{max} (h)	$AUC_{0-\infty}$ (µg·h/L)	$t_{1/2}$ (h)	BA (%)	V_{ss} (L/kg)	CL (L/h·kg)
Mouse	0.3	Intravenous	3/timepoint	4349	0.0833	48527	11.7	-	0.0996	0.00618
Rat	0.3	Intravenous	3/timepoint	5502	0.0333	28106	8.60	-	0.112	0.0107
	1 [a]	Intravenous	3/timepoint	14725	0.0333	72200	8.13	-	0.135	0.0139
	0.3	Oral	3/timepoint	1870	2.00	25473	9.12	90.6	-	-
	1 [a]	Oral	3/timepoint	7465	0.750	59998	7.79	83.1	-	-
	3	Oral	3/timepoint	24471	0.750	260257	9.14	120 [b]	-	-
Dog	0.3	Intravenous	3	730 ± 1.04	0.250 ± 1.00	1908 ± 1.25	1.68 ± 1.24	-	0.388 ± 1.32	0.157 ± 1.25
	0.03	Oral	3	29.6 ± 1.04	2.00 ± 1.00	108 ± 1.09	1.47 ± 1.31	56.5 ± 1.15[c]	-	-
	0.3	Oral	3	303 ± 1.10	0.909 ± 1.18	1137 ± 1.09	1.76 ± 1.29	59.6 ± 1.26	-	-
	3	Oral	3	4033 ± 1.17	0.630 ± 1.49	18503 ± 1.18	2.35 ± 1.10	97.0 ± 1.09[c]	-	-
Monkey	1	Intravenous	3	3998 ± 1.02	0.250 ± 1.00	2565 ± 1.12	1.31 ± 1.11	-	0.247 ± 1.06	0.390 ± 1.12

Geometric mean or geometric mean ± SD; -, Not calculated
a Administration of ^{14}C-finerenone
b Calculated from $AUC_{0-\infty}$ after intravenous administration at 1 mg/kg
c Calculated from $AUC_{0-\infty}$ after intravenous administration at 0.3 mg/kg

4.1.2 Repeated-dose studies

4.1.2.1 Rat (CTD 4.2.3.2.8 and 4.2.3.2.9)

Table 9 shows PK parameters after repeated oral administration of finerenone once daily to male and female rats for 13 or 26 weeks.

Table 9. PK parameters after repeated oral administration of finerenone

Treatment duration	Daily dose (mg/kg)	Sampling point (Day)	C_{max} (μg/L)		AUC_{0-24h} (μg·h/L)	
			Male	Female	Male	Female
13 weeks	3	1	10223	17539	148421	375028
		90	25813	57285	419184	1211627
	10	1	34247	57711	554571	1270613
		90	80808	123245	1375110	2211234
	30	1	94260	123961	1448364	2639222
		90	115355	155810	1821813	2680696
26 weeks	0.5	1	-	3230	-	58200
		164	-	17000	-	349000
	1.5	1	4090	18100	85700	299000
		164	7610	46500	118000	992000
	5	1	17600	32500	209000	566000
		164	42500	101000	704000	1990000
	15	1	50600	-	1000000	-
		164	107000	-	1980000	-

Geometric mean; n = 3/timepoint; -, Not applicable

4.1.2.2 Dog (CTD 4.2.3.2.10 and 4.2.3.2.12)

Table 10 shows PK parameters after repeated oral administration of finerenone once daily to male and female dogs for 4 or 39 weeks.

Table 10. PK parameters after repeated oral administration of finerenone

Treatment duration	Daily dose (mg/kg)	n	Sampling point	C_{max} (μg/L)	AUC_{0-24h} (μg·h/L)
4 weeks	1.5	6	Day 1	1408 ± 1.32	3316 ± 1.30
		6	Day 25	1265 ± 1.28	3868 ± 1.54
	5	6	Day 1	4049 ± 1.17	10415 ± 1.10
		6	Day 25	4637 ± 1.42	19108 ± 1.27
	15	6	Day 1	20950 ± 1.23	98920 ± 1.30
		6	Day 25	22144 ± 1.22	164713 ± 1.49
39 weeks	0.5	8	Day 1	520 ± 1.26	1540 ± 1.35
		8	Week 39	560 ± 1.34	2110 ± 1.36
	1.5	8	Day 1	2080 ± 1.20	5830 ± 1.27
		8	Week 39	2180 ± 1.24	9910 ± 1.32
	5	8	Day 1	6780 ± 1.13	29900 ± 1.26
		8	Week 39	8350 ± 1.57	59500 ± 1.48

Geometric mean ± SD,

4.2 Distribution

4.2.1 Plasma protein binding (CTD 4.2.2.3.1, 4.2.2.3.2, 4.2.2.7.13, and 4.2.2.7.14)

Following the addition of finerenone at 440 to 3150 or 66500 μg/L, ^{3}H-M-1a at 48.4 to 4463 μg/L, ^{14}C-M-1b at 41.8 to 4430 μg/L, ^{3}H-M-2a at 50.7 to 4344 μg/L, or ^{3}H-M-3a[1)] at 45.0 to 4186 μg/L to mouse plasma, the protein binding was 99.9% and 99.9%, 85.3%, 87.9%, 42.0% as well as 17.6%, respectively.

Following the addition of finerenone at 515 to 5270 and 100000 μg/L, ^{3}H-M-1a at 47.0 to 4321 μg/L, ^{14}C-M-1b at 37.4 to 4080 μg/L, ^{3}H-M-2a at 50.7 to 4552 μg/L, or ^{3}H-M-3a at 37.2 to 3846 μg/L to rat plasma, the protein binding was 99.9% and 99.9%, 94.0%, 88.9%, 54.6% as well as 25.9%, respectively.

Following the addition of ^{14}C-finerenone at 529 to 10135 µg/L, ^{3}H-M-1a at 46.0 to 4673 µg/L, ^{14}C-M-1b at 43.2 to 4330 µg/L, ^{3}H-M-2a at 51.0 to 4907 µg/L, or ^{3}H-M-3a at 48.2 to 4485 µg/L to rabbit plasma, the protein binding rate 99.8%, 97.8%, 98.8%, 62.4%, and 23.9%, respectively.

Following the addition of ^{14}C-finerenone at 99.0 to 4394 or 83087 µg/L, ^{3}H-M-1a at 44.8 to 4488 µg/L, ^{14}C-M-1b at 36.7 to 485 or 4090 to 4180 µg/L, ^{3}H-M-2a at 51.5 to 4661 µg/L, or ^{3}H-M-3a at 39.8 to 3834 µg/L to dog plasma, the protein binding was 94.5% and 93.9%, 88.8%, 93.6% and 89.2%, 51.7% as well as 24.7%, respectively.

Following the addition of ^{14}C-finerenone at 95.5 to 4396 and 85069 µg/L to monkey plasma, the protein binding was 97.5% and 95.8%, respectively.

4.2.2 Distribution in blood cells (CTD 4.2.2.3.1)

Following the addition of ^{14}C-finerenone at 103 to 5115 and 102040 µg/L to rat blood, the blood/plasma concentration ratio was 0.549 and 0.601, respectively.

Following the addition of ^{14}C-finerenone at 107 to 5105 and 104423 µg/L to dog blood, the blood/plasma concentration ratio was 0.723 and 0.779, respectively.

4.2.3 Tissue distribution (CTD 4.2.2.3.4)

A single dose of ^{14}C-finerenone at 3 mg/kg was administered orally to male albino rats, and tissue distribution of radioactivity at 1, 2, 4, 8, 24, 72, and 168 hours was evaluated (n = 1/timepoint). In all the tissues evaluated, radioactivity concentrations reached the maxima at 1 to 4 hours. The maximum radioactivity concentration was highest in the blood (9919 µg·eq/L), followed in descending order by the lung (8729 µg·eq/L), liver (6110 µg·eq/L), kidney (papilla) (5841 µg·eq/L), and adrenal gland (medulla) (5356 µg·eq/L). The maximum radioactivity concentration in the brain was <2% of that in the blood. At 168 hours after administration, radioactivity was detected in the adrenal gland (cortex and medulla), heart, Harderian gland, kidney (cortex, medulla, and papilla), liver, lung, and skin, but radioactivity concentrations in these tissues were all 0.1% to 1.5% of the maximum radioactivity concentration.

A single dose of ^{14}C-finerenone at 3 mg/kg was administered orally to female albino rats, and tissue distribution of radioactivity at 2 and 24 hours was evaluated (n = 1/timepoint). Radioactivity concentrations at 24 hours were lower than those at 2 hours in most of the tissues including the blood, except for the eyeball wall, skin, and uterus in which radioactivity concentrations tended to increase with time.

A single dose of ^{14}C-finerenone at 1 mg/kg was administered intravenously to male albino rats, and tissue distribution of radioactivity at 5 minutes and 2 hours was evaluated (n = 1/timepoint). Radioactivity concentrations at 2 hours were lower than those at 5 minutes in most of the tissues including the blood, except for the eyeball wall, Harderian gland, kidney (papilla), prostate gland, vesicular gland, skeletal muscle, skin, testis, thymus, and thyroid in which radioactivity concentrations tended to increase with time.

A single dose of ^{14}C-finerenone at 3 mg/kg was administered orally to male pigmented rats, and tissue distribution of radioactivity at 24, 72, 168, and 336 hours was evaluated (n = 1/timepoint). In all the tissues evaluated, radioactivity concentrations reached the maxima at 24 hours, and higher maximum radioactivity concentrations than that in blood (351 μg·eq/L) were found in the liver (517 μg·eq/L) and eyeball wall (395 μg·eq/L). At 336 hours after administration, radioactivity was detected in the adrenal gland (cortex and medulla), heart, eyeball wall, kidney (cortex and medulla), and liver.

4.2.4 Placental transfer (CTD 4.2.2.3.5)

A single dose of ^{14}C-finerenone at 3 mg/kg was administered orally to female rats on Gestation Day 18, and tissue radioactivity concentrations at 2, 4, 8, 24, and 48 hours were evaluated. Radioactivity was detected in the fetus, and the fetus/maternal blood ratio of $AUC_{0\text{-}24h}$ and fetal blood/maternal blood ratio were 0.06 and 0.09, respectively.

4.3 Metabolism

4.3.1 *In vitro* metabolism (CTD 4.2.2.4.1)

When liver microsomes of mice, rats, rabbits, dogs, and monkeys were incubated with ^{14}C-finerenone at 1 μmol/L at 37°C for 1 hour, the detected metabolites of finerenone include M-1 (formed by oxidation of the dihydropyridine moiety of finerenone), M-2 (formed by hydroxylation of M-1), M-3 (formed by oxidation of M-2), M-4 (dihydrodiol form of finerenone), M-5 (formed by hydroxylation of M-4), and M-6 (formed by hydroxylation of finerenone) irrespective of animal species. Atropisomer ratios for M-1, M-2, and M-3, metabolites detected in mouse, rat, or dog liver microsome, were investigated, and "a"-atropisomer was found to account for 82.0% to 97.0% of each metabolite irrespective of animal species.

When rat, dog, and monkey hepatocytes were incubated with ^{14}C-finerenone at 1 μmol/L at 37°C for 2 hours, the detected metabolites of finerenone included M-1, M-2/M-6,[5)] M-3 (except for dog hepatocytes), M-4, M-5, and M-7 (formed by hydroxylation of finerenone) irrespective of animal species.

4.3.2 *In vivo* metabolism

4.3.2.1 Metabolites in plasma (CTD 4.2.2.4.8, 4.2.2.4.9, 4.2.2.4.10, and 4.2.2.7.17)

Following a single oral administration of ^{14}C-finerenone at 1 mg/kg to male mice (n = 3/timepoint), unchanged finerenone was the predominant form observed in plasma, accounting for 96.8% (percentage of $AUC_{0\text{-}72h}$ of the total plasma radioactivity). In addition, M-1 (0.4%) and M-4/M-7[6)] (0.9%) were detected as the metabolites.

Following a single oral administration of ^{14}C-finerenone at 1 mg/kg to male rats (n = 3/timepoint), unchanged finerenone was the predominant form observed in plasma, accounting for 96.4% (percentage of $AUC_{0\text{-}8h}$ of the total plasma radioactivity). In addition, M-1 (1.0%) and M-4/M-7 (2.4%) were detected as the metabolites.

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5) M-2 and M-6 were co-eluted.
6) M-4 and M-7 were co-eluted.

Following a single oral administration of ^{14}C-finerenone at 3 mg/kg to female dogs (n = 4), unchanged finerenone in plasma accounted for 28.2% (percentage of $AUC_{0\text{-}264h}$ of the total plasma radioactivity), and M-1 (8.1%), M-2 (36.0%), M-3 (1.6%), M-4/M-7 (11.1%), and M-5 (0.6%) were detected as metabolites. Atropisomer ratios for M-1, M-2, and M-3 were investigated, and "a"-atropisomer was found to account for 91.2%, 89.1%, and 90.7%, respectively.

4.3.2.2 Metabolites in urine, feces, and bile (CTD 4.2.2.4.9, 4.2.2.4.10, 4.2.2.7.16, and 4.2.2.7.17)

Following a single oral administration of ^{14}C-finerenone at 1 mg/kg to male rats (n = 5), unchanged finerenone excreted into urine until 168 hours post-dose accounted for 0.640% (percentage relative to the administered radioactivity), and M-1 (0.165%), M-2 (4.98%), M-3 (6.91%), M-4/M-7[6)] (2.36%), and M-5 (0.356%) were detected as metabolites. Unchanged finerenone excreted into feces accounted for 7.85%, and M-1 (0.953%), M-2 (8.10%), M-3 (19.9%), M-4/M-7 (4.86%), and M-5 (7.30%) were detected as metabolites. Atropisomer ratios for M-1, M-2, and M-3 in urine and feces were investigated, and "a"-atropisomer was found to account for 85.6%, 93.2%, and 88.2% in urine, respectively, and 88.3%, 94.1%, and 87.3% in feces, respectively.

Following a single oral administration of ^{14}C-finerenone at 1 mg/kg to bile-duct-cannulated male rats (n = 4), unchanged finerenone excreted into urine until 24 hours post-dose accounted for 0.698%, and M-1 (0.239%), M-2 (2.78%), M-3 (3.58%), M-4/M-7 (1.4%), and M-5 (0.270%) were detected as metabolites. Unchanged finerenone excreted into feces accounted for 2.43%, and M-1 (0.114%), M-2 (2.77%), M-3 (0.163%), M-4/M-7 (2.59%), and M-5 (0.508%) were detected as metabolites. In addition, M-2 (2.16%), M-3 (24.2%), and M-5 (5.47%) were detected as biliary metabolites.

Following a single intravenous administration of ^{14}C-finerenone at 1 mg/kg to bile-duct-cannulated male rats (n = 5), unchanged finerenone excreted into urine until 24 hours post-dose accounted for 0.586%, and M-1 (0.0917%), M-2 (2.08%), M-3 (3.22%), M-4/M-7 (1.28%), and M-5 (0.504%) were detected as metabolites. Unchanged finerenone excreted into feces accounted for 2.77%, and M-1 (0.161%), M-2 (2.40%), M-3 (0.173%), M-4/M-7 (1.50%), and M-5 (0.280%) were detected as metabolites. In addition, M-2 (0.661%), M-3 (24.2%), and M-5 (5.03%) were detected as biliary metabolites.

Following a single oral administration of ^{14}C-finerenone at 3 mg/kg to female dogs (n = 4), unchanged finerenone excreted into urine until 336 hours post-dose accounted for 1.26%, and M-1 (0.122%), M-2 (27.8%), M-3 (4.16%), M-4/M-7 (3.81%), and M-5 (2.46%) were detected as metabolites. Unchanged finerenone excreted into feces accounted for 2.86%, and M-1 (0.246%), M-2 (14.7%), M-3 (0.856%), M-4/M-7 (3.44%), and M-5 (6.08%) were detected as metabolites. Atropisomer ratios for M-1, M-2, and M-3 in urine and feces were investigated, and "a"-atropisomer was found to account for 89.3%, 81.3%, and 83.7% in urine, respectively, and 86.6%, 87.1%, and 84.3% in feces, respectively.

4.4 Excretion

4.4.1 Excretion into urine and feces (CTD 4.2.2.5.1 and 4.2.2.5.2)

Following a single oral or intravenous administration of ^{14}C-finerenone at 1 mg/kg to male rats (n = 5 for both), radioactivity excreted into urine and feces until 168 hours post-dose (percentage relative to the administered radioactivity) accounted for 19.5% and 75.7% after the oral administration, respectively, and 21.4% and 74.0% after the intravenous administration, respectively.

Following a single oral administration of ^{14}C-finerenone at 3 mg/kg to female dogs (n = 4), radioactivity excreted into urine and feces until 336 hours post-dose accounted for 52.7% and 42.0%, respectively.

4.4.2 Excretion into bile (CTD 4.2.2.5.1)

Following a single oral (n = 4) or intravenous (n = 5) administration of ^{14}C-finerenone at 1 mg/kg to bile-duct-cannulated male rats, radioactivity excreted into bile, urine, and feces until 24 hours post-dose (percentage relative to the administered radioactivity) accounted for 52.7%, 12.1%, and 9.27% after the oral administration, respectively, and 44.1%, 10.9%, and 7.78% after the intravenous administration, respectively.

4.4.3 Excretion into milk (CTD 4.2.2.5.4)

Following a single intravenous administration of ^{14}C-finerenone at 1 mg/kg to lactating rats, radioactivity excreted into milk until 24 (n = 3) and 48 hours (n = 2) post-dose (percentage relative to the administered radioactivity) accounted for approximately 20% for both.

4.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA concluded that non-clinical pharmacokinetics of finerenone was appropriately evaluated.

5. Toxicity and Outline of the Review Conducted by PMDA

The applicant submitted the data of the following toxicity studies of finerenone: Single-dose toxicity, repeated-dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, and other studies (juvenile animal toxicity and phototoxicity studies). In this section, unless otherwise specified, exposure to finerenone is expressed as an amount of the unbound (free) form.

5.1 Single-dose toxicity

Single-dose toxicity studies in mice and rats were conducted. No single-dose toxicity studies of finerenone in non-rodents were conducted. Results obtained from the first dose in a repeated-dose toxicity study in dogs were used to evaluate acute toxicity of finerenone (Table 11).

Table 11. Single-dose toxicity studies

Test system	Route of administration	Dose (mg/kg)	Major findings	Approximate lethal dose (mg/kg)	Attached document CTD
Female mouse (NMRI)	Oral and intravenous	(oral) 2000 (intravenous) 30, 200	(oral) No acute toxicity (intravenous) 200: Death (2/3), clonic convulsion, hyperpnea	(oral) >2000 (intravenous) 200	4.2.3.1.1
Female rat (Wistar)	Oral	50, 300, 2000	300: Death (2/3), lateral position, labored breathing, decreased locomotor activity	300	
Male and female dogs (beagle)	Oral	0,[a] 1.5, 5, 15	Acute toxicity evaluated in 4-week repeated oral dose toxicity study No acute toxicity	>15	4.2.3.2.10

a PEG400

5.2 Repeated-dose toxicity

Repeated-dose toxicity studies in mice (13 weeks), rats (4, 13, and 26 weeks), and dogs (4, 13, and 39 weeks) were conducted (Table 12). Findings attributable to finerenone included changes in blood electrolyte concentration (low blood Na level and high blood K level) and effects on the adrenal gland. The applicant discussed that these findings were related to the pharmacological action and thus toxicologically irrelevant. In addition, concerning the change in the prostate gland in dogs that received finerenone at 1.5 mg/kg for 39 weeks, the applicant discussed that it was unlikely to raise clinical problems because a similar change was also observed in a toxicity study of eplerenone in dogs (*Toxicol Pathol.* 2013;41:271-9); and the change is considered to have reflected hormonal imbalance attributable to the pharmacological action of finerenone but mild without histopathological changes. Exposure to finerenone ($AUC_{0\text{-}24h}$) at the no observed adverse effect level (NOAEL) in repeated-dose toxicity studies in rats (26 weeks) and dogs (39 weeks) (rats, 5 mg/kg/day for males and 1.5 mg/kg/day for females; dogs, 0.5 mg/kg/day for males and 5 mg/kg/day for females) was 327 to 461 µg·h/L and 116 to 3272 µg·h/L, respectively, which were 6 to 8 times (rats) and 2 to 60 times (dogs) the exposure ($AUC_{0\text{-}24h}$) at the maximum recommended clinical dose.

Table 12. Repeated-dose toxicity studies

Test system	Route of administration	Treatment duration	Dose (mg/kg/day)	Major findings	NOAEL (mg/kg/day)	Attached document CTD
Male and female mouse (CD-1)	Oral	13 weeks (once daily)	(male) 0,[a] 1, 3, 10 (female) 0,[a] 0.75, 2.5, 7.5	≥0.75: High adrenal gland weight 7.5: Hypertrophy of the zona glomerulosa in the adrenal gland cortex 10: High testis weight, seminiferous epithelial cell desquamation	3 (male) 7.5 (female)	4.2.3.2.4
Male and female rat (Wistar)	Oral	4 weeks (once daily) + 4-week withdrawal	0,[b] 3, 10, 30	≥3: Increased urine volume, low blood Na level, high blood K and Ca levels, hypertrophy of the zona glomerulosa in the adrenal gland cortex ≥10: Reduced body weight gain, increased water intake, high BUN level, high ALT and ALP levels (female), concentrated cytoplasm in the liver (female), basophilic renal tubule in the kidney 30: Effects on female reproductive organs (foamy corpora lutea, endometrial and myometrial atrophy in the uterus, epithelial atrophy in the uterine cervix, epithelial atrophy in the vagina), ureteral dilatation and inflammation (female), transitional epithelial hyperplasia and inflammatory cell infiltration in the bladder, proximal renal tubular necrosis and mineralization in the kidney (female) Reversible	3	4.2.3.2.6
Male and female rat (Wistar)	Oral	13 weeks (once daily)	0,[b] 3, 10, 30	≥3: Hypertrophy of the zona glomerulosa in the adrenal gland cortex ≥10: Low blood Na level, vacuolation in the zona glomerulosa in the adrenal gland cortex (female), hepatocyte hypertrophy (male) and concentrated cytoplasm (female) in the liver, basophilic renal tubule, proximal renal tubular necrosis, and mineralization in the kidney (female), effect on reproductive organs (foamy corpora lutea) 30: Body weight loss, reduced body weight gain, worsened clinical signs (low motor activity, emaciation, pale skin, piloerection) (female), high blood K level, clear bile duct in the liver (female), hyperplasia of the renal pelvis transitional epithelium in the kidney (female), increased sinus histiocytes and adipocytes in the mesenteric lymph node, diffuse atrophy of the pancreas, salivary gland, lacrimal gland, and mammary gland (female), effects on female reproductive organs (atretic follicle, increased pale interstitial gland, large corpora lutea, endometrial and myometrial atrophy in the uterus, epithelial atrophy in the uterine cervix, alterations in the uterine surface and cervical epithelium, epithelial atrophy and alteration in the vagina)	10 (male) 3 (female)	4.2.3.2.8
Male and female rat (Wistar)	Oral	26 weeks (once daily)	(male) 0,[b] 1.5, 5, 15 (female) 0,[b] 0.5, 1.5, 5	≥0.5: High blood Ca level, high blood K level (female), hypertrophy of the zona glomerulosa in the adrenal gland cortex ≥1.5 (male): Harderization of the lacrimal gland[d] and mononuclear infiltrate[d] 5: Worsened clinical signs (pale skin, piloerection) (female), high BUN level (female) ≥5: Low blood Na level (male), high adrenal gland weight 15 (male), 5 (female): Body weight loss, reduced body weight gain 15 (male): Diffuse atrophy of the lacrimal gland[d]	5 (male) 1.5 (female)	4.2.3.2.9
Male and female dog (beagle)	Oral	4 weeks (once daily) + 2-week withdrawal	0,[c] 1.5, 5, 15	≥5: High pancreas weight (female),[e] eosinophilic alteration of the zona glomerulosa in the adrenal gland cortex 15: Body weight loss, reduced body weight gain, decreased food intake (female), low blood Na level, high blood K level, high BUN (female), high adrenal gland weight (female) Reversible	5	4.2.3.2.10
Male and female dog (beagle)	Oral	13 weeks (once daily)	0,[c] 1, 3, 10	≥3: High adrenal gland weight ≥10: Low blood Na level, widening of the zona glomerulosa in the adrenal gland cortex 10: Low thymus weight (female)[e]	10	4.2.3.2.11

Male and female dog (beagle)	Oral	39 weeks (once daily)	0,[c] 0.5, 1.5, 5	≥0.5: Decreased food intake (female), narrowing of zona fasciculata and diffuse hyperplasia of the zona glomerulosa in the adrenal gland cortex ≥1.5: Small prostate gland with low weight,[e] high adrenal gland weight (male)	0.5 (male) 5 (female)	4.2.3.2.12

a 0.5% methyl hydroxyethyl cellulose aqueous solution
b 10% ethanol, 40% macrogol 15 hydroxystearic acid, 50% water
c PEG400
d The applicant determined that it is known as an aging-related change in rats, and toxicological significance was low.
e The applicant determined that it is not accompanied by histopathological changes, and toxicological significance was low.

5.3 Genotoxicity

In vitro genotoxicity studies consisted of a bacterial reverse mutation assay and a chromosomal aberration assay in cultured mammalian cells, and *in vivo* study genotoxicity studies consisted of a mouse micronucleus assay were conducted. No genotoxicity was observed (Table 13).

Table 13. Genotoxicity studies

Study type		Test system	Metabolic activation (treatment)	Concentration (μg/plate or μg/mL) or dose (mg/kg/day)	Result	Attached document CTD
In vitro	Bacterial reverse mutation assay (Ames test)	*Salmonella typhimurium*: TA98, TA100, TA102, TA1535, TA1537	S9 -/+	0,[a] 100, 250, 500, 1000, 2500, 5000	Negative	4.2.3.3.1.1
	Chromosomal aberration assay in cultured mammalian cells	Chinese hamster V79 cells	S9 -, 4 hours	0,[a] 55, 110, 220	Negative	4.2.3.3.1.2
			S9 -, 18 hours	0,[a] 40, 80, 120		
			S9 +, 4 hours	0,[a] 80, 160, 350		
In vivo	Mouse micronucleus assay	Bone marrow of male mouse (NMRI)		0,[b] 250, 500, 1000	Negative	4.2.3.3.2.1

a DMSO
b 0.5% PEG35 castor oil aqueous solution

5.4 Carcinogenicity

Long-term carcinogenicity studies in mice and rats were conducted (Table 14). Although Leydig cell adenoma was observed in mice, it is attributable to hormonal imbalance secondary to high exposure and thus the applicant considered that it is unlikely to lead to problems in clinical use [see Section "5.R.1 Testicular tumor"].

Table 14. Carcinogenicity studies

Test system	Route of administration	Treatment duration	Major lesion	Dose	(mg/kg/day)									Non-carcinogenic dose (mg/kg/day)	Attached document CTD
					0[a]	0[b]	1	3	10	30	0.75	2.5	7.5		
				n (F/M)	M/F	M/F	M				F				
					60/60	60/60	60	60	60	60	60	60	60		
Male and female mice (CD-1)	Oral	2 years	Neoplastic lesion		None									Male: 10 Female: 7.5	4.2.3.4.1.1
			Leydig cell adenoma		2/-	1/-	1	3	0	9	-	-	-		
			Non- neoplastic lesion		Reduced body weight gain (male), alopecia (female), sparse fur (female), lens opacity (male), pale and enlarged testis, dilation and atrophy of seminiferous tubule										
Male and female rats (Wistar)	Oral	2 years	Major lesion	Dose	(mg/kg/day)									Male: 20 Female: 10	4.2.3.4.1.2
					0[c]	0[b]	2		6	20	1	3	10		
				n (F/M)	M/F	M/F	M				F				
					60/60	60/60	60		60	60	60	60	60		
			Neoplastic lesion		None										
			Non- neoplastic lesion		Body weight loss, reduced body weight gain, decreased food intake (male), decreased water intake, changes in electrolytes, high adrenal gland weight (female), pale adrenal gland, hypertrophy and vacuolation of the zona glomerulosa in the adrenal gland cortex, hyperplasia of adrenal medulla										

a 0.5% methyl hydroxyethyl cellulose aqueous solution
b Physiological saline
c 10% ethanol, 40% macrogol 15 hydroxystearic acid, 50% water

5.5 Reproductive and developmental toxicity

The applicant conducted a study of fertility and early embryonic development to implantation in male and female rats, studies for effects on embryo-fetal development in rats and rabbits, and a study for effects on pre- and postnatal development, including maternal function in rats (Table 15). Decreased fetal weight and double aortic arch were observed in the study for effects on embryo-fetal development in rats, and increased locomotor activity was observed in the study for effects on pre- and postnatal development, including maternal function in rats. The applicant considered it necessary to provide information about these findings through the package insert because they raise a concern about the effect in humans [see Section "5.R.2 Effects on fetuses"]. Exposure to finerenone ($AUC_{0\text{-}24h}$) in maternal animals at the embryo-fetal NOAEL (3 mg/kg/day for rats, 2.5 mg/kg/day for rabbits) in the studies for effects on embryo-fetal development in rats and rabbits was 567 and 723 μg·h/L, respectively, which were 10 times (rats) and 13 times (rabbits) the exposure ($AUC_{0\text{-}24h}$) at the clinical dose.

Table 15. Reproductive and developmental toxicity studies

Study type	Test system	Route of administration	Treatment duration	Dose (mg/kg/day)	Major findings	NOAEL (mg/kg/day)	Attached document CTD
Fertility and early embryonic development to implantation	Male and female rat (Wistar)	Oral	(male) 28 days prior to mating to 1 day before necropsy (once daily) (female) 14 days prior to mating to Gestation Day 7 (once daily)	0,[a] 3, 10, 30	Parental animal: ≥3: Body weight loss, reduced body weight gain 30: Increased water intake, increased urine volume Fertility and early embryonic development: ≥10: Low ovary weight 30: Decreases in numbers of corpora lutea,[c] implantation,[c] and live conceptuses, and increased postimplantation loss[d]	Parental animal (general toxicity): <3 (male fertility): 30 (female fertility, early embryonic development): 3	4.2.3.5.1.1
Embryo-fetal development	Female rat (Wistar)	Oral	Gestation Days 6 to 17 (once daily)	0,[a] 3, 10, 30	Maternal animal: ≥10: Reduced body weight gain, decreased food intake 30: Increased water intake, increased urine volume Fetus: ≥10: Decreased fetal weight, decreased placenta weight,[e] delayed ossification 30: Double aortic arch, complex malformation of the heart and major vessels,[c] malformation of the lung and spleen,[c] edema, shortened umbilical cord, enlarged fontanelle	Maternal animal: 3 Embryo and fetus: 3	4.2.3.5.2.2
	Female rabbit (Himalayan)	Oral	Gestation Days 6 to 20 (once daily)	0,[b] 0.25, 0.75, 2.5	Maternal animal: 2.5: Body weight loss, reduced body weight gain, decreased food intake Fetus: None	Maternal animal: 0.75 Embryo and fetus: 2.5	4.2.3.5.2.4
Effects on pre- and postnatal development, including maternal function	Female rat (Wistar)	Oral	Gestation Day 6 to Lactation Day 21 (once daily)	0,[a] 1, 3, 10	Maternal animal: 10: Reduced body weight gain, decreased food intake, decreases in numbers of corpora lutea and implantation[c] Offspring: ≥3: High count of postnatal deaths, low body weight at birth, increased locomotor activity 10: Reduced body weight gain, delayed pinna unfolding	Maternal animal: 3 Offspring: 1	4.2.3.5.3.2

a 10% ethanol, 40% macrogol 15 hydroxystearic acid, 50% water
b 0.5% methyl hydroxyethyl cellulose aqueous solution
c The applicant determined that it was within the range of historical data and toxicological significance was low.
d The applicant determined that although it was not significantly different from that in the control group from a statistical viewpoint, it was the finding suggesting the effect on early embryonic development as with the low count of live conceptuses.
e The applicant determined that no abnormalities were observed in appearance, and toxicological significance was low.

5.6 Local tolerance

Local tolerance in the gastrointestinal tract was evaluated based on results from the repeated-dose toxicity studies in rats and dogs [see Section “5.2 Repeated-dose toxicity”] and carcinogenicity studies [see Section “5.4 Carcinogenicity”]. The applicant considered finerenone locally tolerable.

5.7 Other toxicity studies

5.7.1 Toxicity in juvenile animals

A repeated-dose toxicity study (13 weeks) and a study of fertility in juvenile rats were conducted (Table 16). Exposure to finerenone (bound + unbound forms) ($AUC_{0\text{-}24h}$) at NOAEL in the repeated-dose toxicity study in juvenile rats (13 weeks) was 1480000 to 3300000 μg·h/L.

Table 16. Study on juvenile animals

Study type	Test system	Route of administration	Treatment duration	Dose (mg/kg/day)	Major findings	NOAEL (mg/kg/day)	Attached document CTD
Repeated-dose studies Toxicity	Juvenile male and female rat (Wistar)	Oral	13 weeks, 14 to approximately 106 days after birth (once daily) + 4-week withdrawal	0,[a] 1, 3, 10	≥1: Increased urine volume (male), hypertrophy of the zona glomerulosa in the adrenal gland cortex 10: Vacuolation in the zona glomerulosa in the adrenal gland cortex, hypertrophy of zona fasciculata in the adrenal gland cortex (male) Reversible (except for vacuolation in the zona glomerulosa in the adrenal gland cortex)	10	4.2.3.5.4.2
Fertility	Juvenile female rat (Wistar)	Oral	13 weeks, 14 to 107 days after birth (once daily)	0,[a] 1, 3, 10	None	10	4.2.3.5.4.3

a 0.5% methyl hydroxyethyl cellulose aqueous solution (before weaning)/10% ethanol, 40% macrogol 15 hydroxystearic acid, 50% water (after weaning)

5.7.2 Phototoxicity

In vitro, 2 phototoxicity studies were conducted. In a study, finerenone was shown to be phototoxic, but variations in results among assays potentially attributable to changes in study conditions were observed. Another study was conducted under corrected study conditions, and the results showed finerenone to be non-phototoxic (Table 17). Based on the above, the applicant considered finerenone to be non-phototoxic.

Table 17. Phototoxicity studies

Study type	Test system	Study method	Result	Attached document CTD
Phototoxicity studies	Mouse fibroblast Balb/c 3T3	Cells were exposed to UV-A at room temperature or not exposed to UV-A at 37°C in the presence of finerenone at 0 to 500 μg/mL for 50 minutes, and cell viability was calculated.	Phototoxic	4.2.3.7.7.1
Phototoxicity studies	Mouse fibroblast Balb/c 3T3	Cells were exposed to UV-A or not exposed to UV-A at 37°C in the presence of finerenone at 0 to 300 μg/mL for 50 minutes, and cell viability was calculated.	Non-phototoxic	4.2.3.7.7.2

5.7.3 Safety of metabolites

When administered to humans, finerenone is mainly metabolized into M-1, M-2, and M-3, its naphthyridine metabolites [see Section "6.2.2.4 Mass balance study"], and exposure to each metabolite of finerenone in the repeated-dose toxicity studies, carcinogenicity studies, and studies for effects on embryo-fetal development was similar to that in humans. In view of the above, the applicant considered that the toxicity had been evaluated including that of these metabolites.

5.R Outline of the review conducted by PMDA

Based on the submitted data and the following review, PMDA concluded that non-clinical toxicity evaluation presented no findings potentially leading to problems in clinical use of finerenone.

5.R.1 Testicular tumor

The applicant's explanation about the appropriateness of extrapolating this finding to humans, i.e., Leydig cell adenoma observed in males in the finerenone 30 mg/kg group in the 2-year carcinogenicity study in mice:

Leydig cell adenoma in rodents is observed after administration of a drug that is antiandrogenic or alters sex hormone levels (*Histopathology of Preclinical Toxicity Studies.* 4th edition. 2012:615-66). Leydig cells, which express MR, are involved in modulation of testosterone production stimulated by aldosterone (*Mol Cell Endocrinol.* 2005;243:35-42). The concerned finding is, therefore, considered attributable to hormonal imbalance induced by finerenone through MR that affects testosterone production. Furthermore, exposure at the non-carcinogenic dose in mice is 17 times that at the maximum recommended clinical dose, and thus the clinical use would not raise any problem of Leydig cell adenoma.

PMDA determined that the applicant's explanation is acceptable.

5.R.2 Effects on fetuses

The applicant's explanation about whether multiple findings in the reproductive and developmental toxicity studies would lead to problems in clinical use:

Findings in the study of fertility and early embryonic development to implantation in rats included low ovary weight at ≥10 mg/kg as well as decreases in numbers of corpora lutea, implantation, and live conceptuses and increased postimplantation loss at 30 mg/kg. Because remarkably reduced body weight gain was also observed at 30 mg/kg, the findings at this dose are considered attributable to maternal toxicity and thus unlikely to be relevant to humans. The exposure in rats at 10 mg/kg (958 μg·h/L) accompanied by low ovary weight is as high as 17 times that at the maximum recommended clinical dose, and thus the clinical use is considered unlikely to raise problems of low ovary weight.

Findings in the study for effects on embryo-fetal development in rats included decreased fetal weight indicative of embryo-fetal toxicity, variations such as delayed ossification, edema, shortened umbilical cord, and enlarged fontanelle, and double aortic arch suggestive of teratogenicity. The exposure in rats at 30 mg/kg (1390 μg·h/L) accompanied by double aortic arch is as high as 25 times that at the maximum recommended clinical dose, and thus the clinical use is considered unlikely to raise

problems related to this finding. However, the double aortic arch, which is deemed as a rare finding, was also observed in the dose-finding study in rats for the study for effects on embryo-fetal development, and the relationship to finerenone cannot be ruled out. Accordingly, the package insert will provide information about these findings except for the variations (double aortic arch and decreased fetal weight) and a cautionary statement that finerenone should be used in pregnant women or women of childbearing potential only if the expected therapeutic benefits outweigh the possible risk associated with treatment.

In the study for effects on pre- and postnatal development, including maternal function in rats, postnatal deaths, reduced body weight gain, increased locomotor activity, and delayed pinna unfolding were observed. These findings are potentially attributable to the excessive pharmacological action of finerenone in offspring with underdeveloped kidneys because no clinical signs were observed in the juvenile animal toxicity studies in which animals at 14 days of age or older received finerenone [see Section "5.7.1 Toxicity in juvenile animals"]; and rat kidney rapidly develops from birth to Postnatal Day 11 (*Birth Defects Res B Dev Reprod Toxicol.* 2003;68:111-20). In addition, no effects on the central nervous system were observed in the juvenile animal toxicity studies and 13-week repeated-dose toxicity study in which rats at 6 weeks of age or older received finerenone [see Section "5.2 Repeated-dose toxicity"]. Finerenone is hardly transferred into the brain through the blood-brain barrier [see Section "4.2.3 Tissue distribution"], but some of the findings are considered to have resulted from exposure of fetal brain to finerenone, which passes the placenta [see Section "4.2.4 Placental transfer"]. MR is widely expressed across the brain, and inhibition against it potentially affects behaviors (*Pharmacol Biochem Behav.* 1997;56:507-13). The package insert will include information about increased locomotor activity because it cannot be ruled out that administration of finerenone during pregnancy results in a similar finding.

PMDA considers that it is almost acceptable to include the cautionary statement for pregnant women or women of childbearing potential in the package insert (draft), but it is also necessary to include information about the low ovary weight in rats in the package insert because this finding occurred at a dose leading to exposure 17 times that at the maximum recommended clinical dose, and it cannot be ruled out that the clinical use raises no concerns.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

6.1 Summary of biopharmaceutic studies and associated analytical methods

The formulation used in the Japanese phase II study (Study 16816), foreign phase II study (Study 16243), and global phase III studies (Studies 16244 and 17530) in patients with CKD associated with type 2 diabetes mellitus as well as the study for effects of food (Study 16536) is identical to the to-be-marketed formulation, except for [redacted] and [redacted] of [redacted] in [redacted]. Dissolution test results demonstrated bioequivalence (BE) in accordance with "Guideline for Bioequivalence Studies for Formulation Changes of Oral Solid Dosage Forms" (PMSB/ELD Notification No. 64 dated February 14, 2000, partially revised by PFSB/ELD Notification No. 0229-10 dated February 29, 2012) (BE Guidelines for Formulation Change).

Plasma and urinary concentrations of finerenone and its major metabolites (M-1a, M-1b, M-2a, M-2b, M-3a, and M-3b[1)]) were determined by LC-MS/MS. The lower limit of quantitation was 0.10 μg/L for finerenone and 0.50 μg/L for the metabolites in plasma specimens and 1.00 μg/L for finerenone and 5.00 μg/L for the metabolites in urinary specimens. Radioactivity of ^{14}C- or ^{3}H-labeled compound of finerenone or its major metabolite (M-1a, M-1b, M-2a, or M-3a) was determined by a liquid scintillation counter.

6.1.1 Relative BA study (Study 15526, CTD 5.3.1.2.2 [Reference data], Study period, March to April 20[redacted])

A 3-treatment, 3-period crossover study (a ≥3-day washout period) was conducted to investigate relative bioavailability (BA) and dose-proportionality in 12 healthy adult non-Japanese men who orally received a single dose of finerenone 1.25 mg (one 1.25 mg tablet), 5 mg (four 1.25 mg tablets), or 10 mg (one 10 mg tablet) in the fasted state during a treatment period.

The geometric mean ratios [90% confidence interval (CI)] of C_{max}/D and $AUC_{0-\infty}/D$ of finerenone at 10 mg to those at 1.25 mg were 0.9052 [0.7881, 1.0397] and 1.0151 [0.9017, 1.1428]; the geometric mean ratios [90% CI] of C_{max}/D and $AUC_{0-\infty}/D$ of finerenone at 5 mg to those at 1.25 mg were 1.0991 [0.9569, 1.2625] and 1.0349 [0.9193, 1.1650]; and the geometric mean ratios [90% CI] of C_{max}/D and $AUC_{0-\infty}/D$ of finerenone at 10 mg to those at 5 mg were 0.8236 [0.7170, 0.9460] and 0.9809 [0.8713, 1.1043]. Median t_{max} of finerenone at all doses were similar (0.500-0.750 hours).

6.1.2 Absolute BA study (Study 16535, CTD 5.3.1.1.1 [Reference data], Study period, July to October 20[redacted])

A 2-treatment, 2-period crossover study (a ≥7-day washout period) was conducted in 16 healthy adult non-Japanese men who intravenously received a single dose of finerenone 1 mg or orally received a single dose of 5 mg in the fasted state during a treatment period. The absolute BA of finerenone (geometric mean ratio [90% CI] of $AUC_{0-\infty}/D$ after the oral administration to that after the intravenous administration) was 0.4352 [0.3920, 0.4832]. CL (geometric mean) of finerenone after a single intravenous administration of finerenone 1 mg was 22.3 L/h with V_{ss} of 52.6 L.

6.1.3 Study for effects of food (Study 16536, CTD 5.3.1.2.5 [Reference data], Study period, May to July 20[redacted])

A 3-treatment, 3-period crossover study (a ≥3-day washout period) was conducted to investigate effects of food on PK of finerenone and dose-proportionality in 18 healthy adult non-Japanese men who orally received a single dose of finerenone 10 mg (one 10 mg tablet) or 20 mg (one 20 mg tablet) in the fasted state or a single dose of 20 mg (one 20 mg tablet) in the fed state with a high-fat, high-calorie meal during a treatment period.

The geometric mean ratios [90% CI] of C_{max} and $AUC_{0-\infty}$ of finerenone after administration of finerenone 20 mg in the fed state to those after administration in the fasted state were 0.8127 [0.7014, 0.9416] and 1.2090 [1.1251, 1.2991]. Median t_{max} of finerenone after administration in the fed state (2.47 hours) was delayed compared with that after administration in the fasted state (0.75 hours).

The geometric mean ratios [90% CI] of C_{max}/D and $AUC_{0-\infty}$/D of finerenone after administration of finerenone 20 mg to those after administration of 10 mg were 0.9301 [0.8028, 1.0777] and 0.9943 [0.9254, 1.0684].

6.1.4 BE study (Study 21325, CTD 5.3.1.2.6, Study period, July to August 20[redacted])

A 2-treatment, 2-period crossover study (a ≥3-day washout period) was conducted to investigate BE between two 10 mg tablets, the to-be-marketed formulation, and the 20 mg tablet in 36 healthy adult Japanese men who orally received a single dose of finerenone 20 mg using the 10 mg tablet, the to-be-marketed formulation, or the 20 mg tablet in the fasted state during a treatment period.

The geometric mean ratios [90% CI] of C_{max} and AUC_{0-t} of finerenone after administration using the 10 mg tablets to those after administration using the 20 mg tablets were 1.1766 [1.0626, 1.3027] and 1.0684 [1.0255, 1.1131].

6.2 Clinical pharmacology

Unless otherwise specified, PK parameters are expressed as the mean or mean ± SD.

6.2.1 *In vitro* studies using human biological samples

6.2.1.1 Plasma protein binding and distribution in blood cells (CTD 4.2.2.3.1, 4.2.2.7.13, and 4.2.2.7.14)

Following the addition of ^{14}C-finerenone at 94.5 to 4289 µg/L and 87549 µg/L, ^{3}H-M-1a at 45.9 to 4398 µg/L, ^{14}C-M-1b at 37.0 to 4620 µg/L, ^{3}H-M-2a at 48.6 to 4297 µg/L, or ^{3}H-M-3a[1)] at 35.1 to 3408 µg/L to human plasma, the protein binding was 91.7% and 87.4%, 94.2%, 96.1%, 82.6%, and 32.2%, respectively.

Following the addition of ^{14}C-finerenone at 5287, 4934, 4984, 4988, and 4948 µg/L to human serum albumin, α1-acid glycoprotein, low density lipoprotein (LDL), α-globulin, and γ-globulin, the protein binding was 83.5%, 40.7%, 40.2%, 41.1%, and 15.6%, respectively.

Following the addition of ^{14}C-finerenone at 119 to 6587 and 126870 µg/L to human blood, the blood/plasma concentration ratio was 0.935 and 1.09.

6.2.1.2 *In vitro* metabolism (CTD 4.2.2.4.1)

Human liver microsomes were incubated with ^{14}C-finerenone at 1 µmol/L at 37°C for 1 hour, and finerenone was metabolized into M-1 (14.2% [percentage relative to the total radioactivity]), M-2/M-6[5)] (35.5%), M-3 (1.09%), M-4 (14.5%), M-5 (19.2%), and M-7 (0.93%). Atropisomer ratios for M-1 and M-2 were investigated, and “a”-atropisomer was found to account for 94.6% and 96.2%, respectively.

Human hepatocytes (n = 2) were incubated with ^{14}C-finerenone at 1 µmol/L at 37°C for 2 hours, and finerenone was metabolized into M-1 (20.3%, 17.5% [individual values]), M-2/M-6 (6.80%, 5.31%), M-4 (13.2%, 12.1%), M-5 (8.68%, 6.50%), and M-7 (1.63%, 1.69%).

6.2.1.3 Identification of CYP isoforms involved in metabolism of finerenone (CTD 4.2.2.4.2)

A system expressing each of human cytochrome P450 (CYP) isoforms (CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2J2, CYP3A4, CYP3A5, CYP3A7, CYP4A11, CYP4F2, CYP4F3A, CYP4F3B, and CYP4F12) was incubated with ^{14}C-finerenone at 1 μmol/L at 37°C, and M-1, M-2, M-3, M-4, and M-5 were formed in systems expressing CYP3A4, CYP1A1, CYP2C8, CYP3A5, and CYP3A7, M-7 and M-11 in system expressing CYP2C8, M-6 and M-14 in systems expressing CYP2C8 and CYP3A4, and M-13 in systems expressing CYP1A1.

Human liver microsomes expressing each of human CYP isoforms (CYP1A1, CYP2C8, and CYP3A4) were incubated with finerenone at 0.05 μmol/L at 37°C, and intrinsic clearance of CYP1A1, CYP2C8, and CYP3A4 was 0.22, 0.12 and 1.91 μL/min/pmol, respectively.

Human hepatocytes were incubated with finerenone at 0.2 μmol/L in the presence of an inhibitor against each of the human CYP isoforms at 37°C to investigate an effect of the CYP inhibitor on metabolism of finerenone. Metabolism of finerenone was inhibited in the presence of erythromycin (CYP3A4 inhibitor, 10 μmol/L) and verapamil (CYP3A4 inhibitor, 10 μmol/L) by 77% to 87%, in the presence of gemfibrozil glucuronide (CYP2C8 inhibitor, 100 μmol/L) by 45%, and in the presence of erythromycin + gemfibrozil glucuronide and verapamil + gemfibrozil glucuronide by 97% to 100%.

6.2.1.4 Enzyme inhibition (CTD 4.2.2.4.3, 4.2.2.4.4, 4.2.2.4.5, 4.2.2.4.6, 4.2.2.7.20, and 4.2.2.7.21)

Inhibitory effect of finerenone at 1.0 to 50 μmol/L as well as M-1a, M-1b, M-2a, and M-3a[1)] at 1.6 to 50 μmol/L against metabolism of the substrate of each CYP isoform was investigated using human liver microsomes or a system expressing each of the CYP isoforms (CYP1A1 and CYP2E1) and substrates of CYP isoforms (CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4). Finerenone inhibited CYP1A1 (7-hydroxylation of granisetron), CYP2C8 (*N*-deethylation of amodiaquine), CYP2C9 (4'-hydroxylation of diclofenac), CYP2C19 (4'-hydroxylation of mephenytoin), CYP3A4 (1'-hydroxylation of midazolam), and CYP3A4 (6β-hydroxylation of testosterone) with IC_{50} of 6.7, 6.8, 29, 31, 19, and 12 μmol/L, respectively. M-1a inhibited CYP1A1 and CYP2C9; M-1b inhibited CYP1A1, and M-3a inhibited CYP3A4, with IC_{50} values of 30 and 25, 29, and 30 μmol/L, respectively. IC_{50} of finerenone, M-1a, M-1b, M-2a, and M-3a against the other CYP isoforms was all >50 μmol/L. In addition, human liver microsomes or a system expressing CYP1A1 was incubated with finerenone at 1.0 to 50 μmol/L or M-1a, M-1b, M-2a, or M-3a at 1.6 to 50 μmol/L in the presence or absence of NADPH at 37°C for 30 minutes, followed by incubation with the substrate of each CYP isoform (CYP1A1, CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) to investigate time-dependent inhibitory effect against the substrate of each CYP isoform. Finerenone inhibited CYP1A1, CYP2C8, and CYP3A4, and M-1a, M-1b, and M-3a inhibited CYP1A1 all in a time-dependent manner. Furthermore, human liver microsomes were incubated with finerenone at 1.0 to 50 μmol/L at 37°C for 0 to 30 minutes, followed by incubation with the CYP3A4 substrate (testosterone at 50 μmol/L) in the presence or absence of NAPDH. The CYP3A4 (6β-hydroxylation of testosterone) activity decreased in a manner dependent

on finerenone concentration, incubation time, and NADPH; the inhibitory effect of finerenone against CYP3A4 was found irreversible.

Inhibitory effect of finerenone at 1.0 to 50 µmol/L as well as M-1a, M-1b, M-2a, and M-3a at 1.6 to 50 µmol/L against metabolism of the substrate of each uridine diphosphate-glucuronosyltransferase (UGT) isoform (UGT1A1, UGT1A4, UGT1A6, UGT1A9, UGT2B4, and UGT2B7) was investigated using human liver microsomes and the substrates. IC_{50} of finerenone, M-1a, M-1b, M-2a, and M-3a against glucuronide conjugation of each UGT isoform was all >50 µmol/L.

6.2.1.5 Enzyme induction (CTD 4.2.2.4.7)

Human hepatocytes (n = 3) were incubated with finerenone at 0.11 to 238 µmol/L, M-1a, M-1b, and M-3a[1)] at 0.03 to 80 µmol/L, or M-2a at 0.01 to 25 µmol/L at 37°C to investigate whether finerenone, M-1a, M-1b, M-2a, and M-3a would induce CYP1A2, CYP3A4, CYP2B6, and CYP2C19. Finerenone, M-1a, M-1b, M-2a, and M-3a did not induce mRNA expression or CYP1A2 (*O*-deethylation of phenacetin) activity. Finerenone, M-1a, M-1b, and M-2a increased mRNA expression of CYP3A4 in a concentration-dependent manner at their concentrations up to 79.3 or 238 µmol/L for finerenone, 80 µmol/L for M-1a, 80 µmol/L for M-1b, and 25 µmol/L for M-2a. The maximum expression levels at these concentrations corresponded to 77% to 135%, 63% to 85%, 69% to 80%, and 37% to 41% of the level induced by the positive control (rifampicin at 1.1 to 30 µg/mL). Finerenone did not induce the CYP3A4 (6β-hydroxylation of testosterone) activity, but M-1a, M-1b, and M-2a induced. In addition, finerenone, M-1a, and M-1b increased mRNA expression of CYP2B6 and CYP2C19. The maximum expression levels of CYP2B6 were observed at concentrations of 26.4 to 238 µmol/L for finerenone, 80 µmol/L for M-1a, and 80 µmol/L for M-1b and corresponded to 66% to 95%, 71% to 99%, and 67% to 71% of the level induced by the positive control (rifampicin at 10 to 30 µg/mL). The maximum expression levels of CYP2C19 were observed at concentrations of 26.4 to 79.3 µmol/L for finerenone, 80 µmol/L for M-1a, and 80 µmol/L for M-1b and corresponded to 48% to 71%, 54% to 133%, and 75% to 94% of the level induced by the positive control (rifampicin at 30 µg/mL).

6.2.1.6 Studies on transporters (CTD 4.2.2.7.1, 4.2.2.7.2, 4.2.2.7.3, 4.2.2.7.4, 4.2.2.7.5, 4.2.2.7.6, 4.2.2.7.7, 4.2.2.7.8, 4.2.2.7.9, 4.2.2.7.10, 4.2.2.7.11, 4.2.2.7.12, 4.2.2.7.22, 4.2.2.7.23, 4.2.2.7.24, and 4.2.2.7.25)

Finerenone at 2, 21, and 210 µmol/L were added to Caco-2 cells, and the efflux ratio (apparent permeability coefficient from the basolateral surface to the apical surface/apparent permeability coefficient from the apical surface to the basolateral surface [$P_{app\ B\rightarrow A}/P_{app\ A\rightarrow B}$]) of finerenone was 2.3, 1.5, and 0.9, respectively.

Finerenone at 0.2 to 100 µmol/L and 0.2 to 100 µmol/L were added to Lilly laboratory culture porcine kidney (LLC-PK)1 cells expressing P-glycoprotein (P-gp) and the control cells, and the efflux ratios of finerenone ($P_{app\ B\rightarrow A}/P_{app\ A\rightarrow B}$) were 4.2 to 7.2 and 0.6 to 0.8, respectively.

Finerenone at 0.2 to 100 µmol/L were added to Madin-Darby canine kidney (MDCK) II cells expressing breast cancer resistance protein (BCRP) and the control cells, and the efflux ratios of finerenone ($P_{app\ B\rightarrow A}/P_{app\ A\rightarrow B}$) were 0.50 to 1.3 and 0.55 to 1.1, respectively.

^{14}C-finerenone at 0.5 to 5 μmol/L were added to HEK cells expressing organic anion transporting polypeptide (OATP)1B1 and OATP1B3, and the intracellular finerenone concentration ratios of transporter-gene-transfected cells to vector-transfected cells were 1.0 and 0.9, respectively.

Finerenone at 0.1 to 0.5 μmol/L were added to HEK cells expressing organic cation transporter (OCT)1, and the intracellular finerenone concentration ratio of transporter-gene-transfected cells to vector-transfected cells was 1.00 to 1.11.

Digoxin at 20 μmol/L or dipyridamole at 2 μmol/L (both, substrates of P-gp) and finerenone at 0.6 to 600 μmol/L, M-1a at 0.1 to 100 μmol/L, or M-1b, M-2a and M-3a[1)] at 0.1 to 30 μmol/L were added to LLC-PK1 cells expressing P-gp. Finerenone inhibited P-gp-mediated transport of digoxin and dipyridamole with IC_{50} of 121 and 47 μmol/L, respectively; and M-1a and M-1b inhibited P-gp-mediated transport of dipyridamole with IC_{50} of 70 and 31 μmol/L, respectively.

Topotecan or 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) at 2 μmol/L (both, substrates of BCRP) and finerenone at 0.1 to 300 μmol/L, M-1a, M-2a and M-3a at 20 μmol/L, or M-1b at 0.1 to 30 μmol/L were added to MDCKII cells expressing BCRP. Finerenone inhibited BCRP-mediated transport of Topotecan and PhIP with IC_{50} of 18.1 and 17.4 μmol/L, respectively. Of M-1a, M-1b, M-2a, and M-3a, on the other hand, none inhibited BCRP-mediated transport of Topotecan or PhIP with IC_{50} >20 μmol/L for M-1a, M-2a, and M-3a and >30 μmol/L for M-1b.

To human hepatocytes in sandwich culture, d8-taurocholic acid (d8-TCA) (substrate of bile salt export pump [BSEP]) at 5 μmol/L and finerenone at 0.1 to 100 μmol/L or M-1a, M-1b, M-2a and M-3a at 0.03 to 30 μmol/L were added. Finerenone, M-1a, M-1b, M-2a and M-3a did not inhibit BSEP-mediated transport of d8-TCA.

Metformin at 50 μmol/L and finerenone at 0.5 to 5 μmol/L or M-1a, M-1b, M-2a and M-3a at 0.5 to 5 μmol/L were added to HEK cells expressing multidrug and toxin extrusion (MATE)1 and MATE2K. Finerenone, M-1a, M-1b, M-2a, and M-3a did not inhibit MATE1- or MATE2K-mediated transport of metformin.

To HEK cells expressing OATP1B1, OATP1B3, organic anion transporter (OAT)1, OAT3, OCT1, and OCT2, the following was added: Substrate of each transporter (pravastatin at 5 μmol/L for OATP1B1 and OATP1B3; p-aminohippuric acid (PAH) at 10 μmol/L for OAT1; furosemide at 5 μmol/L for OAT3; and 1-methyl-4-phenylpyridinium (MPP^+) at 5 μmol/L for OCT1 and OCT2) and finerenone (0.2-10 μmol/L for OATP1B1 and OATP1B3; 0.3-3 μmol/L for OAT1, OAT3, and OCT2; and 0.5-5 μmol/L for OCT1), M-1a (0.2-10 μmol/L for OATP1B1 and OATP1B3; 0.25-2.47 μmol/L for OAT1, OAT3, and OCT2; and 0.85-8.5 μmol/L for OCT1), M-1b (0.2-10 μmol/L for OATP1B1 and OATP1B3; 0.52-5.16 μmol/L for OAT1, OAT3, and OCT2; and 0.72-7.17 μmol/L for OCT1), M-2a (0.2-10 μmol/L for OATP1B1 and OATP1B3; 0.31-3.1 μmol/L for OAT1, OAT3, and OCT2; and 0.36-3.57 μmol/L for OCT1), or M-3a (0.2-10 μmol/L for OATP1B1 and OATP1B3; and 0.43-4.25 μmol/L for OAT1, OAT3, OCT2, and OCT1). Finerenone, M-1a and M-1b inhibited

OATP1B1-mediated transport with IC_{50} of 3.2, 3.8, and 3.9 μmol/L, respectively, and M-1a, M-1b, and M-3a inhibited OATP1B3-mediated transport with IC_{50} of 7.6, 7.3, and 3.4 μmol/L, respectively.

6.2.2 Studies in healthy adults

6.2.2.1 Single dose study in healthy non-Japanese adults (Study 15481, CTD 5.3.1.2.4 [Reference data], Study period, September to November 2012)

A 5-treatment, 5-period crossover study (a ≥3-day washout period) was conducted in 24 healthy adult non-Japanese men who orally received a single dose of finerenone 1.25, 2.5, 5, 7.5, or 10 mg in the fasted state during a treatment period. Table 18 shows PK parameters of finerenone in this study.

Table 18. PK parameters of finerenone after single oral administration

Dose (mg)	n	C_{max} (μg/L)	t_{max} [a] (h)	$AUC_{0-\infty}$ (μg·h/L)	$t_{1/2}$ (h)
1.25	24	11.8 (27.4)	0.750	28.4 (37.0)	1.96 (24.9)
2.5	24	23.9 (27.2)	0.500	55.6 (26.1)	2.02 (15.2)
5	24	45.6 (28.3)	0.750	118 (31.8)	2.10 (23.6)
7.5	24	72.1 (26.6)	0.750	193 (31.9)	2.15 (20.6)
10	24	82.3 (40.0)	0.625	216 (40.1)	2.25 (28.8)

Geometric mean (coefficient of variation, %)
a Median

6.2.2.2 Multiple-dose study in healthy non-Japanese adults (Study 13785, CTD 5.3.3.1.2 [Reference data], Study period, August to December 20[redacted])

A total of 29 healthy adult non-Japanese men orally received finerenone 10 mg twice daily, 20 mg twice daily, or 40 mg once daily for 10 days (once daily only on Day 10). Table 19 shows PK parameters of finerenone, M-1, M-2, and M-3. In all dose groups, finerenone, M-1, M-2, and M-3 accounting for 0.952% to 1.40%, 0.363% to 0.502%, 12.8% to 15.0%, and 35.0% to 45.1%, respectively, of the respective dose were excreted into urine for 24 hours post-dose.

Table 19. PK parameters after multiple oral administration of finerenone

Dose (mg)	n	Measurement point (Day)	C_{max} (μg/L)	t_{max} [a] (h)	AUC (μg·h/L)	$t_{1/2}$ (h)
PK parameters of finerenone						
10	11	1	90.5 (37.3)	0.750	208 (34.7)[b]	1.78 (13.7)
	9	10	94.5 (30.9)	0.750	233 (32.7)[c]	2.56 (46.7)
20	9	1	177 (40.0)	0.500	319 (21.3)[b]	1.69 (10.9)
	9	10	171 (39.2)	0.750	421 (27.4)[c]	2.83 (39.7)
40	9	1	287 (44.8)	0.750	929 (62.2)[b]	3.04 (27.5)
	9	10	259 (27.3)	1.00	1020 (55.4)[c]	3.11 (36.7)
PK parameters of M-1						
10	11	1	145 (19.8)	1.00	863 (27.8)[d]	-
	9	10	189 (33.2)	1.00	1280 (47.8)[c]	9.27 (32.6)
20	9	1	246 (28.6)	0.750	1210 (39.3)[d]	-
	9	10	320 (26.2)	1.50	2080 (41.2)[c]	8.87 (32.8)
40	9	1	489 (42.5)	1.50	4640 (65.9)[d]	-
	9	10	541 (30.4)	2.50	5730 (59.9)[c]	10.1 (29.1)
PK parameters of M-2						
10	11	1	51.3 (29.5)	4.00	406 (23.7)[d]	-
	9	10	76.4 (23.8)	2.50	668 (29.4)[c]	8.58 (27.9)
20	9	1	97.5 (19.6)	2.50	742 (12.4)[d]	-
	9	10	140 (15.0)	2.50	1190 (14.9)[c]	7.68 (20.1)
40	9	1	168 (30.5)	4.00	2150 (15.7)[d]	-
	9	10	195 (17.2)	4.00	2800 (24.3)[c]	8.97 (26.5)
PK parameters of M-3						
10	11	1	16.6 (39.2)	4.00	142 (37.2)[d]	-
	9	10	24.6 (20.7)	2.75	245 (19.1)[c]	7.45 (26.8)
20	9	1	41.9 (33.8)	4.00	354 (25.8)[d]	-
	9	10	51.4 (31.0)	4.00	495 (25.0)[c]	7.25 (20.2)
40	9	1	52.3 (77.9)	6.00	743 (63.1)[d]	-
	9	10	60.5 (62.0)	6.00	940 (46.6)[c]	

Geometric mean (coefficient of variation, %); -, Not calculated
a Median
b $AUC_{0-\infty}$
c AUC_{τ}
d AUC_{0-t}

6.2.2.3 Multiple-dose study in healthy Japanese adults (Study 15171, CTD 5.3.3.1.4, Study period, February to May 20[redacted])

A total of 27 healthy adult Japanese men orally received finerenone 10 mg twice daily, 20 mg twice daily, or 40 mg once daily for 10 days (once daily only on Days 1 and 10). Table 20 shows PK parameters of finerenone.

Table 20. PK parameters of finerenone after multiple oral administration

Dose (mg)	n	Measurement point (Day)	C_{max} (μg/L)	t_{max} [a] (h)	AUC_{τ} (μg·h/L)	$t_{1/2}$ (h)
10	9	1	123 (39.3)	1.00	275 (34.0)	2.06 (23.6)
	9	10	145 (47.4)	1.00	421 (50.2)	2.47 (26.3)
20	9	1	213 (30.8)	0.75	440 (36.5)	1.97 (21.8)
	9	10	274 (19.5)	0.75	653 (35.3)	2.52 (31.6)
40	9	1	483 (49.8)	0.75	1220 (34.4)	2.64 (20.3)
	9	10	519 (36.9)	0.75	1630 (32.1)	2.82 (12.0)

Geometric mean (coefficient of variation, %)
a Median

6.2.2.4 Mass balance study (Study 14502, CTD 5.3.1.2.3 [Reference data], Study period, August to October 20[redacted])

A single dose of ^{14}C-finerenone 10 mg was administered orally to 4 healthy adult non-Japanese men using an oral solution, and urinary excretion rate of radioactivity (percentage relative to the administered radioactivity) up to 48 and 240 hours post-dose was 77.5% and 79.6%, respectively, and fecal excretion rate of radioactivity up to 96 and 240 hours post-dose was 19.9% and 21.2%, respectively. In urine, finerenone, M-2, M-3, M-4, and M-5 accounting for 0.825%, 13.1%, 46.3%, 3.95%, and 2.72%, respectively, were excreted, and in feces, finerenone, M-1, M-2, M-3, M-4, and M-5 accounting for 0.184%, 0.0506%, 1.86%, 1.48%, 0.823%, and 9.40%, respectively, were excreted. In plasma, finerenone, M-1, M-2, M-3, M-4/M-7,[6)] and M-5 accounted for 7.1%, 48.9%, 21.5%, 9.0%, 2.4%, and 1.4%, respectively, of AUC of the total radioactivity. Neither chiral inversion nor racemization was observed in any plasma specimens analyzed.

6.2.3 Studies in patients

6.2.3.1 PPK analysis (Analysis 18523, CTD 5.3.3.5.9 [Reference data])

A population pharmacokinetics (PPK) analysis was performed on plasma finerenone concentration data from 5057 sampling points in 2284 patients in the global phase III study in patients with CKD associated with type 2 diabetes mellitus (Study 16244). The PK of finerenone was described as a linear 2-compartment model with the first-order elimination from the central compartment.

Potential covariates for PK parameters (V_c/F, CL/F, and F) included age, body weight, body height, body mass index (BMI), body surface area, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), serum creatinine, γ-glutamyl transpeptidase (GGT), albumin, bilirubin, total protein, lean body mass, baseline eGFR (estimate according to the modification of diet in renal disease [MDRD] equation), baseline eGFR (estimate according to the Chronic kidney disease epidemiology collaboration [CKD-EPI] equation), eGFR at a sampling point (estimate according to the MDRD equation), eGFR at a sampling point (estimate according to the CKD-EPI equation), gender, alcohol consumption, smoking status, race,[7)] ethnic group,[8)] Child-Pugh classification, concomitant sodium-glucose cotransporter (SGLT)2 inhibitor, concomitant CYP3A4 inducer, concomitant CYP3A4 inhibitor, and eGFR category. Other than the already identified covariates of body weight for V_c/F and eGFR-EPI[9)] for CL/F and F, ones additionally identified for the final model were Korean (race) for V_c/F, body height, serum creatinine, smoking status, and concomitant SGLT2 inhibitor for CL/F and F, and GGT for CL/F.

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7) American Indian or Alaska Native, Asian Indian, Black or African American, Chinese, Japanese, Korean, Multiple, Native Hawaiian or other Pacific Islander, not reported, others, Thailander, Caucasian

8) Hispanic or Latino, non-Hispanic, unknown

9) Covariates identified in the PPK analysis on data from Japanese phase II study (Study 16816) and foreign phase II study (Study 16243) in patients with chronic kidney disease associated with type 2 diabetes mellitus.

6.2.4 Study of intrinsic factors

6.2.4.1 Effects of age and gender on PK (Study 14508, CTD 5.3.3.3.2 [Reference data], Study period, February to May 20[redacted])

A total of 36 healthy non-Japanese adults (9 each of young men and women aged 18 to 45 years, 9 each of elderly men and women aged 65 to 80 years) orally received a single dose of finerenone 10 mg in the fasted state. Table 21 shows effects of age and gender on PK parameters of finerenone.

Table 21. Geometric mean ratios of PK parameters

	C_{max}	$AUC_{0-\infty}$
Elderly men/young men	1.2442 [0.9572, 1.6172]	1.2030 [0.9633, 1.5024]
Elderly women/young women	1.8346 [1.4115, 2.3846]	1.4935 [1.1959, 1.8652]
Young women/young men	0.8510 [0.6547, 1.1061]	1.0072 [0.8065, 1.2578]
Elderly men/elderly women	1.2548 [0.9654, 1.6310]	1.2504 [1.0012, 1.5616]

Geometric mean ratio [90% CI]

6.2.4.2 PK in subjects with renal impairment (Study 14509, CTD 5.3.3.3.1 [Reference data], Study period, October 20[redacted] to May 20[redacted])

A single dose of finerenone 10 mg was administered orally in the fasted state to 6 to 11 non-Japanese subjects each with mild (CL_{cr} ≥60 mL/min and <90 mL/min), moderate (CL_{cr} ≥30 mL/min and <60 mL/min), and severe (CL_{cr} ≥15 mL/min and <30 mL/min) renal impairment and 7 non-Japanese subjects with normal renal function (CL_{cr} ≥90 mL/min) of whom age, body weight, and gender were matched to those of subjects with renal impairment. Table 22 shows geometric mean ratios of PK parameters of finerenone in subjects with renal impairment to those in subjects with normal renal function.

Table 22. Geometric mean ratios of PK parameters

	C_{max}	$AUC_{0-\infty}$
Subjects with mild renal impairment	1.2234 [0.7851, 1.9064]	0.8529 [0.4836, 1.5040]
Subjects with moderate renal impairment	1.1306 [0.7689, 1.6623]	1.5144 [0.9250, 2.4794]
Subjects with severe renal impairment	0.9190 [0.6150, 1.3735]	1.3620 [0.8147, 2.2769]

Geometric mean ratio [90% CI]

6.2.4.3 PK in subjects with hepatic impairment (Study 14510, CTD 5.3.3.3.3 [Reference data], Study period, March to September 2014)

A single dose of finerenone 5 mg was administered orally in the fasted state to 9 non-Japanese subjects with mild (Child-Pugh class A) and moderate (Child-Pugh class B) hepatic impairment and 9 subjects with normal hepatic function of whom age, body weight, and gender were matched to those with hepatic impairment. Table 23 shows geometric mean ratios of PK parameters of finerenone in subjects with hepatic impairment to those in subjects with normal hepatic function.

Table 23. Geometric mean ratios of PK parameters

	C_{max}	$AUC_{0-\infty}$
Subjects with mild hepatic impairment	0.9643 [0.7256, 1.2816]	1.0838 [0.8169, 1.4379]
Subjects with moderate hepatic impairment	0.9910 [0.7457, 1.3172]	1.3827 [1.0422, 1.8344]

Geometric mean ratio [90% CI]

6.2.5 Drug interaction studies

6.2.5.1 Pharmacokinetic drug interactions

6.2.5.1.1 Omeprazole and antacids (Study 14506, CTD 5.3.3.4.1 [Reference data], Study period, November 20[redacted] to January 20[redacted])

A 3-treatment, 3-period crossover study (a ≥4-day washout period) was conducted in 11 healthy adult non-Japanese men. In this study, (a) a single dose of finerenone 10 mg was orally administered; (b) omeprazole 40 mg was orally administered once daily for 4 days, and at 2 hours after a single oral administration of omeprazole 40 mg on Day 5, a single dose of finerenone 10 mg was orally administered; or (c) immediately after a single dose of antacids (aluminum oxide 900 mg and magnesium hydroxide 600 mg), a single dose of finerenone 10 mg was orally administered. The geometric mean ratios [90% CI] of C_{max} and $AUC_{0-\infty}$ of finerenone after (b) co-administration of finerenone and omeprazole to those after (a) administration of finerenone alone were 0.9881 [0.8066, 1.2104] and 1.0452 [0.9260, 1.1796]. The geometric mean ratios [90% CI] of C_{max} and $AUC_{0-\infty}$ of finerenone after (c) co-administration of finerenone and antacids to those after (a) administration of finerenone alone were 0.8116 [0.6571, 1.0024] and 1.0220 [0.9011, 1.1591].

6.2.5.1.2 Erythromycin (Study 14504, CTD 5.3.3.4.2 [Reference data], Study period, April to May 20[redacted])

A 2-treatment, 2-period crossover study (a ≥7-day washout period) was conducted in 15 healthy adult non-Japanese men. In this study, a single dose of finerenone 1.25 mg was orally administered; or erythromycin 500 mg was orally administered 3 times a day for 4 days, and on Day 5 a single dose of finerenone 1.25 mg was orally administered with erythromycin 500 mg. The geometric mean ratios [90% CI] of C_{max} and AUC_{0-t} of finerenone, M-1, M-2, and M-3 after co-administration of finerenone and erythromycin to those after administration of finerenone alone were 1.8824 [1.6312, 2.1723] and 3.5072 [3.0426, 4.0427] for finerenone, 0.8622 [0.8251, 0.9008] and 2.5150 [2.2397, 2.8242] for M-1, 0.5195 [0.4663, 0.5801] and 1.2474 [1.1439, 1.3602] for M-2, and 0.2728 [0.2403, 0.3097] and 0.1807 [0.1107, 0.2949] for M-3.

6.2.5.1.3 Verapamil (Study 16910, CTD 5.3.3.4.7 [Reference data], Study period, July to September 20[redacted])

A dosage regimen of a study in 13 healthy adult non-Japanese men was as follows: Period 1, a single dose of finerenone 5 mg was orally administered; and Period 2, verapamil 120 mg was orally administered once daily 3 days before administration of finerenone and then verapamil 240 mg was orally administered once daily for 2 days, and at 6 hours after a single oral dose of verapamil 240 mg on administration day of finerenone, a single dose of finerenone 5 mg was orally administered. The geometric mean ratios [90% CI] of C_{max} and AUC_{0-t} of finerenone, M-1, M-2, and M-3 after co-administration of finerenone and verapamil with to those after administration of finerenone alone were 2.2228 [1.8847, 2.6216] and 2.7050 [2.4308, 3.0101] for finerenone, 0.8364 [0.7469, 0.9366] and 1.7054 [1.5593, 1.8652] for M-1, 0.7161 [0.6567, 0.7809] and 1.0434 [0.9433, 1.1540] for M-2, and 0.3848 [0.3478, 0.4258] and 0.4823 [0.4318, 0.5388] for M-3.

6.2.5.1.4 Gemfibrozil (Study 15112, CTD 5.3.3.4.5 [Reference data], Study period, March to May 20[redacted])

A 2-treatment, 2-period crossover study (a ≥7-day washout period) was conducted in 16 healthy adult non-Japanese men. In this study, a single dose of finerenone 10 mg was orally administered; or gemfibrozil 600 mg was orally administered twice daily for 4 days, and at 1 hour after a single oral dose of gemfibrozil 600 mg on Day 5, a single dose of finerenone 10 mg was orally administered, followed by a single oral administration of gemfibrozil 600 mg 9 hours 30 minutes later. The geometric mean ratios [90% CI] of C_{max} and $AUC_{0-\infty}$ of finerenone, M-1, M-2, and M-3 after co-administration of finerenone and gemfibrozil with to those after administration of finerenone alone were 1.1567 [0.9559, 1.3998] and 1.1005 [0.9855, 1.2289] for finerenone, 1.0847 [0.9516, 1.2365] and 1.0556 [0.9393, 1.1861] for M-1, 1.0863 [1.0076, 1.1711] and 1.0642 [0.9860, 1.1486] for M-2, and 0.9774 [0.8808, 1.0846] and 0.9554 [0.8933, 1.0217] for M-3.

6.2.5.1.5 Midazolam (Study 15111, CTD 5.3.3.4.8 [Reference data], Study period, September to December 20[redacted])

A 2-treatment, 2-period crossover study (a ≥9-day washout period) was conducted in 30 healthy adult non-Japanese men. In this study, a single dose of midazolam 7.5 mg was orally administered; or finerenone 20 mg was orally administered once daily for 9 days, and a single dose of finerenone 20 mg was orally administered with midazolam 7.5 mg on Day 10. The geometric mean ratios [90% CI] of C_{max} and $AUC_{0-\infty}$ of midazolam and 1'-hydroxymidazolam after co-administration of midazolam and finerenone to those after administration of midazolam alone were 1.0921 [0.8979, 1.3283] and 1.1056 [1.0190, 1.1995] for midazolam and 0.9938 [0.7895, 1.2509] and 0.9962 [0.9118, 1.0885] for 1'-hydroxymidazolam.

6.2.5.1.6 Repaglinide (Study 16541, CTD 5.3.3.4.3 [Reference data], Study period, September to December 20[redacted])

A 3-treatment, 3-period crossover study (a ≥7-day washout period) was conducted in 28 healthy adult non-Japanese men. In this study, (a) a single dose of repaglinide 0.5 mg was orally administered; (b) a single dose of repaglinide 0.5 mg was orally administered with finerenone 20 mg; or (c) at 3 hours after a single oral administration of finerenone 20 mg, a single dose of repaglinide 0.5 mg was orally administered. The geometric mean ratios [90% CI] of C_{max} and $AUC_{0-\infty}$ of finerenone after (b) and (c) co-administration of repaglinide and finerenone to those after (a) administration of repaglinide alone were 1.0449 [0.9557, 1.1425] and 1.1159 [1.0592, 1.1757] for (b)/(a) and 1.0452 [0.9559, 1.1428] and 1.1019 [1.0452, 1.1617] for (c)/(a).

6.2.5.1.7 Warfarin (Study 14503, CTD 5.3.3.4.4 [Reference data], Study period, October 20[redacted] to February 20[redacted])

A 2-treatment, 2-period crossover study was conducted in 24 healthy adult non-Japanese men to investigate effects of finerenone on the PK and pharmacodynamic action of warfarin. During the warfarin-alone period, placebo was orally administered once daily for 6 days, and a single dose of warfarin 25 mg was orally co-administered on Day 3. During the finerenone co-administration period, finerenone 20 mg was orally administered once daily for 6 days, a single dose of warfarin 25 mg was orally co-administered on Day 3. These periods were separated by a washout period of ≥17 days. The

geometric mean ratios [90% CI] of C_{max} and $AUC_{0-\infty}$ of warfarin after co-administration of warfarin and finerenone with to those after administration of warfarin alone were 1.0355 [0.9983, 1.0742] and 0.9925 [0.9627, 1.0233] for *R*-warfarin and 1.0294 [0.9930, 1.0672] and 0.9953 [0.9678, 1.0236] for *S*-warfarin. In addition, prothrombin time after administration of warfarin alone was almost the same as that after co-administration of warfarin and finerenone.

6.2.5.1.8 Digoxin (Study 14505, CTD 5.3.3.4.6 [Reference data], Study period, June to September 20[redacted])

A 2-treatment, 2-period crossover study (a ≥5-day washout period) was conducted in 24 healthy adult non-Japanese men. In this study, a single dose of finerenone 20 mg was orally administered followed by once-daily oral administration of digoxin 0.375 mg for 14 days; or during a period in which digoxin 0.375 mg was orally administered once daily for 14 days, finerenone 20 mg was orally administered once daily on Days 5 to 14. The geometric mean ratios [90% CI] of C_{trough} and AUC_{τ} of digoxin after co-administration of digoxin and finerenone to those after administration of digoxin alone were 0.9670 [0.8863, 1.0550] and 1.0172 [0.9540, 1.0846].

6.2.6 QT/QTc evaluation study (Study 15113, CTD 5.3.4.1.2, Study period, June to October 20[redacted])

A 4-treatment, 4-period crossover study (a ≥7-day washout period) was conducted in 60 healthy non-Japanese adults (n = 30/sex) who orally received a single dose of finerenone 20 or 80 mg, moxifloxacin 400 mg, or placebo during a treatment period.

After single oral administration of finerenone 20 or 80 mg, C_{max} (geometric mean [coefficient of variation (CV), %]) was 150 (37.5) and 597 (39.8) µg/L, respectively, $AUC_{0-\infty}$ (geometric mean [CV, %]) was 423 (35.7) and 1970 (37.5) µg·h/L, respectively, and t_{max} (median) was 0.800 h for both doses.

Of differences in mean change from baseline in QTcF between subjects receiving finerenone 20 or 80 mg and subjects receiving placebo (ΔΔQTcF), the upper limit of the one-sided 95% CIs was <10 ms at all sampling points. The lower limit of the one-sided 95% CIs of ΔΔQTcF after administration of moxifloxacin exceeded 5 ms at all sampling points between 1 and 6 hours post-dose.

6.R Outline of the review conducted by PMDA

6.R.1 Difference in PK between Japanese and non-Japanese subjects

The applicant's explanation about difference in PK of finerenone between Japanese and non-Japanese subjects:

After a single oral administration or the first dose of multiple oral administration of finerenone in healthy adults who were Japanese subjects (Study 15171, n = 27, mean body weight of 65.8 kg) or Caucasian subjects (Studies 13784, 13785, 14502, 14504, 14506, 14508, 14509, 14510, 15112, 15113, 15481, 15526, 16535, 16536, 16538, 16910, 18290, and 19092; n = 404; mean body weight of 80.6 kg), the geometric means (CV, %) of dose-adjusted AUC and C_{max} were 26.7 (36.9) µg·h/L/mg and 11.7 (39.4) µg/L/mg, respectively, in Japanese subjects and 19.9 (35.1) µg·h/L/mg and 8.03 (34.2) µg/L/mg, respectively, in Caucasian subjects, and the geometric mean ratios [90% CI] of

dose-adjusted AUC and C_{max} in Japanese subjects than those in Caucasian subjects were 1.385 [1.235, 1.554] and 1.493 [1.337, 1.668], respectively. The trend of higher exposure in Japanese subjects than in Caucasian subjects was considered attributable to lower mean body weight in Japanese subjects than in Caucasian subjects. In addition, the PPK analysis on plasma finerenone concentration data from the global phase III study (Study 16244) in patients with CKD associated with type 2 diabetes mellitus [see Section "6.2.3.1 PPK analysis"] showed that median estimates [first quartile, third quartile] of AUC_{τ} and C_{max} at steady state after once-daily administration of finerenone 20 mg were 695 [595, 838] μg·h/L and 175 [155, 211] μg/L, respectively, in Japanese patients and 656 [561, 785] μg·h/L and 152 [134, 174] μg/L, respectively, in Caucasian patients, between which no clear differences were observed. Based on the above, there are no differences in PK between Japanese and non-Japanese patients with CKD associated with type 2 diabetes mellitus that may impact the efficacy or safety of finerenone.

PMDA's view:
The PPK analysis on plasma finerenone concentration data in patients with CKD did not indicate any clear differences in exposure to finerenone between Japanese and Caucasian patients, but data from clinical studies in healthy Japanese and Caucasian adults showed that exposure to finerenone tended to be higher in Japanese than in Caucasians; AUC and C_{max} in Japanese were 1.385 and 1.493 times higher than those in Caucasians. The difference was explained to be potentially attributable to the difference in body weight. Finerenone, however, is intended to be administered at a fixed dose irrespective of the body weight. PMDA therefore considers it necessary to review whether it is appropriate to apply the dosage regimen of finerenone for non-Japanese patients to Japanese patients as well in Section "7.R.7 Dosage and administration" continuously in view of dose-response relationships of the efficacy and safety in Japanese and foreign clinical studies.

6.R.2 Variations of exposure to finerenone in patients with hepatic impairment

The applicant's explanation about use of finerenone in patients with hepatic impairment:
In the foreign phase I study (Study 14510) in which finerenone was administered to subjects with mild (Child-Pugh class A) and moderate (Child-Pugh class B) hepatic impairment and subjects with normal hepatic function to investigate the effect of hepatic impairment on PK of finerenone, AUC and C_{max} of finerenone did not differ between subjects with mild hepatic impairment and subjects with normal hepatic function; and AUC was 1.38 times higher in subjects with moderate hepatic impairment than in subjects with normal hepatic function but C_{max} did not differ [see Section "6.2.4.3 PK in subjects with hepatic impairment"]. The small effect of hepatic impairment on AUC was considered attributable to the low hepatic elimination of finerenone (24.4%), of which CYP3A4-mediated first pass metabolism occurs on the intestinal wall. The effect of severe (Child-Pugh class C) hepatic impairment on PK of finerenone has not been investigated because patients with severe hepatic impairment were excluded from clinical studies. The exposure to finerenone predicted on the basis of the Child-Pugh score is unlikely to be correct, and information allowing estimation of plasma concentrations in patients with severe hepatic impairment is not available. The applicant, however, considers it probable for severe hepatic impairment to increase exposure to finerenone. Administration of finerenone 10 mg to patients with severe hepatic impairment would result in plasma concentrations higher than those after administration of finerenone 20 mg to patients without hepatic impairment,

potentially leading to increased serum potassium levels. Thus, the package insert will provide a cautionary statement that use of finerenone in patients with severe hepatic impairment should be avoided.

PMDA's view:
In subjects with mild hepatic impairment, exposure to finerenone was not increased compared with that in subjects with normal hepatic function, and in subjects with moderate hepatic impairment, the exposure to finerenone was increased. In view of the extent of the increase and from a pharmacokinetic viewpoint, PMDA considers it unnecessary to give cautionary advice such as dose reduction to the concerned patient population. In patients with severe hepatic impairment, finerenone has not been used, leaving an extent of the increase in exposure to finerenone unknown, and it cannot be ruled out that the increased exposure may exceed the qualified level. Accordingly, finerenone, if administered to such patients, would cause serious effects such as serious hyperkalaemia. For the dosage regimen in patients with hepatic impairment and cautionary statement in the package insert, details should be discussed based on not only PK data in this section but also clinical study results [see Section "7.R.3.4 Use of finerenone in patients with hepatic impairment"].

6.R.3 CYP3A4-mediated drug-drug interactions

The applicant's explanation about drug-drug interactions after co-administration of finerenone and CYP3A4 inhibitor or inducer:
Results from *in vitro* studies in human hepatocytes indicated that CYP3A4 was primarily responsible for metabolism of finerenone in the liver, and CYP2C8 was responsible for the remainder [see Section "6.2.1.3 Identification of CYP isoforms involved in metabolism of finerenone"]. In clinical pharmacology studies (Studies 14504 and 16910), the geometric mean ratios [90% CI] of C_{max} and AUC_{0-t} of finerenone after co-administration of finerenone and erythromycin or verapamil (moderate CYP3A4 inhibitor for either) to those after administration of finerenone alone were 1.8824 [1.6312, 2.1723] and 3.5072 [3.0426, 4.0427] or 2.2228 [1.8847, 2.6216] and 2.7050 [2.4308, 3.0101], respectively [see Sections "6.2.5.1.2 Erythromycin" and "6.2.5.1.3 Verapamil"]. In addition, by a physiologically-based pharmacokinetics (PBPK) model analysis,[10)] geometric mean ratios (CV, %) of C_{max} and AUC_{0-t} of finerenone after co-administration of finerenone and each of itraconazole (potent CYP3A4 inhibitor) 200 mg twice daily, clarithromycin (potent CYP3A4 inhibitor) 500 mg twice daily, fluvoxamine (weak CYP3A4 inhibitor) 100 mg twice daily, rifampicin (potent CYP3A4 inducer) 600 mg once daily, and efavirenz (moderate CYP3A4 inducer) 600 mg one daily to administration of finerenone alone were estimated to be 2.37 (20) and 6.31 (39), 2.25 (17) and 5.28 (40), 1.38 (10) and 1.57 (16), 0.14 (20) and 0.07 (25), and 0.32 (18) and 0.19 (21), respectively. In addition, PPK analysis[11)] on data including the foreign phase II study (Study 14563) showed that concomitant amiodarone (weak CYP3A4 inhibitor) would increase AUC of finerenone 1.21 times.

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10) PK-Sim was used. The PBPK model used was verified by the following results: Estimated time-course blood concentrations after administration of finerenone almost agreed with measured values on time-course blood concentrations after a single-dose administration and multiple-dose administration of finerenone; predicted geometric mean ratios of C_{max} and AUC after co-administration of finerenone and erythromycin or verapamil were almost consistent with measured values in clinical studies; and in PBPK models of CYP3A4 inhibitors and inducers, estimated time-course blood concentrations after co-administration of a CYP3A4 inhibitor or inducer and CYP3A4 substrate almost agreed with the measured values.

11) PPK analysis (Analysis 13880, CTD 5.3.3.5.3 [Reference data]) performed on plasma finerenone concentration data from foreign phase I studies in healthy adults (Studies 13782, 13784, 13785, 14508, 14509, and 13786) and a foreign phase II study in patients with chronic heart failure (Study 14563)

In view of the above, potent CYP3A4 inhibitors, if co-administered, may remarkably increase blood concentrations of finerenone, and thus co-administration with these inhibitors was proposed to be contraindicated. Moderate and weak CYP3A4 inhibitors, if co-administered, may increase plasma concentrations of finerenone, but Study 16244 in which the dose was adjusted according to serum potassium showed that exposure to finerenone inversely correlated with serum potassium, leading to the applicant's view that such co-administration could be accommodated by appropriate monitoring and dose adjustment. The applicant therefore proposed to list these inhibitors in the Precautions for Co-administration section and provide cautionary statements that patient's conditions including the serum potassium level should be carefully monitored when finerenone is started or the dose is adjusted, and the dose should be adjusted according to serum potassium. In addition, potent or moderate CYP3A4 inducers, if co-administered, may remarkably decrease blood concentrations of finerenone, resulting in its reduced efficacy. The applicant therefore proposed to list these inducers in the Precautions for Co-administration section and provide a cautionary statement that substitution of a non-CYP3A4 inducing drug or weak inducer should be considered.

PMDA's view:

Because the PBPK model was verified by measured values and estimates for co-administration with moderate CYP3A4 inhibitors, estimated exposure for co-administration with a CYP3A4 inhibitor or inducer in the concerned PBPK model is potentially unreliable for quantitative discussion. The safety data on finerenone administered at a daily dose of >20 mg in clinical studies, however, are limited, and actually co-administration with erythromycin and verapamil, moderate CYP3A4 inhibitors, increased AUC of finerenone 3.5 and 2.7 times. In view of the above, PMDA considers it necessary to advise a caution about co-administration with CYP3A4 inhibitors. Concerning co-administration with moderate and weak CYP3A4 inhibitors, the applicant proposed to list them in the Precautions for Co-administration section in view of the extent of the increase in exposure to finerenone by the co-administration and to provide the cautionary statement that a risk associated with the increased exposure should be controlled by monitoring serum potassium levels, etc. Concerning co-administration with potent CYP3A4 inhibitors, which were expected to further increase the exposure than moderate ones, the applicant proposed to contraindicate co-administration with these inhibitors in view of the limited experience with their concomitant use in clinical studies. PMDA accepted the above applicant's proposals. Concerning co-administration with CYP3A4 inducers, the applicant proposed to provide a cautionary statement that concomitant use of these inducers should be avoided wherever possible in view of potential loss of the efficacy of finerenone resulted from the co-administration. PMDA accepted the applicant's proposal. In addition, because experience with concomitant use of CYP3A4 inhibitors and inducers in clinical studies is limited, the applicant should collect information continuously and provide new findings to healthcare professionals immediately when they become available. For cautionary statements on drug-drug interactions with finerenone, PMDA will make a final conclusion, taking account of comments raised in the Expert Discussion.

6.R.4 BE between to-be-marketed formulations

The applicant's explanation about BE between 10 and 20 mg tablets to-be-marketed formulations:

The level of formulation changes between the 10 mg and 20 mg tablets corresponds to "Level [redacted]" according to the "Guideline for Bioequivalence Studies for Different Strengths of Oral Solid Dosage Forms" (PMSB/ELD Notification No. 64 dated February 14, 2000, partially revised by PFSB/ELD Notification No. 0229-10 dated February 29, 2012) (BE Guidelines for Different Strengths). The dissolution test performed in accordance with the guidelines revealed that the 10 mg tablets dissolved faster than the 20 mg tablets under the test condition at pH 5.0. This result did not meet the criteria for BE defined in the BE Guidelines for Different Strengths. In response to this finding, a human BE study (Study 21325) using the 10 mg tablets and 20 mg tablets, to-be-marketed formulations, was conducted, and a single dose of finerenone 20 mg (two 10 mg tablets or one 20 mg tablet) was orally administered in the fasted state. The geometric mean ratios [90% CI] of C_{max} and AUC_{0-t} of finerenone after administration of the 10 mg tablets to those after administration of the 20 mg tablets were 1.1766 [1.0626, 1.3027] and 1.0684 [1.0255, 1.1131], respectively, and the upper limit of 90% CI of the geometric mean ratio of C_{max} exceeded the acceptance limit (1.25), resulting a failure to demonstrate BE. C_{max} after administration of the 10 mg tablets tended to be higher than that after administration of the 20 mg tablets, to-be-marketed formulations, and the difference in C_{max} between the formulations may reflect the difference in dissolution profile between them, as presented by the dissolution test, in which the 10 mg tablets tended to dissolve faster than the 20 mg tablets.

PMDA's view:

Because finerenone is assumed to be started or re-started at a once-daily dose of 10 mg depending on the patient's condition [see Section "7.R.7 Dosage and administration"], not only the 20 mg tablets suitable for the recommended dose but also the 10 mg tablets should be made available in clinical practice. Basically, if formulations of different specifications are available, and ones with different strengths are assumed to be interchangeably used in clinical practice, these formulations should be biologically equivalent. The recommended dosage regimen of finerenone is 20 mg administered once daily, but access to the 10 mg tablets should not be delayed just because of a failure to demonstrate BE, given that the 10 mg tablets are needed for use in patients with renal impairment as defined by eGFR <60 mL/min/1.73 m^2 and patients with high serum potassium levels, and that the concerned formulation was used in the global phase III studies (Studies 16244 and 17530). Therefore, both 10 and 20 mg tablets should be available as the commercial formulations with a cautionary statement that the two formulations should not be interchangeably used simply on a strength basis.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted efficacy and safety evaluation data from 5 studies, presented in Table 24. The applicant additionally submitted results from the global phase III study (Study 17530) after this application was filed.

Table 24. Main evaluation data on efficacy and safety

Data category	Region	Study	Phase	Study population	Number of subjects enrolled	Outline of dosage regimen	Main endpoints
Evaluation	Japan	Study 15171	I	Healthy Japanese adults	36	Placebo or finerenone 40 mg was orally administered once daily for 10 days Placebo, finerenone 10 mg, or 20 mg was orally administered twice daily for 10 days	Safety
	Foreign	Study 16243	II	Non-Japanese patients with diabetic nephropathy	823	Placebo, finerenone 1.25 mg, 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, or 20 mg was orally administered once daily for 90 days	Efficacy Safety
	Japan	Study 16816	II	Japanese patients with diabetic nephropathy	96	Placebo, finerenone 1.25 mg, 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, or 20 mg was orally administered once daily for 90 days	Efficacy Safety
	Global	Study 16244 (FIDELIO)	III	Patients with diabetic kidney disease	5734	Placebo or finerenone was orally administered once daily. In the finerenone group, finerenone was started at 10 mg or 20 mg according to eGFR, and then the dose was adjusted to 0 mg (interruption), 10 mg, or 20 mg according to serum potassium and eGFR.	Efficacy Safety
	Global	Study 17530 (FIGARO)	III	Patients with diabetic kidney disease	7437	Placebo or finerenone was orally administered once daily. In the finerenone group, finerenone was started at 10 mg or 20 mg according to eGFR, and then the dose was adjusted to 0 mg (interruption), 10 mg, or 20 mg according to serum potassium and eGFR.	Efficacy Safety

7.1 Phase I studies

7.1.1 Japanese phase I study (Study 15171, CTD 5.3.3.1.4, Study period, February to May 20[redacted])

A randomized, single-blind study was conducted to investigate the safety and PK/pharmacodynamics (PD) after single and multiple doses of finerenone in healthy adult Japanese men (target sample size, 36 subjects) at a single study center in Japan. In this study, placebo, finerenone 10 or 20 mg was orally administered in the fasted state twice daily for 10 days (once daily only on Days 1 and 10); and placebo or finerenone 40 mg was orally administered in the fasted state once daily for 10 days.

A total of 36 enrolled subjects received the study drug and all of them were included in the safety analysis population.

Adverse events occurred in 4 of 9 subjects in the placebo group, 5 of 9 subjects in the finerenone 10 mg group, 2 of 9 subjects in the 20 mg group, and 4 of 9 subjects in the 40 mg group. The event reported by more than 1 subject in any group was C-reactive protein increased (2 subjects in the placebo group, 0 subjects in the finerenone 10 mg group, 1 subject in the 20 mg group, 1 subject in the 40 mg group). Neither deaths nor serious adverse events occurred. An adverse event leading to discontinuation of the study drug occurred in 1 subject (myalgia) in the placebo group.

7.2 Phase II studies

7.2.1 Japanese phase II study (Study 16816, CTD 5.3.5.1.1, Study period, October 2013 to November 2014)

A randomized, double-blind, parallel-group study was conducted to investigate the efficacy (evaluation on the basis of UACR) and safety of finerenone at different doses in patients with diabetic nephropathy accompanying type 2 diabetes mellitus (target sample size, 88 patients [11 per group]) at 16 study centers in Japan.

This study consisted of the run-in period up to 12 weeks[12)] and double-blind period, and patients were randomly assigned to receive placebo or finerenone 1.25, 2.5, 5, 7.5, 10, 15, or 20 mg[13)] at a ratio of 1:1:1:1:1:1:1:1.

During the double-blind period, placebo or finerenone 1.25, 2.5, 5, 7.5, 10, 15, or 20 mg was administered once daily for 90 days. Doses of concomitant drugs were kept unchanged during the study in principle.

Mainly, patients with diabetic nephropathy aged ≥18 years who met the following criteria were included in the study:

- Type 2 diabetes mellitus that meets at least 1 of the following criteria:
  - Receiving oral antidiabetic agents or insulin
  - Having a medical history of fasting plasma glucose ≥7.0 mmol/L (126 mg/dL)
  - Having a medical history of plasma glucose at 2 hours in oral glucose tolerance test ≥11.1 mmol/L (200 mg/dL)
  - Having HbA1c ≥6.5% during the run-in period or a medical history of such laboratory value
- Receiving clinical diagnosis of diabetic nephropathy by meeting any of the following criteria during the run-in period and at the screening visit:
  - Persistent very high albuminuria (UACR ≥300 mg/g [34 mg/mmol] in 2 of 3 first morning void urine samples) and eGFR ≥30 mL/min/1.73 m^2 and <90 mL/min/1.73 m^2
  - Persistent high albuminuria (UACR ≥30 mg/g and <300 mg/g [≥3.4 mg/mmol and <34 mg/mmol] in 2 of 3 first morning void urine samples) and eGFR ≥30 mL/min/1.73 m^2 and <90 mL/min/1.73 m^2
- Receiving an ACE inhibitor or ARB at the minimum recommended dose specified in the Japanese guidelines or higher for ≥3 months on the dosage regimen unchanged for the last ≥4 weeks. For patients with eGFR of 30 to 45 mL/min/1.73 m^2, receiving a non-potassium-sparing diuretic at screening on the dosage regimen unchanged for the last ≥4 weeks
- Having the serum potassium level of ≤4.8 mmol/L during the run-in period and at the screening visit

12) During the run-in period, patients made a screening visit within 14 days of randomization to be checked for eligibility. At this visit, patients were screened for the following conditions: They were receiving an ACE inhibitor or ARB at the minimum recommended dose specified in the local guidelines in Japan (Study 16816) or outside Japan (Study 16243) or higher; they met all the inclusion criteria; and they did not meet the exclusion criteria.

13) This study initially planned to randomly allocate patients to 1 of 6 groups, placebo, finerenone 1.25 mg, 2.5 mg, 5 mg, 7.5 mg, and 10 mg groups, at a ratio of 1:1:1:1:1:1, but after the safety and tolerability at these doses were confirmed by the data monitoring committee, the finerenone 15 mg and 20 mg groups were added. After addition of the finerenone 15 mg and 20 mg groups, patients were randomly allocated in such a manner that distribution of patients across the groups would be well balanced.

All of the randomized 96 patients (12 in the placebo group, 12 in the finerenone 1.25 mg group, 12 in the 2.5 mg group, 12 in the 5 mg group, 12 in the 7.5 mg group, 12 in the 10 mg group, 12 in the 15 mg group, and 12 in the 20 mg group) received the study drug and were included in the safety analysis population. Of them, 95 patients (12, 12, 12, 12, 11, 12, 12, and 12) were included in the full analysis set (FAS) and the efficacy analysis population, and the remaining 1 patient who had no post-baseline UACR value was excluded from the analyses. Discontinuation occurred in 3 patients (0, 1, 0, 0, 1, 1, 0, and 0) because of adverse events in 1 patient (0, 0, 0, 0, 0, 1, 0, and 0), protocol deviation in 1 patient (0, 1, 0, 0, 0, 0, 0, and 0), and consent withdrawal in 1 patient (0, 0, 0, 0, 1, 0, 0, and 0).

Table 25 shows the ratio of UACR on Day 90 to that at baseline, the primary endpoint.

Table 25. Ratio of UACR (g/kg) on Day 90 to baseline (FAS)

	Placebo (N = 12)	Finerenone						
		1.25 mg (N = 12)	2.5 mg (N = 12)	5 mg (N = 12)	7.5 mg (N = 11)	10 mg (N = 12)	15 mg (N = 12)	20 mg (N = 12)
Baseline[a]	287.74	191.93	144.35	235.18	446.87	260.38	228.67	127.67
Day 90[a]	392.91	156.30	144.60	165.82	267.59	204.07	200.62	68.99
Ratio to baseline[b,c]	1.062 [0.824, 1.369]	0.937 [0.730, 1.203]	0.938 [0.730, 1.206]	0.918 [0.707, 1.192]	0.745 [0.574, 0.967]	0.825 [0.618, 1.102]	0.893 [0.704, 1.132]	0.712 [0.556, 0.912]
Ratio to placebo[b,c]	-	0.882 [0.639, 1.219]	0.884 [0.639, 1.221]	0.865 [0.627, 1.192]	0.702 [0.505, 0.975]	0.777 [0.560, 1.078]	0.841 [0.607, 1.165]	0.670 [0.481, 0.934]

a Median
b Least squares mean [two-sided 90% CI]
c Analysis of covariance (ANCOVA) using the dose group and type of albuminuria at screening (very high albuminuria or high albuminuria) as factors and logarithmic transformed value of baseline UACR nested by type of albuminuria at screening as a covariate. For the patients with missing data on Day 90 due to study discontinuation, the UACR value either at the discontinuation or follow-up, whichever was higher, was used.

Table 26 shows incidences of adverse events occurring from the first dose of the study drug to 3 days after the last dose and events reported by more than 1 patient in any group. None of the deaths, serious adverse events, and adverse events leading to discontinuation of the study drug occurred.

Table 26. Incidences of adverse events (safety analysis population)

MedDRA PT	Placebo (N = 12)	Finerenone						
		1.25 mg (N = 12)	2.5 mg (N = 12)	5 mg (N = 12)	7.5 mg (N = 12)	10 mg (N = 12)	15 mg (N = 12)	20 mg (N = 12)
All adverse events	50.0 (6)	58.3 (7)	33.3 (4)	50.0 (6)	50.0 (6)	50.0 (6)	50.0 (6)	41.7 (5)
Cataract	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	16.7 (2)	0 (0)
Constipation	8.3 (1)	0 (0)	0 (0)	16.7 (2)	0 (0)	0 (0)	8.3 (1)	0 (0)
Nasopharyngitis	16.7 (2)	16.7 (2)	8.3 (1)	0 (0)	0 (0)	16.7 (2)	8.3 (1)	8.3 (1)
Diabetes mellitus	0 (0)	0 (0)	0 (0)	16.7 (2)	0 (0)	0 (0)	8.3 (1)	0 (0)
Epistaxis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	16.7 (2)	0 (0)	0 (0)

Incidence: % (n)

7.2.2 Foreign phase II study (Study 16243, CTD 5.3.5.1.4, Study period, June 2013 to August 2014)

A randomized, double-blind, parallel-group study was conducted to investigate the efficacy (evaluation on the basis of UACR) and safety of finerenone at different doses in patients with diabetic nephropathy accompanying type 2 diabetes mellitus (target sample size, 90 per group) at 148 study centers outside Japan.

This study consisted of the run-in period up to 12 weeks[12)] and double-blind period, and patients were stratified using the region (North America, Europe, Asia, or others) and type of albuminuria at screening visit (high albuminuria or very high albuminuria) as factors and assigned to receive placebo or finerenone 1.25, 2.5, 5, 7.5, 10, 15, or 20 mg[13)] at the ratio of 1:1:1:1:1:1:1:1.

During the double-blind period, placebo or finerenone 1.25, 2.5, 5, 7.5, 10, 15, or 20 mg was administered once daily for 90 days. Doses of concomitant drugs were kept unchanged during the study in principle.

The key inclusion criteria in the Japanese phase II study were also applied [see Section "7.2.1 Japanese phase II study"].

Of randomized 823 patients, 821 patients (94 in the placebo group, 96 in the finerenone 1.25 mg group, 92 in the 2.5 mg group, 100 in the 5 mg group, 97 in the 7.5 mg group, 98 in the 10 mg group, 125 in the 15 mg group, 119 in the 20 mg group) were included in the safety analysis population, the remaining 2 patients who had not received the study drug were excluded from the analysis. In addition, 812 patients (94, 96, 92, 98, 96, 96, 123, and 117) were included in the FAS and the efficacy analysis population, and the remaining 9 patients who had no post-baseline UACR values were excluded from the analyses. Discontinuation occurred in 59 patients (4, 6, 5, 10, 7, 8, 11, and 8) because of adverse events in 35 patients (3, 5, 4, 6, 5, 2, 8, and 2), protocol deviation in 10 patients (1, 1, 1, 1, 0, 3, 2, and 1) and consent withdrawal in 8 patients (0, 0, 0, 1, 2, 1, 1, and 3).

Table 27 shows the ratio of UACR on Day 90 to that at baseline, the primary endpoint, in which a significant dose-dependency was observed ($P < 0.0001$, test for linear contrast, one-sided significance level of 0.05).

Table 27. Ratio of UACR (g/kg) on Day 90 to baseline (FAS)

	Placebo (N = 94)	Finerenone						
		1.25 mg (N = 96)	2.5 mg (N = 92)	5 mg (N = 98)	7.5 mg (N = 96)	10 mg (N = 96)	15 mg (N = 123)	20 mg (N = 117)
Baseline[a]	182.87	216.83	158.86	174.84	163.50	262.99	161.07	206.98
Day 90[a]	157.10	213.73	153.13	162.23	109.74	147.80	99.33	124.24
Ratio to baseline[b,c]	0.938 [0.829, 1.061]	0.869 [0.772, 0.979]	0.890 [0.786, 1.009]	0.824 [0.730, 0.929]	0.739 [0.653, 0.835]	0.708 [0.627, 0.800]	0.630 [0.563, 0.705]	0.585 [0.523, 0.654]
Ratio to placebo[b,c]	-	0.926 [0.799, 1.074]	0.949 [0.818, 1.101]	0.878 [0.758, 1.017]	0.787 [0.680, 0.912]	0.755 [0.651, 0.875]	0.671 [0.584, 0.772]	0.624 [0.542, 0.718]

a Median
b Least squares mean [two-sided 90% CI]
c ANCOVA using the dose group, type of albuminuria at screening (high albuminuria or very high albuminuria), and region (Europe, North America, Asia, or others) as factors and logarithmic transformed value of baseline UACR nested by type of albuminuria at screening as a covariate
For the patients with missing data on Day 90 due to study discontinuation, the UACR value either at the discontinuation or follow-up, whichever was higher, was used.

Table 28 shows incidences of adverse events occurring from the first dose of the study drug to 3 days after the last dose and events reported by ≥2.5% of patients in any group.

Table 28. Incidences of adverse events (safety analysis population)

MedDRA PT	Placebo (N = 94)	Finerenone						
		1.25 mg (N = 96)	2.5 mg (N = 92)	5 mg (N = 100)	7.5 mg (N = 97)	10 mg (N = 98)	15 mg (N = 125)	20 mg (N = 119)
All adverse events	50.0 (47)	50.0 (48)	55.4 (51)	50.0 (50)	55.7 (54)	59.2 (58)	48.8 (61)	53.8 (64)
Constipation	1.1 (1)	0 (0)	3.3 (3)	1.0 (1)	0 (0)	1.0 (1)	1.6 (2)	0 (0)
Diarrhoea	2.1 (2)	5.2 (5)	2.2 (2)	4.0 (4)	2.1 (2)	2.0 (2)	2.4 (3)	4.2 (5)
Nausea	3.2 (3)	2.1 (2)	2.2 (2)	2.0 (2)	1.0 (1)	3.1 (3)	0 (0)	0.8 (1)
Fatigue	0 (0)	2.1 (2)	4.3 (4)	3.0 (3)	1.0 (1)	0 (0)	1.6 (2)	1.7 (2)
Influenza	1.1 (1)	3.1 (3)	2.2 (2)	1.0 (1)	0 (0)	0 (0)	0 (0)	0.8 (1)
Nasopharyngitis	5.3 (5)	7.3 (7)	4.3 (4)	8.0 (8)	9.3 (9)	5.1 (5)	3.2 (4)	6.7 (8)
Urinary tract infection	2.1 (2)	0 (0)	1.1 (1)	3.0 (3)	4.1 (4)	0 (0)	0.8 (1)	1.7 (2)
Blood creatine phosphokinase increased	1.1 (1)	2.1 (2)	3.3 (3)	1.0 (1)	3.1 (3)	3.1 (3)	1.6 (2)	2.5 (3)
Blood creatinine increased	1.1 (1)	0 (0)	2.2 (2)	1.0 (1)	0 (0)	2.0 (2)	1.6 (2)	3.4 (4)
C-reactive protein increased	1.1 (1)	1.0 (1)	1.1 (1)	1.0 (1)	3.1 (3)	1.0 (1)	0 (0)	0 (0)
Glomerular filtration rate decreased	2.1 (2)	2.1 (2)	3.3 (3)	4.0 (4)	2.1 (2)	2.0 (2)	1.6 (2)	0.8 (1)
Arthralgia	2.1 (2)	1.0 (1)	3.3 (3)	1.0 (1)	2.1 (2)	3.1 (3)	1.6 (2)	0.8 (1)
Back pain	1.1 (1)	2.1 (2)	1.1 (1)	4.0 (4)	1.0 (1)	0 (0)	1.6 (2)	3.4 (4)
Muscle spasms	2.1 (2)	0 (0)	2.2 (2)	1.0 (1)	4.1 (4)	1.0 (1)	4.0 (5)	2.5 (3)
Dizziness	2.1 (2)	6.3 (6)	1.1 (1)	3.0 (3)	1.0 (1)	3.1 (3)	4.0 (5)	0.8 (1)
Cough	1.1 (1)	2.1 (2)	1.1 (1)	1.0 (1)	3.1 (3)	3.1 (3)	0.8 (1)	1.7 (2)
Hypertension	4.3 (4)	2.1 (2)	2.2 (2)	1.0 (1)	2.1 (2)	3.1 (3)	0 (0)	0 (0)
Hyperkalaemia	0 (0)	2.1 (2)	1.1 (1)	1.0 (1)	1.0 (1)	0 (0)	2.4 (3)	2.5 (3)
Oedema peripheral	2.1 (2)	2.1 (2)	2.2 (2)	1.0 (1)	0 (0)	1.0 (1)	0.8 (1)	2.5 (3)

Incidence: % (n)

No adverse events leading to death occurred.

Serious adverse events occurred in 3.2% (3 of 94) of patients in the placebo group, 5.2% (5 of 96) of patients in the 1.25 mg group, 3.3% (3 of 92) of patients in the 2.5 mg group, 7.0% (7 of 100) of patients in the 5 mg group, 8.2% (8 of 97) of patients in the 7.5 mg group, 2.0% (2 of 98) of patients in the 10 mg group, 4.8% (6 of 125) of patients in the 15 mg group, and 3.4% (4 of 119) of patients in the 20 mg group, and the events reported by ≥1.5% of patients in any group were blood potassium increased (0% in the placebo group, 0% in the 1.25 mg group, 1.1% in the 2.5 mg group, 0% in the 5 mg group, 1.0% in the 7.5 mg group, 0% in the 10 mg group, 1.6% in the 15 mg group, and 0.8% in the 20 mg group) and hyperkalaemia (0%, 2.1%, 0%, 1.0%, 1.0%, 0%, 1.6%, and 1.7%). Adverse events for which a causal relationship to the study drug could not be ruled out were blood potassium increased (0%, 0%, 1.1%, 0%, 1.0%, 0%, 0.8%, and 0.8%) and hyperkalaemia (0%, 2.1%, 0%, 1.0%, 1.0%, 0%, 1.6%, and 0.8%).

Adverse events leading to discontinuation of the study drug occurred in 3.2% (3 of 94) of patients in the placebo group, 5.2% (5 of 96) of patients in the 1.25 mg group, 4.3% (4 of 92) of patients in the 2.5 mg group, 5.0% (5 of 100) of patients in the 5 mg group, 5.2% (5 of 97) of patients in the 7.5 mg group, 2.0% (2 of 98) of patients in the 10 mg group, 6.4% (8 of 125) of patients in the 15 mg group, and 1.7% (2 of 119 patients) in the 20 mg group, and the events reported by ≥1.5% of patients in any group were blood potassium increased (0% in the placebo group, 0% in the 1.25 mg group, 1.1% in the 2.5 mg group, 0% in the 5 mg group, 1.0% in the 7.5 mg group, 0% in the 10 mg group, 1.6% in the 15 mg group, and 0.8% in the 20 mg group) and hyperkalaemia (0%, 2.1%, 0%, 1.0%, 1.0%, 0%, 1.6%, and 0.8%). Adverse events for which a causal relationship to the study drug could not be ruled out were blood potassium increased (0%, 0%, 1.1%, 0%, 1.0%, 0%, 0.8%, and 0.8%) and hyperkalaemia (0%, 2.1%, 0%, 1.0%, 1.0%, 0%, 1.6%, and 0.8%).

7.3 Phase III studies

7.3.1 Global phase III study (a) (Study 16244, CTD 5.3.5.1.6, Study period, September 2015 to April 2020)

A randomized, double-blind study was conducted to investigate the effect of finerenone in delaying the occurrence of the renal composite endpoint in patients with type 2 diabetes mellitus and a diagnosis of diabetic kidney disease (target sample size, 5800 patients for randomization[14]; number of events required for the primary endpoint [onset of renal failure, sustained decrease of eGFR ≥40% from baseline over at least 4 weeks, renal death], 1068[15]) at 1024 study centers in and outside Japan.

This study consisted of the run-in period of 4 to 16 weeks, screening period up to 2 weeks, double-blind period, and follow-up period, and patients were stratified using the region (North America, Europe, Asia, Latin America, or others), type of albuminuria at screening visit (high albuminuria or very high albuminuria), and eGFR at screening visit (≥25 mL/min/1.73 m^2 and <45 mL/min/1.73 m^2, ≥45 mL/min/1.73 m^2 and <60 mL/min/1.73 m^2, or ≥60 mL/min/1.73 m^2) as factors for allocation.

For the regimen, (a) patients with eGFR ≥60 mL/min/1.73 m^2 received finerenone 20 mg or placebo once daily; and (b) patients with eGFR ≥25 mL/min/1.73 m^2 and <60 mL/min/1.73 m^2 started finerenone 10 mg or placebo once daily followed by the dose adjustment according to the guidance in Table 29. Where necessary from a safety viewpoint, dose reduction or interruption of the study drug was allowed, and after the dose reduction or interruption where applicable, the dose increase or resumption according to the guidance in Table 29 was also allowed.

Table 29. Guidance for dose-adjustment based on serum potassium

Serum potassium (mmol/L)	Dose
On the study drug	
≤4.8	In case of 10 mg once daily administration, increase to 20 mg once daily (only when a decrease in eGFR is <30%). In case of the study drug 20 mg once daily administration, continue it.
4.9-5.5	Continue the same dose.
>5.5	Interrupt the study drug, and re-measure serum potassium within 72 hours.
After interruption of the study drug	
<5.0	Resume the study drug on the 10 mg once-daily administration.
≥5.0	Continue the interruption of the study drug. Monitor serum potassium levels, and when it is ≤5.0 mmol/L, resume the study drug on the 10 mg once-daily administration.

Key inclusion criteria were as follows:

- Type 2 diabetes mellitus as defined in the standard by the American Diabetes Association (Standards of Medical Care in Diabetes - 2010. *Diabetes Care*. 2010;S11-61)

[14] The target sample size was initially 4800 but then increased by 1000 because the incidence of event for the primary endpoint was lower than expected.

[15] If a total of 1068 events for the primary endpoint occur, a test with a two-sided significance level of 3.3333% assuming a true hazard ratio of 0.80 would have a statistical power of ≥90%. The sample size necessary for randomization was estimated to be 4690 based on the following assumptions: The planned treatment period of 44 months (33 months of the enrollment period and 11 months of the longest treatment period for the last enrolled patient); annual event incidence of 12% in the placebo group; a common annual lost to follow-up rate of 0.7% in both treatment groups; and an annual discontinuation rate of 5% in the finerenone group. With potential certain changes in enrollment pattern during the enrollment period considered, the target sample size for randomization was projected to be 4800.

- Diabetic kidney disease that meets any of the following criteria:
  - Persistent high albuminuria (UACR ≥30 mg/g and <300 mg/g in 2 of 3 first morning void urine samples), eGFR ≥25 mL/min/1.73 m^2 and <60 mL/min/1.73 m^2, and a medical history of diabetic retinopathy
  - Persistent very high albuminuria (UACR ≥300 mg/g in 2 of 3 first morning void urine samples) and eGFR ≥25 mL/min/1.73 m^2 and <75 mL/min/1.73 m^2
- Having the serum potassium level of ≤4.8 mmol/L during the run-in period and at the screening visit
- Either an ACE inhibitor or ARB or both were administered for ≥4 weeks before the run-in period; once the run-in period was started, either an ACE inhibitor or ARB (but not both) was administered; and at the screening, either an ACE inhibitor or ARB (but not both) was administered at the maximum tolerated proposed dose for ≥4 weeks.

Key exclusion criteria were as follows: (a) UACR >5000 mg/g at the run-in or screening visit; (b) systolic blood pressure (SBP) <90 mmHg at the run-in or screening visit, and heart failure with reduced left ventricular ejection fraction rated at New York Heart Association (NYHA) class II to IV at the run-in visit.

In addition, the dosage regimen of the ACE inhibitor or ARB as well the other antihypertensives and hypoglycemics were kept unchanged wherever possible while the study drug was used.

Overall population

Of randomized 5734 patients (2868 in the placebo group, 2866 in the finerenone group), 5674 patients (2841, 2833) were included in the FAS and the efficacy analysis population, and the remaining 60 patients were excluded from the analyses because of GCP violation. A total of 5658 patients (2831 and 2827) who received the study drug were included in the safety analysis population.

Discontinuation occurred in 18 patients (9, 9) because of consent withdrawal in 10 patients (6, 4) and lost to follow-up in 8 patients (3, 5). The treatment period with the study drug in the FAS (median [range]) was 27.039 (0-51.48) months in the finerenone group and 27.203 (0-51.52) months in the placebo group.

Table 30 shows the initial dose and status of dose adjustment.

Table 30. Initial dose and status of dose adjustment (safety analysis population)

Initial dose	Placebo (N = 2831)	Finerenone (N = 2827)
10 mg once daily	2609	2613
No dose increase	481	688
1 time of dose increase	1724	1509
≥2 times of dose increase	404	416
20 mg once daily	222	214
No dose reduction	129	100
1 time of dose reduction	62	90
≥2 times of dose reduction	31	24

n

In this study, 1 interim analysis session was planned to guide the decision regarding early termination for efficacy when two-thirds of events required for the primary endpoint accumulated. The Haybittle-Peto rule was used to adjust type I error probability associated with the interim analysis. As recommended by the Independent Data Monitoring Committee that reviewed the interim analysis result, the study was continued until the target number of events for the primary endpoint accumulated.

The primary efficacy endpoint was time to first onset of renal composite endpoint.[16)] Table 31 shows results on renal composite endpoint, cardiovascular composite endpoint,[16)] and their components as well as all-cause deaths. For the primary endpoint, the hazard ratio was 0.825, and the event rate was significantly lower in the finerenone group than in the placebo group (P = 0.0014; stratified Log-rank test using region, type of albuminuria at screening visit, and eGFR at screening visit as stratification factors; two-sided significance level of 0.03282695). Figures 1 and 2 show Kaplan-Meier curves on time to onset of the renal composite endpoint and cardiovascular composite endpoint. In the following sections, unless otherwise specified, "end-stage renal disease (ESRD)" in the renal composite endpoint was defined as the initiation of chronic hemo- or peritoneal dialysis for at least 90 days or renal transplantation; and "sustained eGFR <15 mL/min/1.73 m^2" and "sustained decrease of eGFR ≥40% from baseline" were defined as such sustained decrease of eGFR confirmed by 2 measurement sessions separated by at least 4 weeks and performed by the standard method.

Table 31. Incidences of efficacy endpoints (FAS)

	Placebo (N = 2841)	Finerenone (N = 2833)	Hazard ratio [two-sided 95% CI][a]
Renal composite endpoint (first)	21.1 (600)	17.8 (504)	0.825 [0.732, 0.928]
Renal failure	8.3 (235)	7.3 (208)	0.869 [0.721, 1.048]
ESRD	4.9 (139)	4.2 (119)	0.858 [0.672, 1.096]
Sustained eGFR <15 mL/min/1.73 m^2	7.0 (199)	5.9 (167)	0.824 [0.671, 1.013]
Sustained decrease of eGFR ≥40% from baseline	20.3 (577)	16.9 (479)	0.815 [0.722, 0.920]
Renal death	<0.1 (2)	<0.1 (2)	-
Cardiovascular composite endpoint (first)	14.8 (420)	13.0 (367)	0.860 [0.747, 0.989]
Cardiovascular death	5.3 (150)	4.5 (128)	0.855 [0.675, 1.083]
Non-fatal myocardial infarction	3.1 (87)	2.5 (70)	0.796 [0.581, 1.090]
Non-fatal stroke	3.1 (87)	3.2 (90)	1.027 [0.765, 1.380]
Hospitalization for cardiac failure	5.7 (162)	4.9 (139)	0.857 [0.683, 1.076]
All-cause deaths	8.6 (244)	7.7 (219)	0.895 [0.746; 1.075]

Incidence: % (n)
-; Not calculated
a Stratified Cox proportional hazards model using the dose group as a factor and the region (North America, Europe, Asia, Latin America, or others), type of albuminuria at screening visit (high albuminuria or very high albuminuria), and eGFR at screening visit (≥25 mL/min/1.73 m^2 and <45 mL/min/1.73 m^2, ≥45 mL/min/1.73 m^2 and <60 mL/min/1.73 m^2, or ≥60 mL/min/1.73 m^2) as stratification factors

16) Events were classified and assessed by the independent Clinical Endpoint Committee (CEC) under the blinded condition to determine the applicability to the predetermined endpoint.

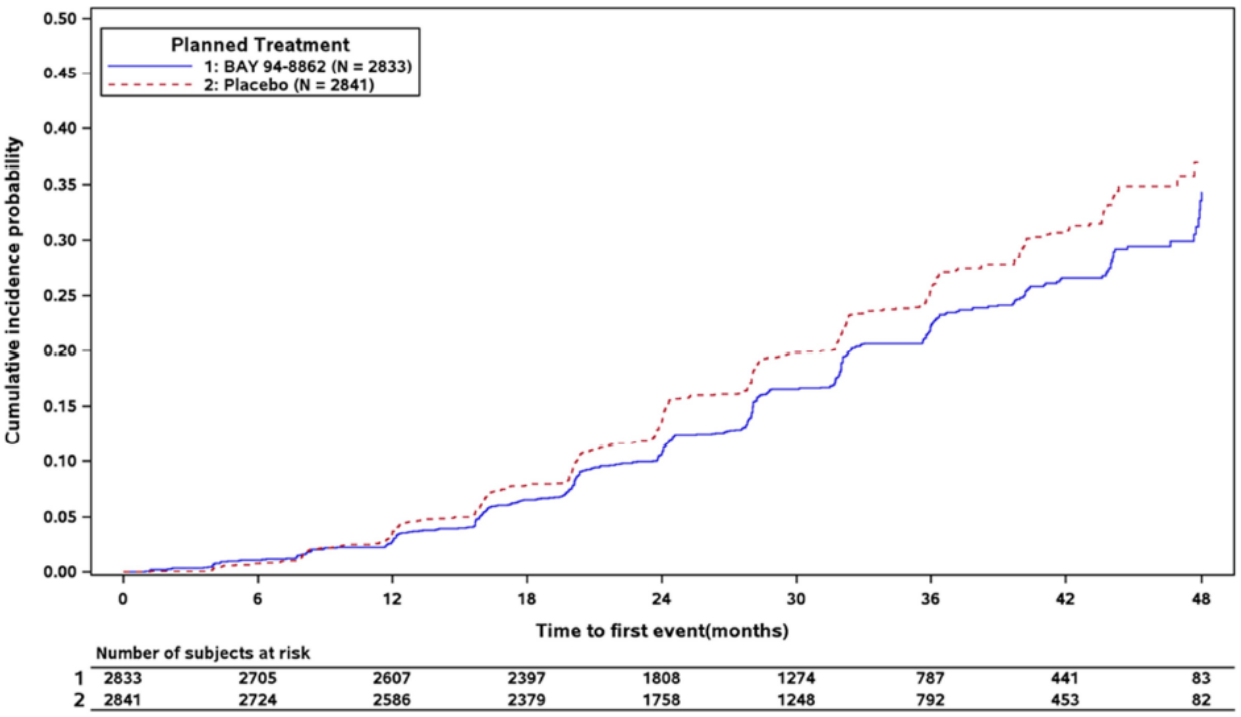


Figure 1. Kaplan-Meier curve for time to first onset of renal composite endpoint (FAS)

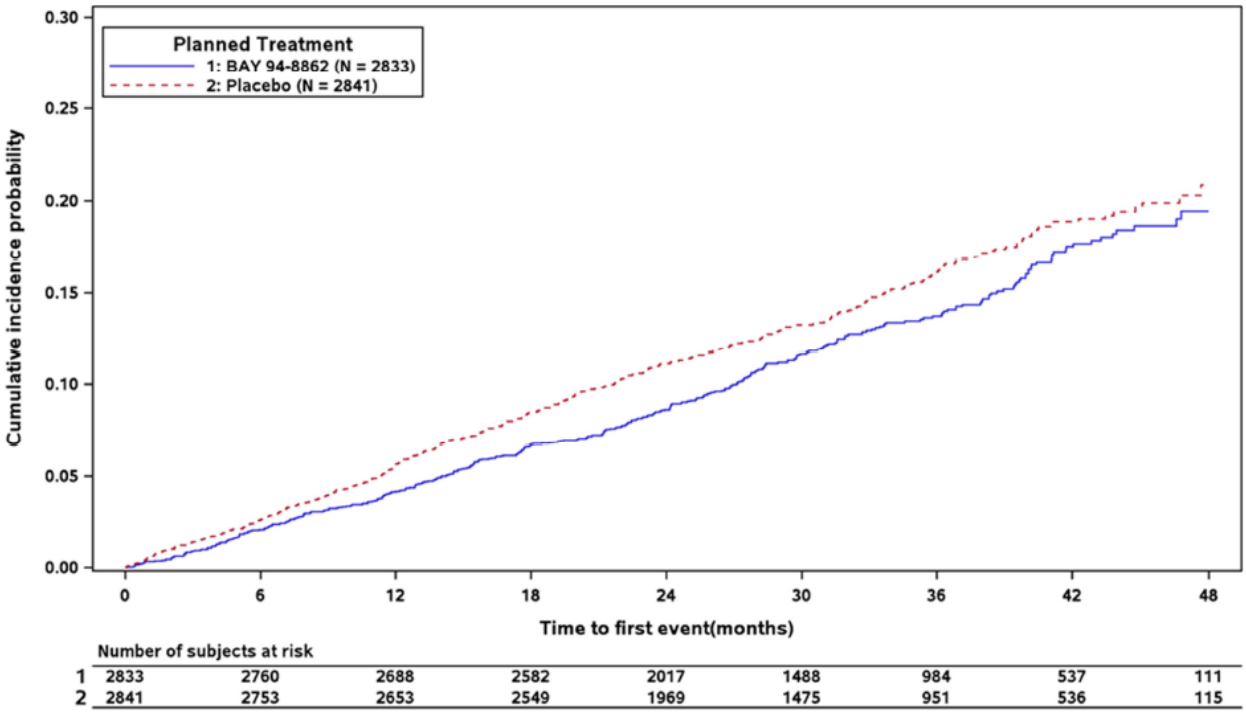


Figure 2. Kaplan-Meier curve for time to first onset of cardiovascular composite endpoint (FAS)

Table 32 shows incidences of adverse events occurring from the first dose of the study drug to 3 days after the last dose[17] and events reported by ≥5% of patients in either group.

[17] Adverse events occurring from 3 days after interruption of the study drug to resumption were not included.

Table 32. Adverse events reported by ≥5% of patients in either group (safety analysis population)

MedDRA PT	Placebo (N = 2831)	Finerenone (N = 2827)
All adverse events	87.5 (2478)	87.3 (2468)
Hyperkalaemia	7.8 (221)	15.8 (446)
Nasopharyngitis	8.8 (250)	8.5 (241)
Hypertension	9.6 (273)	7.5 (212)
Anaemia	6.7 (191)	7.4 (209)
Oedema peripheral	10.7 (304)	6.6 (186)
Diarrhoea	6.7 (189)	6.5 (184)
Upper respiratory tract infection	6.7 (189)	6.4 (181)
Glomerular filtration rate decreased	4.7 (133)	6.3 (179)
Urinary tract infection	6.8 (192)	6.3 (179)
Back pain	6.2 (175)	6.2 (175)
Hypoglycaemia	6.9 (194)	5.3 (151)
Dizziness	5.4 (153)	5.2 (146)
Arthralgia	5.3 (149)	5.0 (142)
Bronchitis	5.3 (151)	4.7 (134)
Constipation	5.8 (163)	4.6 (131)
Pneumonia	6.4 (181)	4.5 (128)

Incidence: % (n)

Adverse events leading to death occurred in 4.8% (135 of 2831) of patients in the placebo group and 3.1% (89 of 2827) of patients in the finerenone group, and the events reported by ≥0.2% of patients in either group were acute myocardial infarction (0.2% in the placebo group, 0.2% in the finerenone group), cardiac arrest (0.2%, 0.2%), cardiac failure (0.2%, <0.1%), cardiovascular disorder (0.2%, 0.1%), myocardial infarction (0.2%, 0.1%), death (0.6%, 0.4%), sudden death (0.2%, <0.1%), pneumonia (0.2%, <0.1%), and cerebrovascular accident (0.2%, 0.2%). There were no adverse events leading to death for which a causal relationship to the study drug could not be ruled out.

Serious adverse events occurred in 34.3% (971 of 2831) of patients in the placebo group and 31.9% (902 of 2827) of patients in the finerenone group, and the events reported by ≥1% of patients in either group were pneumonia (3.6%, 2.5%), acute kidney injury (1.8%, 2.0%), hyperkalaemia (0.4%, 1.5%), and hypoglycaemia (1.1%, 0.7%). The above events for which a causal relationship to the study drug could not be ruled out occurred in 1.2% (34 of 2831) of patients in the placebo group and 1.7% (48 of 2827) of patients in the finerenone group.

Adverse events leading to discontinuation of the study drug occurred in 5.9% (168 of 2831) of patients in the placebo group and 7.3% (207 of 2827) of patients in the finerenone group, and the events reported by ≥0.5% of patients in either group were blood potassium increased (0.2%, 0.5%) and hyperkalaemia (0.7%, 1.8%). The above events for which a causal relationship to the study drug could not be ruled out occurred in 2.1% (59 of 2831) of patients in the placebo group and 3.3% (94 of 2827) of patients in the finerenone group.

Japanese population

All of the 415 randomized patients (207 in the placebo group, 208 in the finerenone group) were included in the FAS and the efficacy analysis population. A total of 413 patients (205 and 208) who received the study drug were included in the safety analysis population. Discontinuation occurred in 4 patients (3,1) all because of consent withdrawal. The treatment period with the study drug in the FAS

(median [range]) was 35.713 (0.00-48.56) months in the placebo group and 35.565 (1.61-48.79) months in the finerenone group.

Table 33 shows results on renal composite endpoint, cardiovascular composite endpoint, and their components as well as all-cause deaths.

Table 33. Incidences of efficacy endpoints in Japanese population (FAS)

	Placebo (N = 207)	Finerenone (N = 208)	Hazard ratio [two-sided 95% CI][a]
Renal composite endpoint (first)	21.3 (44)	20.2 (42)	0.911 [0.596, 1.392]
Renal failure	7.2 (15)	10.1 (21)	1.349 [0.695, 2.617]
ESRD	1.9 (4)	4.3 (9)	2.186 [0.673, 7.101]
Sustained eGFR <15 mL/min/1.73 m^2	6.8 (14)	9.6 (20)	1.377 [0.695, 2.726]
Sustained decrease of eGFR ≥40% from baseline	20.8 (43)	20.2 (42)	0.933 [0.609, 1.429]
Renal death	0 (0)	0 (0)	-
Cardiovascular composite endpoint (first)	6.3 (13)	7.2 (15)	1.116 [0.531, 2.347]
Cardiovascular death	1.9 (4)	1.4 (3)	0.735 [0.164, 3.286]
Non-fatal myocardial infarction	1.4 (3)	0.5 (1)	0.310 [0.032, 2.977]
Non-fatal stroke	2.4 (5)	3.4 (7)	1.339 [0.425, 4.223]
Hospitalization for cardiac failure	0.5 (1)	2.4 (5)	4.827 [0.564, 41.316]
All-cause deaths	7.7 (16)	2.4 (5)	0.298 [0.109, 0.814]

Incidence: % (n)
-: Not calculated
a Stratified Cox proportional hazards model using the dose group as a factor and the region (North America, Europe, Asia, Latin America, or others), type of albuminuria at screening visit (high albuminuria or very high albuminuria), and eGFR at screening visit (≥25 mL/min/1.73 m^2 and <45 mL/min/1.73 m^2, ≥45 mL/min/1.73 m^2 and <60 mL/min/1.73 m^2, or ≥60 mL/min/1.73 m^2) as stratification factors

Table 34 shows incidences of adverse events occurring from the first dose of the study drug to 3 days after the last dose[17)] and events reported by ≥5% of patients in either group.

Table 34. Adverse events reported by ≥5% of patients in either group in Japanese population (safety analysis population)

MedDRA PT	Placebo (N = 205)	Finerenone (N = 208)
All adverse events	97.1 (199)	97.6 (203)
Nasopharyngitis	43.4 (89)	45.2 (94)
Back pain	7.8 (16)	12.0 (25)
Hyperkalaemia	11.2 (23)	11.1 (23)
Constipation	9.8 (20)	10.6 (22)
Hyperuricaemia	9.8 (20)	10.1 (21)
Influenza	9.8 (20)	8.7 (18)
Cataract	9.8 (20)	8.2 (17)
Blood potassium increased	2.0 (4)	8.2 (17)
Diarrhoea	8.3 (17)	7.7 (16)
Contusion	7.3 (15)	7.7 (16)
Bronchitis	5.9 (12)	7.2 (15)
Eczema	5.4 (11)	6.3 (13)
Vomiting	2.9 (6)	5.8 (12)
Muscle spasms	6.8 (14)	5.3 (11)
Arthralgia	4.9 (10)	5.3 (11)
Nephrogenic anaemia	3.9 (8)	5.3 (11)
Hypertension	2.9 (6)	5.3 (11)
Hypoglycaemia	6.8 (14)	4.3 (9)
Large intestine polyp	7.3 (15)	3.8 (8)
Gastrooesophageal reflux disease	6.3 (13)	3.8 (8)
Periodontitis	5.4 (11)	2.9 (6)

Incidence: % (n)

Adverse events leading to death occurred in 6.3% (13 of 205) of patients in the placebo group and 1.4% (3 of 208) of patients in the finerenone group, and there were no events reported by ≥1% of patients in either group. There were no adverse events for which a causal relationship to the study drug could not be ruled out.

Serious adverse events occurred in 31.2% (64 of 205) of patients in the placebo group and 22.6% (47 of 208) of patients in the finerenone group, and the events reported by ≥2% of patients in either group were cataract (3.4%, 2.9%), large intestine polyp (2.9%, 1.9%), and pneumonia (2.4%, 0.5%). The above events for which a causal relationship to the study drug could not be ruled out occurred in 0% (0 of 205) of patients in the placebo group and 1.0% (2 of 208) of patients in the finerenone group (pancreatitis acute and hyperkalaemia in 1 patient each).

Adverse events leading to discontinuation of the study drug occurred in 9.3% (19 of 205) of patients in the placebo group and 8.2% (17 of 208) of patients in the finerenone group, and the events reported by ≥1% of patients in either group were blood potassium increased (0%, 1.0%), hyperkalaemia (0%, 1.0%), lung neoplasm malignant (0.5%, 1.0%), metastases to lymph nodes (1.0%, 0%), small cell lung cancer (1.0%, 0%), and renal dysfunction (1.0%, 1.0%). The above events for which a causal relationship to the study drug could not be ruled out occurred in 1.5% (3 of 205) of patients in the placebo group and 4.3% (9 of 208) of patients in the finerenone group.

7.3.2 Global phase III study (b) (Study 17530, CTD 5.3.5.1.7, Study period, September 2015 to February 2021)

A randomized, double-blind study was conducted to investigate the effect of finerenone in delaying the occurrence of the cardiovascular composite endpoint in patients with type 2 diabetes mellitus and a diagnosis of diabetic kidney disease (target sample size, 7400 patients for randomization[18]; number of events required for the primary endpoint [cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, and hospitalization for heart failure], 970-976[19]) at 1019 study centers in and outside Japan.

This study consisted of the run-in period of 4 to 16 weeks, screening period up to 2 weeks, and double-blind period, and patients were stratified using the region (North America, Europe, Asia, Latin America, or others), type of albuminuria at screening visit (high albuminuria or very high albuminuria), eGFR at screening visit (≥25 mL/min/1.73 m^2 and <45 mL/min/1.73 m^2, ≥45 mL/min/1.73 m^2 and <60 mL/min/1.73 m^2, or ≥60 mL/min/1.73 m^2), and presence or absence of a medical history of cardiovascular diseases as factors for allocation.

18) The target sample size was initially 6400 but then increased by 1000 because the incidence of event for the primary endpoint was lower than expected.

19) If a total of 970 to 976 events for the primary endpoint occur, a test with a both-sided significance level of 5% assuming a true hazard ratio of 0.80 would have a statistical power of ≥90%. The sample size necessary for randomization was estimated to be 6212 to 6286 based on the following assumptions: The planned treatment period of 44 to 48 months (33 to 41 months of the enrollment period and 7 to 11 months of the longest treatment period for the last enrolled patient); annual event incidence of 8% in the placebo group; a common annual lost to follow-up rate of 0.7% in both treatment groups; and an annual discontinuation rate of 5% in the finerenone group. With potential certain changes in enrollment pattern during the enrollment period considered, the target sample size for randomization was projected to be 6400.

The dosage regimen, key inclusion criteria except for provisions for albuminuria and eGFR below, key exclusion criteria, and provisions for concomitant drugs were the same as those in Study 16244 [see Section "7.3.1 Global phase III study (a)"].

- Diabetic kidney disease that meets any of the following criteria:
  - Persistent high albuminuria (UACR ≥30 mg/g and <300 mg/g in 2 of 3 first morning void urine samples) and eGFR ≥25 mL/min/1.73 m^2 and ≤90 mL/min/1.73 m^2
  - Persistent very high albuminuria (UACR ≥300 mg/g in 2 of 3 first morning void urine samples) and eGFR ≥60 mL/min/1.73 m^2

Overall population

Of the 7437 randomized patients (3714 in the placebo group, 3723 in the finerenone group), 7352 patients (3666, 3686) were included in the FAS and the efficacy analysis population, and the remaining 85 patients were excluded from the analyses because of GCP violation. A total of 7341 patients (3658,[20)] 3683) who received the study drug were included in the safety analysis population. Discontinuation occurred in 18 patients (13, 5) because of consent withdrawal in 8 patients (7, 1) and lost to follow-up in 10 patients (6, 4). The treatment period with the study drug in the FAS (median [range]) was 35.893 (0-61.37) months in the placebo group and 35.877 (0-61.01) months in the finerenone group.

Table 35 shows the initial dose and status of dose adjustment.

Table 35. Initial dose and status of dose adjustment (safety analysis population)

Initial dose	Placebo (N = 3658)	Finerenone (N = 3683)
10 mg once daily	1366	1371
No dose increase	211	311
≥1 time of dose increase	1155	1060
20 mg once daily	2292	2312
No dose reduction	1242	1189
≥1 time of dose reduction or interruption	1050	1123

n

In this study, 1 interim analysis session was planned to guide the decision regarding early termination for efficacy when two-thirds of events required for the primary endpoint accumulated. The Haybittle-Peto rule was used to adjust type I error probability associated with the interim analysis. As recommended by the Independent Data Monitoring Committee that reviewed the interim analysis result, the study was continued until the target number of events for the primary endpoint accumulated. The primary efficacy endpoint was time to first onset of cardiovascular composite endpoint.[16)] Table 36 shows results on cardiovascular composite endpoint, renal composite endpoint,[16)] and their components as well as all-cause deaths. For the primary endpoint, the hazard ratio was 0.87, and the event rate was significantly lower in the finerenone group than in the placebo group (P = 0.0264; stratified Log-rank test using region, type of albuminuria at screening visit, eGFR at screening visit, and presence or absence of a medical history of cardiovascular diseases as stratification factors;

[20)] One patient who had been initially allocated to the placebo group actually received finerenone throughout the study period, and thus was included in the finerenone group.

two-sided significance level of 0.04967388,). Figures 3 and 4 show Kaplan-Meier curves on time to onset of the cardiovascular composite endpoint and renal composite endpoint.

Table 36. Incidences of efficacy endpoints (FAS)

	Placebo (N = 3666)	Finerenone (N = 3686)	Hazard ratio [two-sided 95% CI][a]
Cardiovascular composite endpoint (first)	14.2 (519)	12.4 (458)	0.87 [0.76, 0.98]
Cardiovascular death	5.8 (214)	5.3 (194)	0.90 [0.74, 1.09]
Non-fatal myocardial infarction	2.8 (102)	2.8 (103)	0.99 [0.76, 1.31]
Non-fatal stroke	3.0 (111)	2.9 (108)	0.97 [0.74, 1.26]
Hospitalization for cardiac failure	4.4 (163)	3.2 (117)	0.71 [0.56, 0.90]
Renal composite endpoint (first)	10.8 (395)	9.5 (350)	0.87 [0.76, 1.01]
Renal failure	1.7 (62)	1.2 (46)	0.72 [0.49, 1.05]
ESRD	1.3 (49)	0.9 (32)	0.64 [0.41, 1.00]
Sustained eGFR <15 mL/min/1.73 m^2	1.0 (38)	0.8 (28)	0.71 [0.43, 1.16]
Sustained decrease of eGFR ≥40% from baseline	10.5 (385)	9.2 (338)	0.87 [0.75, 1.00]
Renal death	<0.1 (2)	0 (0)	-
All-cause deaths	10.1 (370)	9.0 (333)	0.89 [0.77, 1.04]

Incidence: % (n)
-: Not calculated
a Stratified Cox proportional hazards model using the dose group as a factor and the region (North America, Europe, Asia, Latin America, or others), type of albuminuria at screening visit (high albuminuria or very high albuminuria), eGFR at screening visit (≥25 mL/min/1.73 m^2 and <45 mL/min/1.73 m^2, ≥45 mL/min/1.73 m^2 and <60 mL/min/1.73 m^2, or ≥60 mL/min/1.73 m^2), and presence or absence of a medical history of cardiovascular diseases as stratification factors

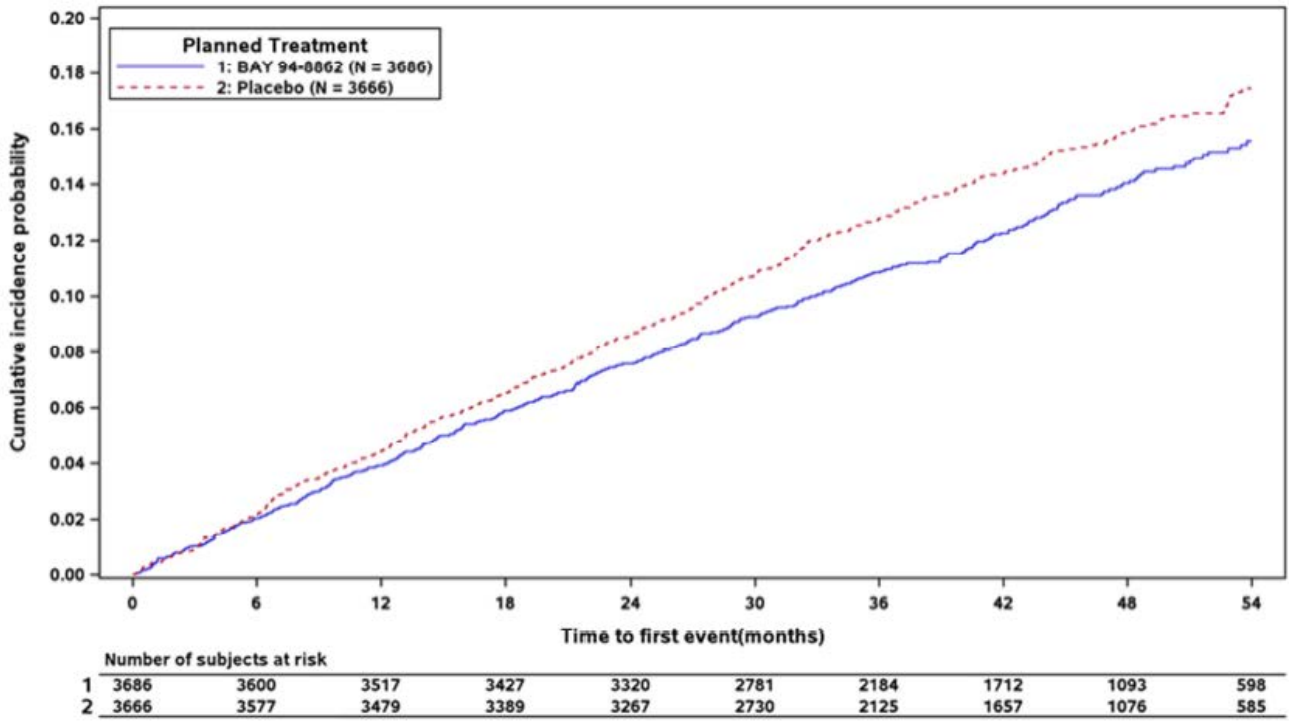


Figure 3. Kaplan-Meier curve for time to first onset of cardiovascular composite endpoint (FAS)

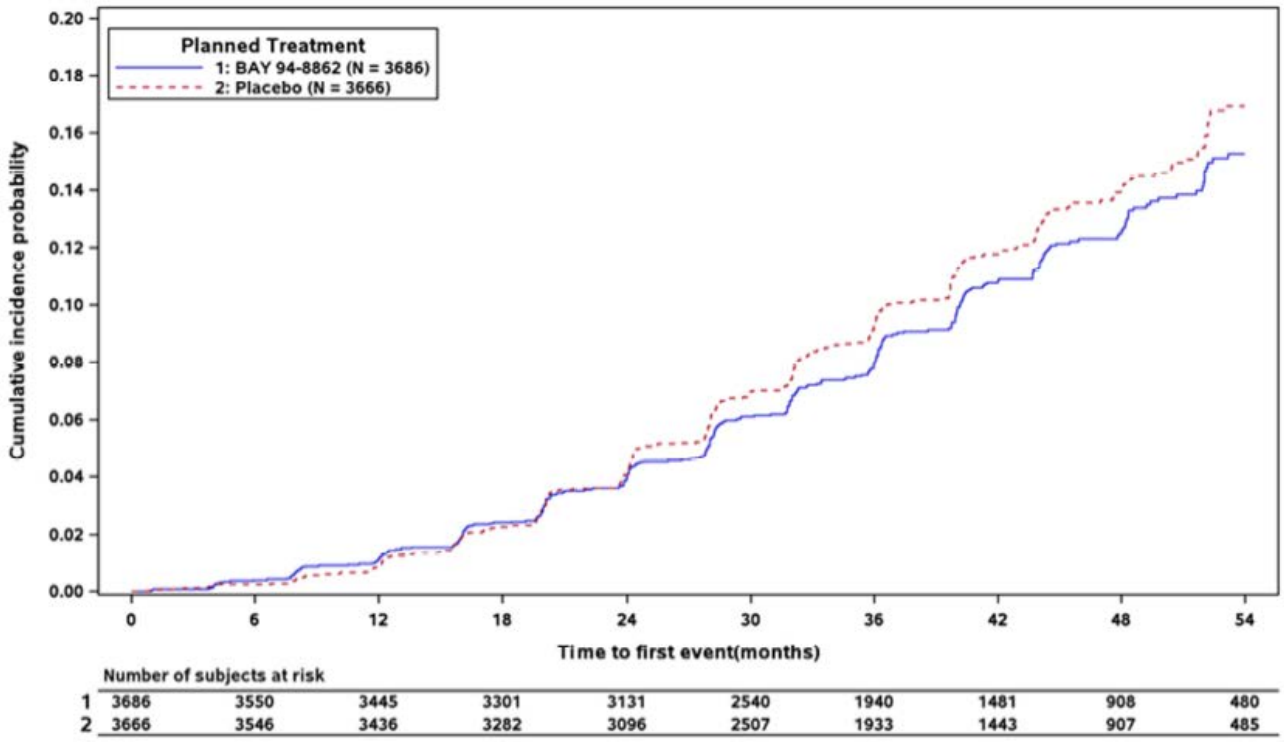


Figure 4. Kaplan-Meier curve for time to first onset of renal composite endpoint (FAS)

Table 37 shows incidences of adverse events occurring from the first dose of the study drug to 3 days after the last dose[17)] and events reported by ≥5% of patients in either group.

Table 37. Adverse events reported by ≥5% of patients in either group (safety analysis population)

MedDRA PT	Placebo (N = 3658)	Finerenone (N = 3683)
All adverse events	85.5 (3129)	85.1 (3134)
Hyperkalaemia	4.4 (161)	9.1 (335)
Nasopharyngitis	8.9 (327)	8.6 (318)
Arthralgia	7.2 (262)	8.1 (300)
Back pain	6.9 (253)	7.1 (261)
Urinary tract infection	6.6 (240)	6.8 (252)
Diarrhoea	6.1 (222)	6.5 (239)
Upper respiratory tract infection	5.6 (205)	6.1 (226)
Anaemia	5.6 (206)	5.9 (216)
Hypertension	8.4 (308)	5.6 (207)
Oedema peripheral	7.7 (280)	5.4 (198)
Dizziness	4.6 (169)	5.3 (195)
Bronchitis	4.9 (181)	5.3 (194)
Hypoglycaemia	4.9 (181)	5.1 (189)
Constipation	4.7 (171)	5.1 (186)
Pneumonia	5.6 (206)	3.9 (143)

Incidence: % (n)

Adverse events leading to death occurred in 2.7% (100 of 3658) of patients in the placebo group and 2.1% (79 of 3683) of patients in the finerenone group, and the events reported by ≥0.2% of patients in either group were death (0.2% in the placebo group, 0.2% in the finerenone group), COVID-19 (0.2%, 0.1%), and pneumonia (0.2%, 0.1%). Of the adverse events leading to death, adverse events for which a causal relationship to the study drug could not be ruled out occurred in 2 patients in the placebo group.

Serious adverse events occurred in 33.2% (1215 of 3658) of patients in the placebo group and 31.4% (1158 of 3683) of patients in the finerenone group, and the events reported by ≥1% of patients in either group were pneumonia (3.1%, 2.0%), cellulitis (0.8%, 1.1%), and acute kidney injury (1.3%, 1.0%). The above events for which a causal relationship to the study drug could not be ruled out occurred in 0.7% (27 of 3658) of patients in the placebo group and 1.0% (35 of 3683) of patients in the finerenone group.

Adverse events leading to discontinuation of the study drug occurred in 5.0% (183 of 3658) of patients in the placebo group and 5.6% (207 of 3683) of patients in the finerenone group, and the event reported by ≥0.5% of patients in either group was hyperkalaemia (0.3%,d 1.0%). The above events for which a causal relationship to the study drug could not be ruled out occurred in 1.4% (53 of 3658) of patients in the placebo group and 2.6% (97 of 3683) of patients in the finerenone group.

Japanese population

All of the 503 randomized patients (253 in the placebo group, 250 in the finerenone group) were included in the FAS and the efficacy analysis population. A total of 503 patients (252,[20] 251) who received the study drug were included in the safety analysis population. Discontinuation occurred in 5 patients (3, 2) because of consent withdrawal in 3 patients (2,d 1) and lost to follow-up in 2 patients (1, 1). The treatment period with the study drug in the FAS (median [range]) was 46.784 (0.95-58.87) months in the placebo group and 47.474 (0.95-58.61) months in the finerenone group.

Table 38 shows results on cardiovascular composite endpoint, renal composite endpoint, and their components as well as all-cause deaths.

Table 38. Incidences of efficacy endpoints in Japanese population (FAS)

	Placebo (N = 253)	Finerenone (N = 250)	Hazard ratio [two-sided 95% CI][a]
Cardiovascular composite endpoint (first)	7.1 (18)	4.8 (12)	0.65 [0.31, 1.36]
Cardiovascular death	1.2 (3)	0.8 (2)	0.64 [0.11, 3.83]
Non-fatal myocardial infarction	0.8 (2)	1.2 (3)	1.59 [0.26, 9.52]
Non-fatal stroke	4.0 (10)	2.0 (5)	0.48 [0.17, 1.42]
Hospitalization for cardiac failure	1.6 (4)	0.8 (2)	0.48 [0.09, 2.64]
Renal composite endpoint (first)	7.5 (19)	8.8 (22)	1.16 [0.63, 2.14]
Renal failure	0.4 (1)	1.6 (4)	4.53 [0.50, 40.94]
ESRD	0.8 (2)	1.2 (3)	1.56 [0.26, 9.33]
Sustained eGFR <15 mL/min/1.73 m^2	0.4 (1)	1.6 (4)	4.53 [0.50, 40.94]
Sustained decrease of eGFR ≥40% from baseline	7.5 (19)	8.8 (22)	1.18 [0.64, 2.19]
Renal death	0	0	-
All-cause deaths	4.3 (11)	2.0 (5)	0.46 [0.16, 1.32]

Incidence: % (n)

-: Not calculated

a Stratified Cox proportional hazards model using the dose group as a factor and the region (North America, Europe, Asia, Latin America, or others), type of albuminuria at screening visit (high albuminuria or very high albuminuria), eGFR at screening visit (≥25 mL/min/1.73 m^2 and <45 mL/min/1.73 m^2, ≥45 mL/min/1.73 m^2 and <60 mL/min/1.73 m^2, or ≥60 mL/min/1.73 m^2), and presence or absence of a medical history of cardiovascular diseases as stratification factors

Table 39 shows incidences of adverse events occurring from the first dose of the study drug to 3 days after the last dose[17] and events reported by ≥5% of patients in either group.

Table 39. Adverse events reported by ≥5% of patients in either group in Japanese population (safety analysis population)

MedDRA PT	Placebo (N = 252)	Finerenone (N = 251)
All adverse events	97.6 (246)	96.4 (242)
Nasopharyngitis	45.2 (114)	47.8 (120)
Hyperuricaemia	5.2 (13)	13.1 (33)
Influenza	13.9 (35)	11.6 (29)
Diabetes mellitus	7.1 (18)	11.2 (28)
Back pain	11.9 (30)	10.8 (27)
Diarrhoea	9.5 (24)	10.8 (27)
Arthralgia	8.7 (22)	10.8 (27)
Constipation	11.9 (30)	10.4 (26)
Cataract	9.9 (25)	10.0 (25)
Muscle spasms	7.9 (20)	9.6 (24)
Diabetic retinopathy	4.4 (11)	9.2 (23)
Hypoglycaemia	4.4 (11)	9.2 (23)
Contusion	9.1 (23)	8.4 (21)
Bronchitis	8.3 (21)	8.0 (20)
Eczema	7.1 (18)	8.0 (20)
Insomnia	4.0 (10)	6.8 (17)
Blood potassium increased	2.4 (6)	6.4 (16)
Gastrooesophageal reflux disease	7.5 (19)	6.0 (15)
Large intestine polyp	6.7 (17)	6.0 (15)
Hyperkalaemia	2.4 (6)	6.0 (15)
Upper respiratory tract inflammation	2.4 (6)	5.6 (14)
Hepatic steatosis	2.8 (7)	5.2 (13)
Chronic gastritis	2.4 (6)	5.2 (13)
Dizziness	6.3 (16)	3.6 (9)
Headache	5.2 (13)	3.6 (9)
Oedema peripheral	5.6 (14)	3.2 (8)
Hypertension	5.6 (14)	2.8 (7)

Incidence: % (n)

Adverse events leading to death occurred in 2.0% (5 of 252) of patients in the placebo group and 2.0% (5 of 251) of patients in the finerenone group, and there were no events reported by ≥1% of patients in either group. Of the adverse events leading to death, adverse events for which a causal relationship to the study drug could not be ruled out occurred in 1 patient in the placebo group.

Serious adverse events occurred in 35.7% (90 of 252) of patients in the placebo group and 30.7% (77 of 251) of patients in the finerenone group, and the events reported by ≥1% of patients in either group were cataract (1.6%, 1.6%), glaucoma (0%, 1.2%), large intestine polyp (2.4%, 3.2%), cellulitis (0.8%, 2.8%), pneumonia (1.2%, 0.4%), femur fracture (0%, 1.6%), diabetes mellitus (2.0%, 2.0%), colon cancer (1.2%, 1.2%), lung neoplasm malignant (1.2%, 0.8%), prostate cancer (1.2%, 0.8%), type 2 diabetes mellitus (1.2%, 0.4%), and pancreatitis acute (0%, 1.2%). The above events for which a causal relationship to the study drug could not be ruled out occurred in 0.8% (2 of 252) of patients in the placebo group and 0% (0 of 251) of patients in the finerenone group.

Adverse events leading to discontinuation of the study drug occurred in 7.5% (19 of 252) of patients in the placebo group and 5.6% (14 of 251) of patients in the finerenone group, and the events reported by ≥0.5% of patients in either group were liver disorder (0%, 0.8%), blood potassium increased (0%, 0.8%), pancreatic carcinoma (0.8%, 0%), and rash (0.8%, 0.4%). The above events for which a causal relationship to the study drug could not be ruled out occurred in 2.4% (6 of 252) of patients in the placebo group and 3.2% (8 of 251) of patients in the finerenone group.

7.R Outline of the review conducted by PMDA

7.R.1 Clinical positioning of finerenone

The applicant's explanation about clinical positioning of finerenone in treatment of CKD in Japan:
CKD is defined as a ≥3 month-long condition meeting either or both of (a) evident presence of renal disorder confirmed by urine abnormality or diagnostic imaging, hematological, or pathological finding (especially, presence of proteinuria ≥0.15 g/gCr [albuminuria ≥30 mg/gCr] is important); and (b) GFR <60 mL/min/1.73 m^2 (Evidence-based Clinical Practice Guideline for CKD 2018). CKD, if progressed, would result in end-stage renal disease, which requires dialysis therapy or renal transplantation, seriously affecting the quality of life. In addition, CKD is accompanied by increased morbidity and mortality of cardiovascular diseases, and a risk of cardiovascular deaths at a stage before start of dialysis is high (*PLoS One.* 2016;11:e0158765, Clinical Practice Guideline for CKD 2012 [in Japanese]). Because one of major causes of CKD is diabetes mellitus, patients with type 2 diabetes mellitus are recommended to receive an intensive therapy for prevention and treatment of CKD, which comprises of improvement of lifestyle including diet as well as intervention for optimization of plasma glucose, blood pressure, and serum lipid (Evidence-based Clinical Practice Guideline for CKD 2018). For drug therapies, Japanese and foreign guidelines (Evidence-based Clinical Practice Guideline for CKD 2018, Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease [2013], etc.) recommend ACE inhibitors or ARBs as standard of care. In addition, the foreign guidelines recently issued (*Kidney Int.* 2020;98:839-48, American Diabetes Association, *Diabetes Care.* 2020;43:S135-51) recommend SGLT2 inhibitors for patients with CKD associated with type 2 diabetes mellitus, and in Japan, dapagliflozin propylene glycolate hydrate, an SGLT2 inhibitor, was approved for the indication of CKD in 2021.

Pathological hyperactivation of MR in CKD is one of the causes of organ dysfunction and increases morbidity and mortality of cardiorenal diseases (*Hypertension.* 2015;65:257-63). Of the conventional drugs for treatment of CKD, ACE inhibitors and ARBs target molecules involved in metabolism and hemodynamics, and SGLT2 inhibitors improve plasma glucose and alleviate glomerular hyperfiltration mediated by tubuloglomerular feedback, thereby exerting renoprotection (*The Journal of the Japanese Society of Internal Medicine.* 2018;107:841-7), while no MR antagonists that can be indicated for CKD are available. Accordingly, despite the presence of the standard of care and addition of novel treatment methods, there are medical needs for additional therapeutic options to further reduce morbidity and mortality of cardiorenal diseases in patients with CKD associated with type 2 diabetes mellitus. Finerenone is a nonsteroidal, selective MR antagonist. Because of its high selectivity for the concerned receptor, finerenone is considered unlikely to cause adverse drug reactions such as gynaecomastia at doses exerting cardiorenal protection.

The efficacy and safety of finerenone were demonstrated by Studies 16244 and 17530 in patients with type 2 diabetes mellitus and a diagnosis of diabetic kidney disease who had received an ACE inhibitor or ARB at the maximum tolerated dose for ≥4 weeks. Based on the above, finerenone is intended to be used as an add-on drug in patients with type 2 diabetes mellitus and a diagnosis of diabetic kidney disease who have received standard of care including an ACE inhibitor or ARB.

PMDA's view:
To delay pathological progression of CKD, control of the renin-angiotensin (RA) system is a key, and ACE inhibitors and ARBs are recommended as the standard of care in Japanese and foreign guidelines. Finerenone was demonstrated to be superior to placebo in terms of the primary efficacy endpoint and have clinically acceptable safety in Studies 16244 and 17530 conducted in patients with type 2 diabetes mellitus and a diagnosis of diabetic kidney disease who had received standard of care including an ACE inhibitor or ARB at the maximum tolerated dose [see Sections "7.R.2.1 Evaluation results on efficacy of finerenone in global phase III studies (Studies 16244 And 17530)" and "7.R.3 Safety"]. In addition, in view of the efficacy evaluation in the Japanese populations in Studies 16244 and 17530 [see Section "7.R.2.3 Efficacy of finerenone in Japanese patients"], finerenone is expected to be effective in Japanese patients as well and the safety is acceptable as long as appropriate selection of eligible patients and cautions are in place.

Based on the above, PMDA considers it meaningful to provide access to finerenone for use in clinical practice in Japan as a therapeutic option with the novel mechanism of action, which is intended to be added to standard of care in patients with type 2 diabetes mellitus and a diagnosis of diabetic kidney disease receiving an ACE inhibitor or ARB. Use of finerenone in patients with nondiabetic CKD, patients not receiving an ACE inhibitor or ARB, patients with eGFR or UACR not meeting the inclusion criteria in Studies 16244 and 17530, and patients with end-stage renal disease and on maintenance dialysis are continuously reviewed in Section "7.R.5 Indication and eligible patients."

7.R.2 Efficacy

7.R.2.1 Evaluation results on efficacy of finerenone in global phase III studies (Studies 16244 and 17530)

The applicant's explanation about efficacy of finerenone in patients with CKD associated with type 2 diabetes mellitus:
Although hyperactivation of MR accelerates decreases in cardiac and renal functions in patients with CKD [see Section "7.R.1 Clinical positioning of finerenone], the applicant considered it difficult to evaluate both cardioprotection and renoprotection of finerenone in a single study in light of the risk of renal events that differs depending on CKD stage (Evidence-based Clinical Practice Guideline for CKD 2018). Thus, the applicant planned to conduct the following 2 studies in an independent-and-parallel manner to investigate if finerenone would reduce the risk of progression to end-stage renal disease and the risk of cardiovascular events in patients with CKD: Study 16244 was to include patients with CKD at relatively late stages to evaluate renal events as the primary endpoint; and Study 17530 was to include patients with CKD at various stages including patients with early stages to evaluate cardiovascular events as the primary endpoint.

Based on the above development plan of finerenone, the primary endpoint in Study 16244 was designed as a composite endpoint comprising not only events related to renal prognosis such as onset of "renal failure" ("ESRD" or sustained eGFR <15 mL/min/1.73 m^2), the established endpoint, and renal death but also sustained decrease of eGFR ≥40% from baseline for ≥4 weeks (hereinafter, "renal failure" means renal failure ["ESRD" or sustained eGFR <15 mL/min/1.73 m^2] defined as the renal composite endpoint in Studies 16244 and 17530). "Sustained decrease of eGFR ≥40% from baseline

for ≥4 weeks" was included as a component of the primary endpoint because the scientific workshop sponsored by the National Kidney Foundation in collaboration with the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) (*Am J Kidney Dis.* 2020;75:84-104) as well as "Guidelines for clinical evaluation of chronic kidney disease" in Japan (*The Japanese Journal of Nephrology.* 2018;60:67-100) support "sustained decrease in eGFR by ≥30% to 40%" as a surrogate endpoint appropriate for end-stage renal disease. Study 16244 using such a composite endpoint as the primary endpoint showed that the hazard ratio [two-sided 95% CI] of finerenone to placebo was 0.83 [0.73, 0.93] in terms of the renal composite endpoint, demonstrating the superiority of finerenone to placebo. In addition, of components of the renal composite endpoint, all except for renal death showed the hazard ratio of finerenone to placebo was less than 1 (Table 31). Renal death occurred in 2 patients each in both groups, presenting no difference between the groups. A change in eGFR per year from baseline to visit for discontinuation of the study drug or visit at end of study (least squares mean [two-sided 95% CI]) was −3.776 [−4.015, −3.537] mL/min/1.73 m^2 in the placebo group and −3.627 [−3.864, −3.390] mL/min/1.73 m^2 in the finerenone group, showing an intergroup difference of 0.149 [−0.187, 0.485] mL/min/1.73 m^2. A change in eGFR per year from Month 4[21)] to visit for discontinuation of the study drug or visit at end of study (least squares mean [two-sided 95% CI]) was −3.966 [−4.268, −3.664] mL/min/1.73 m^2 in the placebo group and −2.657 [−2.956, −2.357] mL/min/1.73 m^2 in the finerenone group, showing an intergroup difference of 1.310 [0.884, 1.735] mL/min/1.73 m^2.

Study 17530 was conducted using "cardiovascular death and non-fatal cardiovascular events (non-fatal myocardial infarction, non-fatal stroke, and hospitalization for cardiac failure)" as the primary endpoint. The study showed that the hazard ratio [two-sided 95% CI] of finerenone to placebo was 0.87 [0.76, 0.98], demonstrating the superiority of finerenone to placebo. In addition, all of components of the cardiovascular composite endpoint showed the hazard ratio of finerenone to placebo was less than 1 (Table 36).

Based on the above, the applicant considers that the efficacy of finerenone in patients with CKD associated with type 2 diabetes mellitus was demonstrated in terms of delaying the occurrence of both renal and cardiovascular composite endpoints.

PMDA's view:

The therapeutic goal of CKD is to improve the outcome, but risks of renal composite endpoint and cardiovascular composite endpoint corresponding to the outcome differ depending on the stage of CKD. In view of the above, the applicant conducted 2 confirmatory studies in patients with renal disorder of which a severity range differed and evaluated the respective endpoints for development. This applicant's development strategy is appropriate. Results from the overall populations in Studies 16244 and 17530 demonstrated the superiority of finerenone to placebo in terms of the respective primary endpoints. In addition, results on each component of the primary composite endpoint for the respective studies supported the efficacy of finerenone demonstrated by ones on the primary endpoint.

21) "Month 4" was selected as a change point after which a decrease in eGFR was supposed to reflect the pathological condition because PPK and pharmacodynamic analyses on changes in eGFR (mL/min/1.73 m^2) in the foreign phase II study (Study 16243) suggested that the initial effect of finerenone on eGFR would reach 99% steady-state on Day 85, and at Month 4, it was likely to be stabilized in most of the patients.

Therefore, Studies 16244 and 17530 demonstrated the clinically meaningful efficacy of finerenone in patients with CKD associated with type 2 diabetes mellitus, the target population of these studies.

7.R.2.2 Appropriateness of Japan's participation in global phase III studies (Studies 16244 and 17530)

PMDA asked the applicant to explain the appropriateness of Japan's participation in Studies 16244 and 17530 including investigation of intrinsic and extrinsic ethnic factors.

The applicant's explanation:

For intrinsic ethnic factors, proportions of patients with type 2 diabetes mellitus complicated by diabetic kidney diseases in Japanese and non-Japanese population were as follows: Of Japanese patients with type 2 diabetes mellitus, 32% and 7% also had high albuminuria and very high albuminuria, respectively (*Diabetes Care.* 2007;30:989-92); and of non-Japanese patients with type 2 diabetes mellitus, 39% and 10% also had high albuminuria and very high albuminuria, respectively (*Kidney International.* 2006;69:2057-63). These ethnic groups showed similar proportions. In addition, a comparison of patient characteristics between Japanese and foreign phase II studies in patients with diabetic nephropathy accompanying type 2 diabetes mellitus (Studies 16816 and 16243) revealed no clear differences in age, gender, or baseline values for HbA1c, blood pressure, eGFR, UACR, or serum potassium between the study populations, except for body weight. Of patient characteristics in Studies 16244 and 17530, body weight differed between the overall population and Japanese population as observed between foreign and Japanese phase II studies, but the other attributes potentially impacting the efficacy or safety of finerenone except for UACR (age, gender as well as baseline values for HbA1c, systolic blood pressure, eGFR, and potassium) did not clearly differ between the overall population and Japanese population. Although baseline UACR slightly differed between the overall population and Japanese population in both studies (median; 851.87 mg/g in the overall population and 728.42 mg/g in the Japanese population in Study 16244, and 308.18 mg/g in the overall population and 213.00 mg/g in the Japanese population in Study 17530), the difference in baseline UACR between non-Japanese and Japanese patients is considered to have little impact on the efficacy results in view of efficacy results in subgroups by baseline UACR described in the section below [see Section "7.R.5 Indication and eligible patients"]. In addition, PPK/PD analyses on data from Japanese and foreign phase II studies in patients with diabetic nephropathy (Studies 16243 and 16816) revealed no clear differences in the PK of finerenone or a relationship of PK with PD between the Japanese and non-Japanese populations. For extrinsic ethnic factors, the standard of care for CKD comprises ACE inhibitors and ARBs both in and outside Japan, but their recommended doses differ. In Japanese and foreign phase II studies (Studies 16243 and 16816), doses of ACE inhibitors and ARBs used for the basic treatment differed between the study populations, but baseline blood pressure did not differ. The difference in effect on urinary albumin secondary to antihypertensive effects of ACE inhibitors and ARBs between the Japanese and non-Japanese ethnic groups was considered limited. In Studies 16244 and 17530, the minimum and maximum doses of ACE inhibitors and ARBs were uniformly specified based on the approved doses for CKD (or for hypertension, if not approved for CKD) mainly in the US irrespective of countries and regions. The doses of ACE inhibitors and ARBs were lower in the Japanese population than in the overall population, but based on results from the subgroup analysis on the primary endpoint by doses of ACE inhibitors and ARBs, the differences

between the doses in and outside Japan were considered to have little impact on the efficacy results [see Section "7.R.2.4 Effects of concomitant drugs"]. Of the other concomitant drugs that may impact the efficacy, SGLT2 inhibitors were concomitantly used in 4.6% (259 of 5674) of patients in the overall population and 8.0% (33 of 415) of patients in the Japanese population in Study 16244 and 8.4% (618 of 7352) of patients and 13.3% (67 of 503) of patients in Study 17530, respectively; and GLP-1 receptor agonists were concomitantly used in 6.9% (394 of 5674) of patients and 11.6% (48 of 415) of patients in Study 16244 and 7.5% (550 of 7352) of patients and 9.1% (46 of 503) of patients in Study 17530, respectively. Although all of the concomitant drugs were more widely used in Japanese population, the subgroup analyses in these studies indicated that the differences in use of concomitant drugs between the Japanese and non-Japanese populations had little impact on the efficacy results [see Section "7.R.2.4 Effects of concomitant drugs"]. Based on the above, the applicant considers Japanese's participation in Studies 16244 and 17530 acceptable from a viewpoint of intrinsic and extrinsic ethnic factors.

PMDA's view:
According to the applicant's explanation, investigation of intrinsic and extrinsic ethnic factors before conducting Studies 16244 and 17530 did not find any large differences in factors potentially impacting the efficacy of finerenone between Japanese and non-Japanese ethnic groups, and thus PMDA considers Japan's participation in global studies of Studies 16244 and 17530 acceptable. In addition, some of the patient characteristics differed between the overall population and Japanese population in Studies 16244 and 17530, but the differences between the populations had little impact on the efficacy evaluation for finerenone based on results from the subgroup analyses on the primary endpoint, etc. by the concerned patient characteristics.

7.R.2.3 Efficacy of finerenone in Japanese patients

Results related to renal outcome in the Japanese population in Studies 16244 and 17530 are mainly as follows:

- The hazard ratio [two-sided 95% CI] of finerenone to placebo for the renal composite endpoint in Study 16244 was less than 1, i.e., 0.91 [0.60, 1.39].However, of the hazard ratios of finerenone to placebo for individual components of the renal composite endpoint, one for "renal failure" was greater than 1 [see Section "7.3.1 Global phase III study (a)"].
- In Study 17530, the hazard ratios of finerenone to placebo for the renal composite endpoint, the secondary endpoint, and its individual components were all greater than 1 [see Section "7.3.2 Global phase III study (b)"].
- A change in eGFR per year from baseline to visit for discontinuation of the study drug or visit at end of study (least squares mean [two-sided 95% CI]) in Study 16244 was –3.469 [–4.261, –2.677] mL/min/1.73 m^2 in the placebo group and –3.574 [–4.345, –2.804] mL/min/1.73 m^2 in the finerenone group, showing an intergroup difference of –0.106 [–1.211, 1.000] mL/min/1.73 m^2. In Study 17530, it was –2.005 [–2.585, –1.425] mL/min/1.73 m^2 in the placebo group and –2.895 [–3.480, –2.309] mL/min/1.73 m^2 in the finerenone group, showing an intergroup difference of –0.889 [–1.713, –0.066] mL/min/1.73 m^2. A change in eGFR per year from Month 4 to visit for discontinuation of the study drug or visit at end of study (least squares mean [two-sided 95% CI]) in Study 16244 was –2.868 [–3.504, –2.232] mL/min/1.73 m^2 in the placebo group and –2.658

[–3.278, –2.038] mL/min/1.73 m^2 in the finerenone group, showing an intergroup difference of 0.210 [–0.678, 1.098] mL/min/1.73 m^2. In Study 17530, it was –2.216 [–2.734, –1.699] mL/min/1.73 m^2 in the placebo group and –2.085 [–2.605, –1.565] mL/min/1.73 m^2 in the finerenone group, showing an intergroup difference of 0.131 [–0.603, 0.865] mL/min/1.73 m^2.

In Studies 16244 and 17530, the incidence of "renal failure," a component of the renal composite endpoint, was higher in the finerenone group than in the placebo group in the Japanese population, but not in the overall population. PMDA asked the applicant to explain reasons for the higher incidence and whether finerenone was expected to delay occurrence of the renal composite endpoint in Japanese patients, despite the above result.

The applicant's explanation:

(a) Patient characteristics

Tables 40 and 41 show distributions of patient characteristics that may affect disease progression in Studies 16244 and 17530. Larger proportions of the Japanese population were affected by smoking and hyperuricaemia than those of the overall population, while smaller proportions of the Japanese population were affected by dyslipidaemia and obesity. On the other hand, distribution of each patient characteristic did not substantially differ between the dose groups in either overall or Japanese population. Therefore, the differences in patient characteristics were unlikely to impact the efficacy evaluation in the Japanese population.

Table 40. Distribution of patient characteristics that may affect disease progression (Study 16244, FAS)

	Overall population		Japanese population	
	Placebo (N = 2841)	Finerenone (N = 2833)	Placebo (N = 207)	Finerenone (N = 208)
Smoking	13.8 (392)	14.6 (414)	25.6 (53)	24.5 (51)
Hypertension	97.4 (2768)	96.6 (2737)	99.5 (206)	100 (208)
Hyperuricaemia	20.1 (572)	19.5 (552)	50.7 (105)	47.6 (99)
Dyslipidaemia	45.1 (1280)	45.2 (1281)	31.4 (65)	29.8 (62)
Obesity	38.0 (1079)	39.5 (1119)	10.1 (21)	11.1 (23)
Baseline eGFR (mL/min/1.73 m^2)				
<25	2.4 (69)	2.3 (66)	2.4 (5)	1.4 (3)
≥25 and <45	53.0 (1505)	52.1 (1476)	56.0 (116)	51.0 (106)
≥45 and <60	32.7 (928)	34.3 (972)	30.4 (63)	39.4 (82)
≥60	11.9 (338)	11.2 (318)	11.1 (23)	8.2 (17)
Missing	<0.1 (1)	<0.1 (1)	0 (0)	0 (0)
Baseline UACR (mg/g)				
<30	0.4 (12)	0.4 (11)	0 (0)	0 (0)
≥30 and <300	11.8 (335)	12.4 (350)	14.5 (30)	10.1 (21)
≥300	87.8 (2493)	87.2 (2470)	85.5 (177)	89.9 (187)
Missing	<0.1 (1)	<0.1 (2)	0 (0)	0 (0)

Proportion of applicable patients: % (n)

Table 41. Distribution of patient characteristics that may affect disease progression (Study 17530, FAS)

	Overall population		Japanese population	
	Placebo (N = 3666)	Finerenone (N = 3686)	Placebo (N = 253)	Finerenone (N = 250)
Smoking	17.3 (636)	17.7 (651)	26.9 (68)	32.4 (81)
Hypertension	95.9 (3517)	96.1 (3544)	98.8 (250)	98.4 (246)
Hyperuricaemia	11.2 (411)	11.1 (410)	26.1 (66)	22.4 (56)
Dyslipidaemia	42.3 (1550)	41.1 (1515)	28.5 (72)	30.0 (75)
Obesity	43.0 (1577)	43.2 (1591)	13.8 (35)	15.6 (39)
Baseline eGFR (mL/min/1.73 m^2)				
<25	0.3 (12)	0.4 (15)	0.4 (1)	0.4 (1)
≥25 and <45	16.6 (610)	17.4 (641)	14.6 (37)	14.4 (36)
≥45 and <60	21.5 (789)	20.2 (745)	29.6 (75)	26.8 (67)
≥60	61.5 (2254)	62.0 (2285)	55.3 (140)	58.4 (146)
Missing	<0.1 (1)	0 (0)	0 (0)	0 (0)
Baseline UACR (mg/g)				
<30	2.7 (98)	3.0 (109)	4.0 (10)	2.4 (6)
≥30 and <300	46.0 (1688)	46.8 (1726)	53.8 (136)	57.2 (143)
≥300	51.2 (1878)	50.2 (1851)	42.3 (107)	40.4 (101)
Missing	<0.1 (2)	0 (0)	0 (0)	0 (0)

Proportion of applicable patients: % (n)

(b) Control status of underlying diseases (hypertension, hyperuricemia, dyslipidemia, and diabetes mellitus)

To investigate effects of control statuses of the underlying diseases (hypertension, hyperuricemia, dyslipidemia, and diabetes mellitus) on the efficacy evaluation of finerenone, a comparison of the control status was made between patients with occurrence of the renal composite endpoint and patients without. No clear effects of the control statuses of the underlying diseases were observed.

(c) Effect of medical environment

Past epidemiological data suggest that dialysis tends to be initiated at an earlier stage in foreign countries including the US than in Japan (*Journal of Japanese Society for Dialysis Therapy.* 2013;46:1107-55), but the early initiation of dialysis in foreign countries is being reconsidered. At present, standards for initiation of dialysis do not substantially differ between Japanese and foreign guidelines (*Nephrol Dial Transplant.* 2011;26:2082-6, *Am J Kidney Dis.* 2015;66:884-930). Regarding whether initiation of dialysis differed between the overall population and Japanese population in Studies 16244 and 17530, pooled analysis of these studies was performed because occurrence of "ESRD" is extremely limited in the Japanese population, and differences in inclusion criteria for eGFR and UACR between Studies 16244 and 17530 are unlikely to impact the decision about the initiation of dialysis. The analysis showed that the last measured eGFR (median) before onset of "ESRD" was 13.5 mL/min/1.73 m^2 in the overall population and 7.05 mL/min/1.73 m^2 in the Japanese population, showing only a modest difference. Renal transplantation was not performed in the Japanese population in either study but was performed in the overall population only in Study 16244. In this study, 5 patients in the placebo group and 3 patients in the finerenone group underwent the transplantation. Based on the above, the differences between medical environments in and outside Japan potentially affecting the occurrence of the renal composite endpoint, if any, would have a limited impact on the efficacy results of finerenone in Japanese patients.

(d) Effects of all-cause deaths on renal composite endpoint

In Study 16244, all-cause deaths occurred in 8.6% (244 of 2841) of patients in the placebo group and 7.7% (219 of 2833) of patients in the finerenone group in the overall population, and the hazard ratio [two-sided 95% CI] of finerenone to placebo was 0.895 [0.746, 1.075]. In the Japanese population, on the other hand, all-cause deaths occurred in 7.7% (16 of 207) of patients in the placebo group and 2.4% (5 of 208) of patients in the finerenone group, and the hazard ratio [two-sided 95% CI] of the finerenone group to the placebo group was 0.298 [0.109, 0.814]. The intergroup difference was greater in the Japanese population than in the overall population. In addition, because in the overall population, only 3.5% (200 of 5674) of patients discontinued the study from the first dose of the study drug to Month 16, and discontinuation mostly occurred after Month 16, a comparison of the incidence of all-cause deaths until Month 16 (using as cut-off value) was made between the groups in the overall population and Japanese population. In the Japanese population, deaths occurred more frequently in the placebo group (8 patients) than in the finerenone group (0 patients) until Month 16. Furthermore, baseline eGFR (mean ± SD) in patients resulting in all-cause deaths in the Japanese population was 37.31 ± 10.68 mL/min/1.73 m^2 in the placebo group and 49.92 ± 18.54 mL/min/1.73 m^2 in the finerenone group; baseline eGFR was lower in the placebo group than in the finerenone group. If these patients had survived, “renal failure” events would have occurred more frequently in the placebo group than in the finerenone group. As described above, in the Japanese population, more patients in the placebo group died before occurrence of the renal composite endpoint than patients in the finerenone group, resulting in the low incidence of “renal failure” in the placebo group. This may have precluded the evaluation of finerenone’s effect on “renal failure.”

In Study 17530, all-cause deaths occurred in 10.1% (370 of 3666) of patients in the placebo group and 9.0% (333 of 3686) of patients in the finerenone group in the overall population, and the hazard ratio [two-sided 95% CI] of finerenone to placebo was 0.89 [0.77, 1.04]. In the Japanese population, on the other hand, all-cause deaths occurred in 4.3% (11 of 253) of patients in the placebo group and 2.0% (5 of 250) of patients in the finerenone group, and the hazard ratio [two-sided 95% CI] of finerenone to placebo was 0.46 [0.16, 1.32]. The intergroup difference in all-cause deaths was greater in the Japanese population than in the overall population as observed in Study 16244. Although no intergroup difference was observed in the number of patients resulting in death until Month 16 (2 in the finerenone group, 2 in the placebo group), baseline eGFR (mean ± SD) in patients with all-cause deaths was 53.40 ± 11.95 mL/min/1.73 m^2 in the placebo group and 65.62 ± 11.11 mL/min/1.73 m^2 in the finerenone group; baseline eGFR was lower in the placebo group than in the finerenone group as found in Study 16244. The differences in the incidence of all-cause deaths and in baseline eGFR in patients with all-cause deaths between the finerenone group and placebo group may have precluded the evaluation of effect of finerenone on “renal failure.”

(e) Incidence of “renal failure” by country

Figures 5 and 6 show forest plots of incidence of “renal failure” in Studies 16244 and 17530 (hazard ratio [two-sided 95% CI]) by country (excluding the countries in which the hazard ratio was not available owing to insufficient number of events). The incidence greatly varied among countries in both studies. The countries in which the hazard ratio was greater than 1 were found to have no clear inter- or intra-study similarities in geographic or ethnic factors.

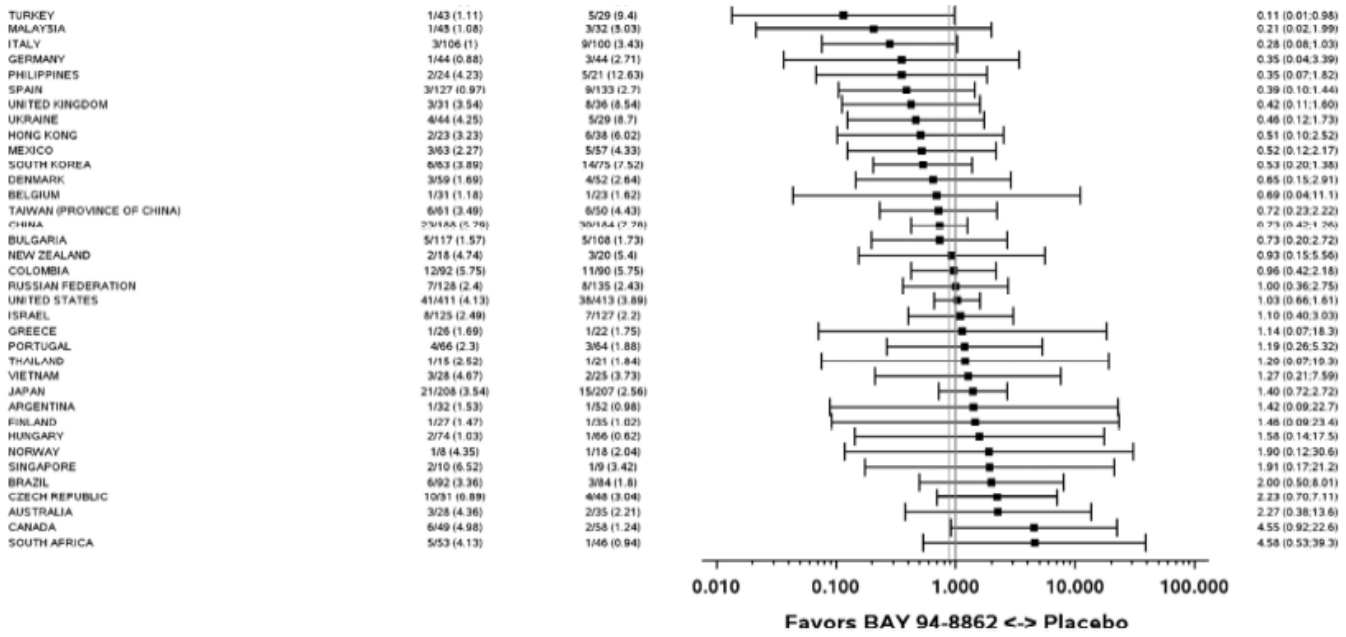
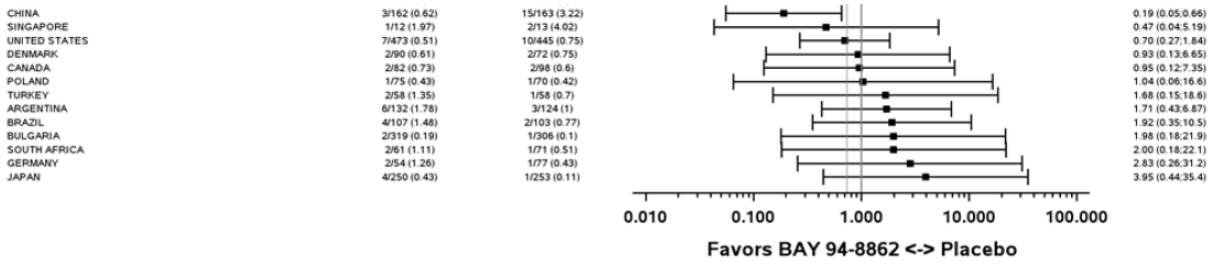


Figure 5. Forest plot of incidence of "renal failure" in Study 16244 by country (FAS, Cox proportional hazards model using the dose group as a factor)



Figures 6. Forest plot of incidence of "renal failure" in Study 17530 by country (FAS, Cox proportional hazards model using the dose group as a factor)

The applicant's consideration about the effect of finerenone in delaying the occurrence of the renal composite endpoint in Japanese patients based on results of the above investigations (a) to (e):

In Study 16244, the hazard ratio [two-sided 95% CI] for sustained decrease of eGFR ≥40%, a component of the renal composite endpoint, was 0.933 [0.609, 1.429]; the hazard ratio in the Japanese population was less than 1 as well. The concerned indicator was shown to correlate with subsequent occurrence of end-stage renal disease and mortality by a large-scale meta-analysis (*JAMA.* 2014;311:2518-31), and similar findings were obtained in Japanese population (*The Japanese Journal of Nephrology.* 2018;60:67-100). In Study 16244, of subjects resulting in "renal failure," 12% (55 of 443) of subjects did not experience a sustained decrease of eGFR ≥40% from baseline for ≥4 weeks before occurrence of "renal failure," while 88% (388 of 443) of subjects experienced this event before occurrence of "renal failure"; most of the patients in Study 16244 experienced a sustained decrease of eGFR ≥40% from baseline before occurrence of "renal failure." In both Studies 16244 and 17530, a decrease in eGFR from baseline to visit for discontinuation of the study drug or visit at end of study was greater in the finerenone group than in the placebo group in the Japanese population, but the difference was negligible; and a decrease in eGFR from Month 4, at which the change in eGFR based on the mechanism of action of finerenone during the early period of the treatment was stabilized, was

smaller in the finerenone group than in the placebo group, suggesting a long-term preventive effect of finerenone against the decrease in eGFR in Japanese subjects as well. In Study 16244, the incidence of "renal failure" was higher in the finerenone group than in the placebo group in the Japanese population, but the difference was small, and the countries or regions in which the hazard ratio was greater than 1 as presented by the forest plot in terms of "renal failure" by country were found to have no clear similarities in geographic or ethnic factors. The concerned higher incidence is considered likely to be an accidental result because of the limited numbers of Japanese patients and patients with the event. In Study 17530, the incidences of the renal composite endpoint and "renal failure," its component, were higher in the finerenone group than in the placebo group (hazard ratio in terms of "renal failure" was 4.53) in the Japanese population, but the concerned results cannot be simply interpreted as ones that deny the efficacy in Japanese because Study 17530 targeted patients with CKD in a wide range of severity including mild disease, thus had a smaller number of occurrences of the renal composite endpoint than Study 16244, and it was not planned to enroll a large enough number of Japanese patients that allowed the applicant to investigate whether results on individual components of the renal composite endpoint in the Japanese population were consistent with those in the overall population.

In Study 17530 in which occurrence of the cardiovascular composite endpoint potentially affecting outcome of patients with CKD was the primary endpoint as with that of the renal composite endpoint in Study 16244, the hazard ratio [95% CI] of finerenone to placebo was 0.65 [0.31, 1.36] in the Japanese population, which was consistent with that in the overall population. In Study 16244 in which the cardiovascular composite endpoint was the secondary endpoint, the hazard ratio [95% CI] of finerenone to placebo was 1.12 [0.53, 2.35] in the Japanese population, showing a different trend from that in the overall population. This difference was considered attributable to the higher incidence of hospitalization for cardiac failure in the finerenone group (2.4%, 5 of 208 patients) than in the placebo group (0.5%, 1 of 207 patients), which was observed in the Japanese population but not in the overall population, the hazard ratios in terms of components other than hospitalization for cardiac failure in the Japanese population showed similar trends to those in the overall population. In Study 17530, however, the incidence of hospitalization for cardiac failure was 1.6% (4 of 253) of patients in the placebo group and 0.8% (2 of 250) of patients in the finerenone group in the Japanese population, not showing a similar trend to that in Study 16244, and thus finerenone would not worsen heart failure.

As described above, the efficacy of finerenone demonstrated in the overall populations in Studies 16244 and 17530 can be expected in Japanese patients with CKD associated with type 2 diabetes mellitus as well.

PMDA's view:
Of the 2 large-scale clinical studies (Studies 16244 and 17530) conducted, Study 16244 demonstrated the superiority of finerenone to placebo in delaying the occurrence of the renal composite endpoint, the primary endpoint, in the overall population and Study 17530 presented a similar result on the secondary endpoint, supporting the result in Study 16244 as the valuable evidence. In Study 16244, the hazard ratios of finerenone to placebo in terms of individual components ("renal failure" as well as its component of "ESRD" and sustained eGFR <15 mL/min/1.73 m^2) of the renal composite endpoint

except for a sustained decrease of eGFR ≥40% from baseline for ≥4 weeks were all greater than 1 in the Japanese population. In Study 17530, the hazard ratios of finerenone to placebo in terms of the renal composite endpoint and individual components were all greater than 1 in the Japanese population. The hazard ratios in terms of most of the efficacy endpoints in the Japanese population were not consistent with those in the overall population. As described above, the results in the Japanese population in Studies 16244 and 17530 are partially inconsistent with those in the overall population. In view of the following points, however, results from Studies 16244 and 17530 conducted as global studies are applicable to each of the participant regions including Japan and concludes that the concerned results overall do not deny the assumption of the global studies that finerenone exerts its effect in delaying the occurrence of the renal composite endpoint in Japanese patients as well.

- In the Japanese and foreign phase II studies (Studies 16243 and 16816) that supported selection of doses in Studies 16244 and 17530, a dose-response relationship for the pharmacodynamic action (change in UACR) did not differ between Japanese and non-Japanese subjects, and distributions of the maintenance dose of finerenone in Studies 16244 and 17530 (dose administered for the longest period in the study period) did not differ between Japanese and non-Japanese subjects [see Section "7.R.7 Dosage and administration"].
- In addition to the above points, no differences between Japanese and non-Japanese subjects potentially impacting the efficacy of finerenone have been presented in any of the intrinsic and extrinsic ethnic factors including the medical environment and pathological condition of patients with CKD associated with type 2 diabetes mellitus. As presented by the forest plots in terms of "renal failure" by country in both studies, the countries in which the hazard ratio was greater than 1 were not found to have clearly similar geographic or ethnic factors.
- In both Studies 16244 and 17530, the numbers of patients who had experienced individual components of the renal composite endpoint were not enough to evaluate consistency between the overall population and Japanese population; especially, the number of occurrences of the renal composite endpoint was smaller in Study 17530, which included patients with CKD in a wider range of severity including mild disease, than in Study 16244.
- Concerning the higher incidence of all-cause deaths in the placebo group than in the finerenone group in the Japanese population in Studies 16244 and 17530, the applicant's discussion that if these patients had survived, "renal failure" would have occurred more frequently in the placebo group than in the finerenone group lacks a definite rationale and thus is not justified, but the imbalance in incidence of all-cause deaths between the groups may have impacted evaluation of the effect of finerenone in delaying the occurrence of the renal composite endpoint in the Japanese population in each study.

Study 17530 demonstrated not only the superiority of finerenone to placebo in delaying the occurrence of the cardiovascular composite endpoint, the primary endpoint, in the overall population, but also consistency between the overall population and Japanese population. In terms of cardiovascular death, a clinically significant event, the hazard ratio of finerenone to placebo was greater than 1 in the Japanese population but not in the overall population in Study 16244. The concerned event less frequently occurred in the finerenone group than in the placebo group in the Japanese population in both Studies 16244 and 17530. In terms of hospitalization for cardiac failure, the hazard ratio of finerenone to placebo was greater than 1 in the Japanese population in Study 16244, but a different

trend was observed in the Japanese population in Study 17530, showing no consistent increasing trend between these studies. Based on the above, finerenone is expected to be effective in delaying the occurrence of the cardiovascular composite endpoint in Japanese patients as well.

As a comprehensive view of the above review, PMDA considers it reasonable to interpret that Japanese patients with CKD associated with type 2 diabetes mellitus are also expected to obtain clinical benefits of finerenone, as observed in the overall population in Studies 16244 and 17530. To avoid a misunderstanding, on the other hand, information about occurrences of renal composite endpoint and cardiovascular composite endpoint as well as their components in the Japanese population should be appropriately provided through the package insert, etc. A final decision on the above conclusion of PMDA will be made, taking account of comments raised at the Expert Discussion.

7.R.2.4 Effects of concomitant drugs

The applicant's explanation about effects of concomitant drugs on the efficacy of finerenone:

(a) Effects of concomitant SGLT2 inhibitors and GLP-1 receptor agonists

Tables 42 to 45 show incidences of the renal composite endpoint and cardiovascular composite endpoint with and without concomitant SGLT2 inhibitors and GLP-1 receptor agonists at baseline in Studies 16244 and 17530. In Study 16244, the hazard ratios of finerenone to placebo in terms of the renal composite endpoint and cardiovascular composite endpoint was greater than 1 in the subgroup with concomitant use either of SGLT2 inhibitors and GLP-1 receptor agonists in the overall population, while in Study 17530, the hazard ratio was less than 1 for the renal composite endpoint and cardiovascular composite endpoint irrespective of concomitant use in the overall population. There are limitations in evaluating whether concomitant SGLT2 inhibitors and GLP-1 receptor agonists would affect the occurrence of the renal composite endpoint and cardiovascular composite endpoint because the number of patients concomitantly receiving these drugs was small. However, the above evaluation does not show any trend of compromised efficacy of finerenone in patients concomitantly receiving these drugs.

Table 42. Incidences of renal composite endpoint with and without concomitant SGLT2 inhibitors and GLP-1 receptor agonists at baseline (Study 16244, FAS)

		Overall population			Japanese population		
		Placebo (N = 2841)	Finerenone (N = 2833)	Hazard ratio [two-sided 95% CI][a]	Placebo (N = 207)	Finerenone (N = 208)	Hazard ratio [two-sided 95% CI][a]
SGLT2 inhibitor	Concomitantly used	7.4 (10/135)	11.3 (14/124)	1.38 [0.61, 3.10]	6.3 (1/16)	5.9 (1/17)	0.72 [0.04, 11.6]
	Not concomitantly used	21.8 (590/2706)	18.1 (490/2709)	0.82 [0.72, 0.92]	22.5 (43/191)	21.5 (41/191)	0.93 [0.60, 1.42]
GLP-1 receptors agonist	Concomitantly used	15.6 (32/205)	16.9 (32/189)	1.17 [0.71, 1.90]	16.0 (4/25)	4.3 (1/23)	0.31 [0.03, 2.80]
	Not concomitantly used	21.5 (568/2636)	17.9 (472/2644)	0.80 [0.71, 0.91]	22.0 (40/182)	22.2 (41/185)	0.94 [0.61, 1.46]

Incidence: % (n/N)

a Stratified Cox proportional hazards model using the dose group as a factor and the region (North America, Europe, Asia, Latin America, or others), type of albuminuria at screening visit (high albuminuria or very high albuminuria), eGFR at screening visit (≥25 mL/min/1.73 m^2 and <45 mL/min/1.73 m^2, ≥45 mL/min/1.73 m^2 and <60 mL/min/1.73 m^2, or ≥60 mL/min/1.73 m^2), and presence or absence of use of an SGLT2 inhibitor or a GLP-1 receptor agonist at baseline as stratification factors

Table 43. Incidences of cardiovascular composite endpoint with and without concomitant SGLT2 inhibitors and GLP-1 receptor agonists at baseline (Study 16244, FAS)

		Overall population			Japanese population		
		Placebo (N = 2841)	Finerenone (N = 2833)	Hazard ratio [two-sided 95% CI][a]	Placebo (N = 207)	Finerenone (N = 208)	Hazard ratio [two-sided 95% CI][a]
SGLT2 inhibitor	Concomitantly used	11.1 (15/135)	12.1 (15/124)	1.12 [0.55, 2.30]	6.3 (1/16)	11.8 (2/17)	1.78 [0.16, 20.1]
	Not concomitantly used	15.0 (405/2706)	13.0 (352/2709)	0.85 [0.74, 0.98]	6.3 (12/191)	6.8 (13/191)	1.08 [0.49, 2.36]
GLP-1 receptors agonist	Concomitantly used	13.7 (28/205)	14.3 (27/189)	1.02 [0.60, 1.74]	0 (0/25)	4.3 (1/23)	-
	Not concomitantly used	14.9 (392/2636)	12.9 (340/2644)	0.85 [0.73, 0.98]	7.1 (13/182)	7.6 (14/185)	1.09 [0.51, 2.33]

Incidence: % (n/N)

-: Not calculated

a Stratified Cox proportional hazards model using the dose group as a factor and the region (North America, Europe, Asia, Latin America, or others), type of albuminuria at screening visit (high albuminuria or very high albuminuria), eGFR at screening visit (≥25 mL/min/1.73 m^2 and <45 mL/min/1.73 m^2, ≥45 mL/min/1.73 m^2 and <60 mL/min/1.73 m^2, or ≥60 mL/min/1.73 m^2), and presence or absence of use of an SGLT2 inhibitor or a GLP-1 receptor agonist at baseline as stratification factors

Table 44. Incidences of renal composite endpoint with and without concomitant SGLT2 inhibitors and GLP-1 receptor agonists at baseline (Study 17530, FAS)

		Overall population			Japanese population		
		Placebo (N = 3666)	Finerenone (N = 3686)	Hazard ratio [two-sided 95% CI][a]	Placebo (N = 253)	Finerenone (N = 250)	Hazard ratio [two-sided 95% CI][a]
SGLT2 inhibitor	Concomitantly used	7.9 (24/304)	7.0 (22/314)	0.70 [0.37, 1.30]	3.1 (1/32)	8.6 (3/35)	-
	Not concomitantly used	11.0 (371/3362)	9.7 (328/3372)	0.88 [0.76, 1.03]	8.1 (18/221)	8.8 (19/215)	1.07 [0.56, 2.05]
GLP-1 receptors agonist	Concomitantly used	10.1 (26/242)	8.1 (25/308)	0.61 [0.34, 1.09]	9.5 (2/21)	20.0 (5/25)	1.54 [0.26, 9.11]
	Not concomitantly used	10.8 (369/3424)	9.6 (325/3378)	0.89 [0.77, 1.04]	7.3 (17/232)	7.6 (17/225)	1.08 [0.55, 2.12]

Incidence: % (n/N)

-: Not calculated

a Stratified Cox proportional hazards model using the dose group as a factor and the region (North America, Europe, Asia, Latin America, or others), type of albuminuria at screening visit (high albuminuria or very high albuminuria), eGFR at screening visit (≥25 mL/min/1.73 m^2 and <45 mL/min/1.73 m^2, ≥45 mL/min/1.73 m^2 and <60 mL/min/1.73 m^2, or ≥60 mL/min/1.73 m^2), presence or absence of a medical history of cardiovascular diseases, and presence or absence of use of an SGLT2 inhibitor or a GLP-1 receptor agonist at baseline as stratification factors

Table 45. Incidences of cardiovascular composite endpoint with and without concomitant SGLT2 inhibitors and GLP-1 receptor agonists at baseline (Study 17530, FAS)

		Overall population			Japanese population		
		Placebo (N = 3666)	Finerenone (N = 3686)	Hazard ratio [two-sided 95% CI][a]	Placebo (N = 253)	Finerenone (N = 250)	Hazard ratio [two-sided 95% CI][a]
SGLT2 inhibitor	Concomitantly used	12.2 (37/304)	7.6 (24/314)	0.49 [0.28, 0.86]	0 (0/32)	2.9 (1/35)	-
	Not concomitantly used	14.3 (482/3362)	12.9 (434/3372)	0.89 [0.78, 1.01]	8.1 (18/221)	5.1 (11/215)	0.61 [0.29, 1.29]
GLP-1 receptors agonist	Concomitantly used	14.9 (36/242)	10.1 (31/308)	0.62 [0.38, 1.03]	0 (0/21)	4.0 (1/25)	-
	Not concomitantly used	14.1 (483/3424)	12.6 (427/3378)	0.89 [0.78, 1.01]	7.8 (18/232)	4.9 (11/225)	0.60 [0.28, 1.27]

Incidence: % (n/N)

-: Not calculated

a Stratified Cox proportional hazards model using the dose group as a factor and the region (North America, Europe, Asia, Latin America, or others), type of albuminuria at screening visit (high albuminuria or very high albuminuria), eGFR at screening visit (≥25 mL/min/1.73 m^2 and <45 mL/min/1.73 m^2, ≥45 mL/min/1.73 m^2 and <60 mL/min/1.73 m^2, or ≥60 mL/min/1.73 m^2), presence or absence of a medical history of cardiovascular diseases, and presence or absence of use of an SGLT2 inhibitor or a GLP-1 receptor agonist at baseline as stratification factors

(b) Effects of doses of ACE inhibitors and ARBs

ACE inhibitors and ARBs were concomitantly used at baseline in 34.2% (1941 of 5674) and 65.6% (3724 of 5674) of patients in the overall population and 8.0% (33 of 415) and 92.0% (382 of 415) of patients in the Japanese population, respectively, in Study 16244; and in 42.7% (3137 of 7352) and 57.3% (4212 of 7352) of patients in the overall population and 6.8% (34 of 503) and 93.4% (470 of 503) of patients in the Japanese population, respectively, in Study 17530. Use status of ACE inhibitors and ARBs differed between Japanese and non-Japanese patients, but a comparison of the efficacy was made between subgroups formed by the dose of an ARB, which were considered eligible for the comparison. Table 46 shows proportions of patients sorted according to the dose of an ARB mainly with respect to the approved dose in the US[22)] in the overall population and Japanese population. Because the approved dose of ARBs differed between clinical settings in and outside Japan, a comparison of the efficacy was made between the subgroups in the overall population according to the dose of an ARB mainly with respect to the approved dose in the US and between ones in the Japanese population according to the dose mainly with respect to the approved dose in Japan[23)] (Tables 47 and 48).

Table 46. Proportions of patients by dose of concomitant ARB at baseline (Studies 16244 and 17530, FAS)

		Study 16244[a]		Study 17530[b]	
Overall population		Placebo (N = 1839)	Finerenone (N = 1873)	Placebo (N = 2092)	Finerenone (N = 2094)
Approved dose mainly in the US	Below upper limit	42.9 (789)	41.8 (783)	47.2 (958)	45.9 (937)
	Above upper limit	57.1 (1050)	58.2 (1090)	53.5 (1134)	54.5 (1157)
Japanese population		Placebo (N = 193)	Finerenone (N = 189)	Placebo (N = 238)	Finerenone (N = 231)
Approved dose mainly in the US	Below upper limit	79.3 (153)	82.5 (156)	90.3 (215)	88.3 (204)
	Above upper limit	20.7 (40)	17.5 (33)	9.7 (23)	11.7 (27)

Proportion of patients: % (n)

a Excluding 5 non-Japanese patients receiving multiple ARBs and 7 non-Japanese patients who were deemed to be ineligible for categorization

b Excluding 16 non-Japanese patients receiving multiple ARBs and 9 non-Japanese patients who were deemed to be ineligible for categorization

22) Approved dose for indication of CKD in the US (for drugs not approved for indication of CKD, the dose for indication of hypertension) except for allisartan and fimasartan not approved in the US. For allisartan and fimasartan, the approved dose for indication of hypertension in China and Korea, respectively.

23) Approved dose for indication of CKD in Japan (for drugs not approved for indication of CKD, the dose for indication of hypertension)

Table 47. Incidences of renal composite endpoint in subgroups by dose of concomitant ARB at baseline (Studies 16244 and 17530, FAS)

		Study 16244			Study 17530		
Overall population		Placebo (N = 1839)	Finerenone (N = 1873)	Hazard ratio [two-sided 95% CI][a]	Placebo (N = 2092)	Finerenone (N = 2094)	Hazard ratio [two-sided 95% CI][b]
Approved dose mainly in the US	Below upper limit	21.9 (173/789)	17.4 (136/783)	0.770 [0.614, 0.966]	11.1 (106/958)	11.3 (106/937)	1.02 [0.77, 1.34]
	Above upper limit	21.8 (229/1050)	18.0 (196/1090)	0.794 [0.655, 0.962]	11.5 (130/1134)	11.1 (129/1157)	0.96 [0.75, 1.23]
Japanese population		Placebo (N = 193)	Finerenone (N = 189)	Hazard ratio [two-sided 95% CI][a]	Placebo (N = 238)	Finerenone (N = 231)	Hazard ratio [two-sided 95% CI][b]
Approved dose in Japan	Below upper limit	25.0 (33/132)	18.7 (26/139)	0.668 [0.397, 1.125]	5.3 (10/188)	9.6 (18/187)	1.89 [0.86, 4.14]
	Above upper limit	14.8 (9/61)	24.0 (12/50)	1.579 [0.655, 3.811]	14.0 (7/50)	4.5 (2/44)	0.40 [0.08, 2.08]

Incidence: % (n/N)

a Stratified Cox proportional hazards model using the dose group as a factor and the region (North America, Europe, Asia, Latin America, or others), type of albuminuria at screening visit (high albuminuria or very high albuminuria), and eGFR at screening visit (≥25 mL/min/1.73 m^2 and <45 mL/min/1.73 m^2, ≥45 mL/min/1.73 m^2 and <60 mL/min/1.73 m^2, or ≥60 mL/min/1.73 m^2) as stratification factors

b Stratified Cox proportional hazards model using the dose group as a factor and the region (North America, Europe, Asia, Latin America, or others), type of albuminuria at screening visit (high albuminuria or very high albuminuria), eGFR at screening visit (≥25 mL/min/1.73 m^2 and <45 mL/min/1.73 m^2, ≥45 mL/min/1.73 m^2 and <60 mL/min/1.73 m^2, or ≥60 mL/min/1.73 m^2), and presence or absence of a medical history of cardiovascular diseases as stratification factors

Table 48. Incidences of cardiovascular composite endpoint in subgroups by dose of concomitant ARB at baseline (Studies 16244 and 17530, FAS)

		Study 16244			Study 17530		
Overall population		Placebo (N = 1839)	Finerenone (N = 1873)	Hazard ratio [two-sided 95% CI][a]	Placebo (N = 2092)	Finerenone (N = 2094)	Hazard ratio [two-sided 95% CI][b]
Approved dose mainly in the US	Below upper limit	13.1 (103/789)	13.0 (102/783)	0.980 [0.742, 1.295]	13.6 (130/958)	12.4 (116/937)	0.91 [0.70, 1.17]
	Above upper limit	14.8 (155/1050)	11.6 (126/1090)	0.752 [0.594, 0.952]	14.6 (166/1134)	12.3 (142/1157)	0.83 [0.67, 1.04]
Japanese population		Placebo (N = 193)	Finerenone (N = 189)	Hazard ratio [two-sided 95% CI][a]	Placebo (N = 238)	Finerenone (N = 231)	Hazard ratio [two-sided 95% CI][b]
Approved dose in Japan	Below upper limit	6.8 (9/132)	7.2 (10/139)	1.026 [0.417, 2.528]	6.9 (13/188)	3.7 (7/187)	0.50 [0.20, 1.26]
	Above upper limit	4.9 (3/61)	10.0 (5/50)	1.549 [0.362, 6.631]	10.0 (5/50)	9.1 (4/44)	1.08 [0.28, 4.19]

Incidence: % (n/N)

a Stratified Cox proportional hazards model using the dose group as a factor and the region (North America, Europe, Asia, Latin America, or others), type of albuminuria at screening visit (high albuminuria or very high albuminuria), and eGFR at screening visit (≥25 mL/min/1.73 m^2 and <45 mL/min/1.73 m^2, ≥45 mL/min/1.73 m^2 and <60 mL/min/1.73 m^2, or ≥60 mL/min/1.73 m^2) as stratification factors

b Stratified Cox proportional hazards model using the dose group as a factor and the region (North America, Europe, Asia, Latin America, or others), type of albuminuria at screening visit (high albuminuria or very high albuminuria), eGFR at screening visit (≥25 mL/min/1.73 m^2 and <45 mL/min/1.73 m^2, ≥45 mL/min/1.73 m^2 and <60 mL/min/1.73 m^2, or ≥60 mL/min/1.73 m^2), and presence or absence of a medical history of cardiovascular diseases as stratification factors

In both studies, a proportion of patients receiving an ARB at a low dose tended to be greater in the Japanese population than in the overall population. Between the subgroups by the dose of an ARB in the overall population, intergroup differences in incidences of the renal composite endpoint and cardiovascular composite endpoint did not tend to differ greatly. In addition, There are limitations in assessing whether the difference in dose of an ARB would affect the occurrence of both endpoints in the Japanese population owing to the small number of events, but no common effect between Studies 16244 and 17530 was observed. The dose of an ARB differed between the overall population and Japanese population in Studies 16244 and 17530 possibly owing to the difference of the approved dose

of ARBs between clinical settings in and outside Japan. The applicant, however, considers that the difference in dose of an ARB has a limited impact on the efficacy of finerenone.

PMDA's view:
It is difficult to investigate whether concomitant SGLT2 inhibitors and GLP-1 receptor agonists would affect the effect of finerenone in delaying the occurrence of the renal composite endpoint and cardiovascular composite endpoint because the numbers of patients receiving these concomitant drugs were small in Studies 16244 and 17530. However, presence or absence of their concomitant use had no common effect on either composite endpoint in the overall population between Studies 16244 and 17530; and finerenone has a mechanism of action different from that of these drugs, thus data in patients concomitantly receiving these drugs have raised no concerns of compromised efficacy of finerenone. The dose of an ARB (absolute value) was lower in the Japanese population than in the overall population in both Studies 16244 and 17530, but the dose of an ARB did not impact the effect of finerenone in delaying the occurrence of either composite endpoint in the overall population, and incidences of the composite endpoint in subgroups by dose of an ARB did not show any consistent trend in the Japanese population in either study. Therefore, The difference in dose of an ARB between clinical settings in and outside Japan has a limited impact on the efficacy of finerenone.

7.R.3 Safety

Based on adverse events in clinical studies and the following review, PMDA considers that no safety problems potentially compromising benefits from clinical use of finerenone have been raised. Based on the above, PMDA concludes that the safety of finerenone in patients with CKD associated with type 2 diabetes mellitus is clinically acceptable in view of the efficacy of finerenone observed in Section "7.R.2 Efficacy."

7.R.3.1 Hyperkalaemia

The applicant's explanation about a risk of hyperkalaemia accompanying use of finerenone:
Tables 49 and 50 show incidences of hyperkalaemia-related events[24)] during the treatment with the study drug in Studies 16244 and 17530.

Table 49. Incidences of hyperkalaemia-related events and high serum potassium level (Study 16244, safety analysis population)

	Overall population		Japanese population	
	Placebo	Finerenone	Placebo	Finerenone
All hyperkalaemia-related events[a]	9.0 (255/2831)	18.3 (516/2827)	12.7 (26/205)	17.8 (37/208)
Events related to study drug	4.8 (135/2831)	11.8 (333/2827)	2.9 (6/205)	9.6 (20/208)
Serious events	0.4 (12/2831)	1.6 (44/2827)	0 (0/205)	0.5 (1/208)
Events leading to discontinuation	0.9 (25/2831)	2.3 (64/2827)	0 (0/205)	1.9 (4/208)
Events leading to hospitalization	0.3 (8/2831)	1.4 (40/2827)	0 (0/205)	0.5 (1/208)
Events leading to death	0 (0/2831)	0 (0/2827)	0 (0/205)	0 (0/208)
Serum potassium level >5.5 mmol/L[b]	9.2 (256/2775)	21.4 (597/2785)	5.9 (12/204)	15.4 (32/208)
Serum potassium level >6.0 mmol/L[c]	1.4 (38/2796)	4.5 (126/2802)	0.5 (1/204)	3.8 (8/208)

Incidence: % (n/N)
a MedDRA Preferred Terms (MedDRA PTs) "Hyperkalaemia" and "Blood potassium increased"
b Patients with serum potassium level >5.5 mmol/L at baseline were excluded from the analysis.
c Patients with serum potassium level >6.0 mmol/L at baseline were excluded from the analysis.

[24)] MedDRA Preferred Terms (MedDRA PTs), "Hyperkalaemia" and "Blood potassium increased"

Table 50. Incidences of hyperkalaemia-related events and high serum potassium level (Study 17530, safety analysis population)

	Overall population		Japanese population	
	Placebo	Finerenone	Placebo	Finerenone
All hyperkalaemia-related events[a]	5.3 (193/3658)	10.8 (396/3683)	4.8 (12/252)	12.0 (30/251)
Events related to study drug	3.1 (114/3658)	6.5 (240/3683)	0.8 (2/252)	3.6 (9/251)
Serious events	0.1 (4/3658)	0.7 (25/3683)	0 (0/252)	0 (0/251)
Events leading to discontinuation	0.4 (13/3658)	1.2 (46/3683)	0 (0/252)	0.8 (2/251)
Events leading to hospitalization	<0.1 (2/3658)	0.6 (21/3683)	0 (0/252)	0 (0/251)
Events leading to death	0 (0/3658)	0 (0/3683)	0 (0/252)	0 (0/251)
Serum potassium level >5.5 mmol/L[b]	6.0 (214/3595)	13.2 (478/3617)	2.0 (5/252)	8.4 (21/251)
Serum potassium level >6.0 mmol/L[c]	1.2 (42/3617)	2.3 (85/3637)	0.4 (1/252)	2.0 (5/251)

Incidence: % (n/N)
a MedDRA PTs "Hyperkalaemia" and "Blood potassium increased"
b Patients with serum potassium level >5.5 mmol/L at baseline were excluded from the analysis.
c Patients with serum potassium level >6.0 mmol/L at baseline were excluded from the analysis.

In both studies, the incidence of hyperkalaemia-related events was approximately twice higher in the finerenone group than in the placebo group in the overall population. Of the hyperkalaemia-related events, however, most were mild or moderate in severity and resolved by the end of study. No hyperkalaemia-related events leading to death occurred, and hyperkalaemia-related events leading to discontinuation of the study drug or hospitalization occurred more frequently in the finerenone group than in the placebo group, but the number of patients with the event was small. In addition, Table 51 shows incidences of serious heart disorders related to hyperkalaemia (bradycardia, ventricular arrhythmia, and sudden cardiac death) and the incidences are not higher in the finerenone group than in the placebo group. Incidences of hyperkalaemia-related events did not clearly differ between the overall population and Japanese population. As described above, the risk of hyperkalaemia can be controlled by implementing dose increase or withdrawal of finerenone according to the serum potassium level as specified in Studies 16244 and 17530.

Table 51. Incidences of serious heart disorders related to hyperkalaemia (Studies 16244 and 17530)

	Study 16244		Study 17530	
	Placebo	Finerenone	Placebo	Finerenone
Bradycardia[a]	0.9 (25/2831)	0.5 (15/2827)	0.8 (29/3658)	0.8 (31/3683)
Ventricular arrhythmia[b]	<0.1 (1/2831)	0 (0/2827)	<0.1 (2/3658)	0 (0/3683)
Sudden cardiac death[c]	1.5 (42/2841)	1.2 (35/2833)	2.0 (73/3666)	1.4 (53/3686)

Incidence: % (n/N)
a Safety analysis population, MedDRA PT "Bradycardia"
b Safety analysis population, MedDRA PT "Ventricular arrhythmia"
c FAS, Sudden cardiac death counted as an efficacy event

PMDA asked the applicant to explain patient characteristics potentially leading to an increased risk of hyperkalaemia-related events.

The applicant's explanation:
Tables 52 and 53 show characteristics of patients who experienced hyperkalaemia-related events in Studies 16244 and 17530.

Table 52. Characteristics of patients at occurrence of hyperkalaemia-related events (Study 16244, safety analysis population)

	Population with hyperkalaemia-related events		Population without hyperkalaemia-related events	
	Placebo (N = 255)	Finerenone (N = 516)	Placebo (N = 2576)	Finerenone (N = 2311[a])
Serum potassium level at baseline (mmol/L)	4.56 ± 0.41	4.52 ± 0.44	4.36 ± 0.46	4.34 ± 0.45
Serum potassium level at occurrence (mmol/L)	5.19 ± 0.57 (N = 247)	5.28 ± 0.56 (N = 499)	-	-
UACR at baseline (mg/g)	1021.83 ± 2.52	898.22 ± 2.65	795.16 ± 2.68	779.02 ± 2.64
UACR at occurrence (mg/g)	1024.18 ± 2.84 (N = 215)	621.00 ± 3.50 (N = 378)	-	-
eGFR at baseline (mL/min/1.73 m^2)	41.90 ± 12.44	40.93 ± 11.00	44.57 ± 12.57	45.12 ± 12.73
eGFR at occurrence (mL/min/1.73 m^2)	34.38 ± 12.98 (N = 248)	33.58 ± 10.90 (N = 502)	-	-

Mean ± SD

a The population parameter was 2310 for calculation of baseline UACR (excluding a patient with a missing baseline UACR value).

Table 53. Characteristics of patients at occurrence of hyperkalaemia-related events (Study 17530, safety analysis population)

	Population with hyperkalaemia-related events		Population without hyperkalaemia-related events	
	Placebo (N = 193)	Finerenone (N = 396)	Placebo (N = 3463)	Finerenone (N = 3287)
Serum potassium level at baseline (mmol/L)	4.56 ± 0.41	4.52 ± 0.43	4.32 ± 0.43	4.31 ± 0.42
Serum potassium level at occurrence (mmol/L)	5.09 ± 0.59 (n = 190)	5.20 ± 0.58 (n = 383)	-	-
UACR at baseline (mg/g)	277.09 ± 3.97	219.11 ± 3.73	290.16 ± 3.51	293.27 ± 3.55
UACR at occurrence (mg/g)	296.33 ± 5.53 (N = 156)	123.92 ± 4.68 (N = 310)	-	-
eGFR at baseline (mL/min/1.73 m^2)	58.06 ± 20.78	56.18 ± 19.31	68.57 ± 21.64	69.03 ± 21.50
eGFR at occurrence (mL/min/1.73 m^2)	48.29 ± 19.75 (N = 191)	46.27 ± 17.28 (N = 388)	-	-

Mean ± SD

In Study 16244, the population with hyperkalaemia-related events tended to have a higher serum potassium level and lower eGFR at baseline than the population without the events. In addition, in the population with a medical history of hyperkalaemia, hyperkalaemia-related events occurred in 15.5% (13 of 84) in the placebo group and 34.2% (25 of 73) in the finerenone group, and serious hyperkalaemia-related events occurred in 2.4% (2 of 84) in the placebo group and 1.4% (1 of 73) in the finerenone group. In the population without a medical history of hyperkalaemia, hyperkalaemia-related events occurred in 8.8% (242 of 2747) in the placebo group and 17.8% (491 of 2754) in the finerenone group, and serious hyperkalaemia-related events occurred in 0.4% (10 of 2747) in the placebo group and 1.6% (43 of 2754) in the finerenone group.

In Study 17530, the population with hyperkalaemia-related events tended to have a higher serum potassium level and lower eGFR at baseline than the population without the events. In addition, in the population with a medical history of hyperkalaemia, hyperkalaemia-related events occurred in 21.4% (6 of 28) in the placebo group and 46.2% (18 of 39) in the finerenone group, and serious hyperkalaemia-related events occurred in 0% (0 of 28) in the placebo group and 5.1% (2 of 39) in the finerenone group. In the population without a medical history of hyperkalaemia, hyperkalaemia-related events occurred in 5.2% (187 of 3630) in the placebo group and 10.4% (378 of

3644) in the finerenone group, and serious hyperkalaemia-related events occurred in 0.1% (4 of 3630) in the placebo group and 0.6% (23 of 3644) in the finerenone group.

Finerenone increases the risk of hyperkalaemia in patients with a high serum potassium level, and Studies 16244 and 17530 enrolled patients with a serum potassium level ≤4.8 mmol/L per the inclusion criteria. In light of the above, PMDA asked the applicant to explain their view about whether finerenone should be contraindicated in patients with hyperkalaemia and patients with a serum potassium level ≥4.8 mmol/L.

The applicant's explanation:
In Studies 16244 and 17530, patients were included based on a serum potassium level at "screening" but not at "baseline (allocation)." As a result, a serum potassium level >4.8 mmol/L in the placebo group and the finerenone group was found at baseline in 13.5% (382 of 2831) of patients and 13.7% (387 of 2827) of patients, respectively, in Study 16244, and 10.2% (373 of 3658) of patients and 10.6% (389 of 3683) of patients, respectively, in Study 17530. The maximum serum potassium level at baseline in the placebo group and the finerenone group was 6.9 mmol/L and 6.2 mmol/L, respectively, in Study 16244, and 6.1 and 6.3 mmol/L, respectively, in Study 17530. Tables 54 and 55 show the results of subgroup analysis on the incidence of hyperkalaemia-related events during treatment with the study drug by baseline serum potassium.

Table 54. Incidences of hyperkalaemia-related events in subgroups by baseline serum potassium in the overall population (Study 16244, safety analysis population)

Baseline serum potassium (mmol/L)		Placebo	Finerenone
≤4.5	All hyperkalaemia-related events[a]	6.7 (125/1858)	15.1 (283/1879)
	Events related to study drug	3.5 (65/1858)	9.3 (175/1879)
	Events leading to discontinuation	0.5 (10/1858)	1.4 (27/1879)
	Serious high potassium events	0.3 (5/1858)	1.5 (28/1879)
	Events leading to hospitalization	0.2 (3/1858)	1.3 (25/1879)
	Events leading to death	0 (0/1858)	0 (0/1879)
>4.5 and ≤4.8	All hyperkalaemia-related events[a]	12.7 (75/591)	21.6 (121/561)
	Events related to study drug	5.9 (35/591)	14.6 (82/561)
	Events leading to discontinuation	1.4 (8/591)	3.6 (20/561)
	Serious high potassium events	0.7 (4/591)	1.6 (9/561)
	Events leading to hospitalization	0.5 (3/591)	1.4 (8/561)
	Events leading to death	0 (0/591)	0 (0/561)
>4.8 and ≤5.0	All hyperkalaemia-related events[a]	13.8 (26/188)	26.2 (50/191)
	Events related to study drug	9.6 (18/188)	20.9 (40/191)
	Events leading to discontinuation	1.6 (3/188)	4.2 (8/191)
	Serious high potassium events	0.5 (1/188)	2.1 (4/191)
	Events leading to hospitalization	0 (0/188)	2.1 (4/191)
	Events leading to death	0 (0/188)	0 (0/191)
>5.0	All hyperkalaemia-related events[a]	14.9 (29/194)	31.6 (62/196)
	Events related to study drug	8.8 (17/194)	18.4 (36/196)
	Events leading to discontinuation	2.1 (4/194)	4.6 (9/196)
	Serious high potassium events	1.0 (2/194)	1.5 (3/196)
	Events leading to hospitalization	1.0 (2/194)	1.5 (3/196)
	Events leading to death	0 (0/194)	0 (0/196)

Incidence: % (n/N)
a MedDRA PTs "Hyperkalaemia" and "Blood potassium increased"

Table 55. Incidences of hyperkalaemia-related events in subgroups by baseline serum potassium in the overall population (Study 17530, safety analysis population)

Baseline serum potassium (mmol/L)		Placebo	Finerenone
≤4.5	All hyperkalaemia-related events[a]	3.6 (93/2608)	7.9 (208/2643)
	Events related to study drug	2.1 (54/2608)	4.5 (120/2643)
	Events leading to discontinuation	<0.1 (1/2608)	0.9 (24/2643)
	Serious high potassium events	0 (0/2608)	0.6 (16/2643)
	Events leading to hospitalization	0 (0/2608)	0.6 (15/2643)
	Events leading to death	0 (0/2608)	0 (0/2643)
>4.5 and ≤4.8	All hyperkalaemia-related events[a]	8.6 (58/675)	15.8 (103/651)
	Events related to study drug	4.9 (33/675)	10.4 (68/651)
	Events leading to discontinuation	0.7 (5/675)	1.7 (11/651)
	Serious high potassium events	0.4 (3/675)	1.2 (8/651)
	Events leading to hospitalization	0.1 (1/675)	0.8 (5/651)
	Events leading to death	0 (0/675)	0 (0/651)
>4.8 and ≤5.0	All hyperkalaemia-related events[a]	12.3 (25/203)	21.1 (47/223)
	Events related to study drug	7.4 (15/203)	13.0 (29/223)
	Events leading to discontinuation	2.0 (4/203)	1.3 (3/223)
	Serious high potassium events	0.5 (1/203)	0.4 (1/223)
	Events leading to hospitalization	0.5 (1/203)	0.4 (1/223)
	Events leading to death	0 (0/203)	0 (0/223)
>5.0	All hyperkalaemia-related events[a]	10.0 (17/170)	22.9 (38/166)
	Events related to study drug	7.1 (12/170)	13.9 (23/166)
	Events leading to discontinuation	1.8 (3/170)	4.8 (8/166)
	Serious high potassium events	0 (0/170)	0 (0/166)
	Events leading to hospitalization	0 (0/170)	0 (0/166)
	Events leading to death	0 (0/170)	0 (0/166)

Incidence: % (n /N)
a MedDRA PTs "Hyperkalaemia" and "Blood potassium increased"

In both studies, patients with a higher baseline serum potassium level tended to experience hyperkalaemia-related events and events leading to discontinuation of the study drug more frequently in either group, but the incidences of serious events and events leading to hospitalization did not tend to be higher in any of the subgroups with a baseline serum potassium level >4.5 mmol/L than one with a baseline serum potassium level ≤4.5 mmol/L. Based on the above, finerenone may not have to be contraindicated in patients with a serum potassium level >4.8 or 5.0 mmol/L, but for use of finerenone in patients with a serum potassium level >5.0 mmol/L, who potentially have an increased risk of hyperkalaemia, a caution should be advised with a statement that finerenone may be started only when it is considered unavoidable for the treatment. The caution for patients with a serum potassium level >4.8 and ≤5.0 mmol/L is described below.

PMDA asked the applicant to explain the appropriateness of the first timing of measuring serum potassium after the start of treatment with finerenone.

The applicant's explanation:
In the foreign phase II study in patients with diabetic nephropathy accompanying type 2 diabetes mellitus (Study 16243), serum potassium was first measured on Day 7. Of 821 patients who received finerenone, 2 patients in the finerenone group experienced hyperkalaemia-related events within 30 days after the first dose (on Days 3 and 29); the first event was mild and resolved 3 days after discontinuation, and the second one was moderate and resolved 24 days after discontinuation. In the Japanese phase II study (Study 16816) conducted in a design similar to that of Study 16243, no

hyperkalaemia-related events occurred throughout the study period. Based on results from the above Japanese and foreign phase II studies, serum potassium was first measured on Day 30 in Studies 16244 and 17530. In Study 16244, of 2827 patients who received finerenone, 55 patients in the finerenone group experienced hyperkalaemia-related events within 30 days after the first dose (accounting for 10.7% of the total patients who experienced the events at any time of the study period), while 24 patients in the placebo group experienced the events (accounting for 9.4% of the total patients). Compared with that in the placebo group, the frequency was not particularly high during a period of 30 days after the first dose but was rather invariable. In the finerenone group, 3 patients experienced serious hyperkalaemia within 30 days after the first dose (on Days 5, 29, and 30, respectively) but were recovering or recovered 2 to 3 days after discontinuation. In Study 17530, of 3683 patients who received finerenone, 35 patients in the finerenone group experienced hyperkalaemia-related events within 30 days after the first dose (accounting for 8.8% of the total patients who experienced the events at any time of the study period), while 14 patients in the placebo group experienced the events (accounting for 7.3% of the total patients). Compared with that in the placebo group, the frequency was not particularly high during a period of 30 days after the first dose but was rather invariable. In the finerenone group, 1 patient experienced serious hyperkalaemia within 30 days after the first dose (on Day 30) but recovered 7 days after discontinuation. The risk of hyperkalaemia did not tend to be higher during an early period of the treatment (first 30 days) than during the subsequent period. The applicant considers it appropriate to measure serum potassium the first time on Day 30 as specified in Studies 16244 and 17530. In patients at a high risk of hyperkalaemia, on the other hand, control of serum potassium can be implemented at an appropriate frequency by advising the following caution: Patients at a high risk of hyperkalaemia (low eGFR, high serum potassium levels, a medical history of hyperkalaemia, etc.) including patients with a baseline serum potassium level >4.8 mmol/L should be more frequently tested for serum potassium.

PMDA's view:

Hyperkalaemia is an event expected from the mechanism of action of finerenone and potentially leads to a clinically serious outcome, and measurement of serum potassium and adjustment of the dosage regimen should be implemented as specified in Studies 16244 and 17530 with close attention paid to an increase in serum potassium levels. In particular, patients with low eGFR, high serum potassium levels, or a medical history of hyperkalaemia tended to experience hyperkalaemia more frequently. The necessity of finerenone treatment therefore should be carefully considered and, if finerenone was used, serum potassium should be measured at a shorter interval for control so that dose reduction or discontinuation of finerenone or other measures can be taken when an increase in serum potassium occurs. In view of a range of baseline serum potassium levels and the incidences of hyperkalaemia-related events by baseline serum potassium level in patients enrolled in these studies, no clinically unacceptable safety concerns are presented in patients with hyperkalaemia and serum potassium levels of >4.8 and ≤5.0 mmol/L and >5.0 mmol/L. PMDA, therefore, considers it possible to use finerenone in patients with hyperkalaemia and a serum potassium level >4.8 and ≤5.0 mmol/L as well, which exceeds the inclusion criteria in Studies 16244 and 17530, as long as appropriate control is implemented in accordance with the caution including serum potassium monitoring. In addition, in patients with hyperkalaemia and a serum potassium level >5.0 mmol/L in whom the other MR antagonists approved in Japan (approved for the indication of hypertension, etc.) are

contraindicated, finerenone may not have to be uniformly prohibited but may be used if benefits outweigh the risks, in view of the incidences of serious events and events leading to hospitalization in these patients, of whom the number is limited though. In both studies, hyperkalaemia-related events occurred not only during an early period of the treatment but also throughout the study period. Serum potassium therefore should be periodically measured while finerenone is being used, not only during the early period of the treatment but also after determination of the maintenance dose. The package insert proposed by the applicant include instructions for monitoring of serum potassium and dose adjustment based on the serum potassium level as well as cautionary statements about hyperkalaemia, and the applicant's proposal is mostly appropriate but will be finalized, taking account of comments raised at the Expert Discussion.

7.R.3.2 Concomitant use with potassium-sparing diuretics

In Studies 16244 and 17530, patients receiving a potassium-sparing diuretic were excluded, and its concomitant use was prohibited during the study. In view of these actions, PMDA asked the applicant to explain their view about whether co-administration of finerenone and an approved potassium-sparing diuretic is appropriate.

The applicant's explanation:

In Studies 16244 and 17530, a part of the patients received potassium-sparing diuretics (amiloride and triamterene) during the study. In Study 16244, 6 patients in the finerenone group concomitantly received the drug, and of these, 1 patient experienced hyperkalaemia twice. The concerned patient was a 73-year-old woman with a serum potassium level of 4.4 mmol/L and eGFR of 44.5 mL/min/1.73 m^2 at baseline. During the study, concomitant use of amiloride was started, then mild hyperkalaemia (5.5 mmol/L) occurred after 7 days of its concomitant use, and finerenone was interrupted but the use of amiloride was continued. While interruption of finerenone was in place, severe hyperkalaemia (6.6 mmol/L) occurred, which led to interruption of amiloride, and 9 days later the event was resolved. Approximately 2 months later, finerenone was resumed. In Study 17530, 10 patients in the finerenone group concomitantly received the drug, and of these, 2 patients experienced hyperkalaemia during its concomitant use or after that. A 56-year-old woman with a serum potassium level of 4.2 mmol/L and eGFR of 41.2 mL/min/1.73 m^2 at baseline experienced the event as the first patient. Triamterene was used before the start of the study and discontinued 1 year and 6 months after the start of finerenone treatment. Three months later, mild hyperkalaemia (5.3 mmol/L) occurred but resolved 5 days after interruption of finerenone. A 76-year-old man with a serum potassium level of 4.3 mmol/L and eGFR of 52.0 mL/min/1.73 m^2 at baseline experienced the event as the second patient. Concomitant use with amiloride was started during the study and mild hyperkalaemia (6.0 mmol/L) occurred after 16 days of its concomitant use. The event was resolved 20 days after interruption of finerenone (21 days after interruption of amiloride). In the other patients concomitantly receiving a potassium-sparing diuretic, no hyperkalaemia-related events[24)] occurred. In clinical settings, patients with CKD associated with type 2 diabetes mellitus are possibly complicated by hypokalaemia. In such patients, potassium-sparing diuretics may be used. Co-administration of a potassium-sparing diuretic and finerenone should be generally avoided because it increases the risk of hyperkalaemia. The applicant, however, considers it acceptable to co-administer these drugs to patients with low serum potassium

levels and thus at a low risk of hyperkalaemia under a physician's appropriate monitoring of serum potassium levels.

Based on the above, concerning concomitant use of potassium-sparing diuretics, physicians may judge that expected benefits outweigh risks in some patients. Therefore, potassium-sparing diuretics should be listed in the Precautions for Co-administration section with a cautionary statement that these drugs may be used only when it is considered unavoidable for the treatment rather than listed in the Contraindications for Co-administration section.

PMDA's view:
In clinical settings, when finerenone is considered for patients with CKD receiving an approved potassium-sparing diuretic, switchover from an approved potassium-sparing diuretic to finerenone is expected rather than co-administration in view of the effect of finerenone to retain serum potassium. In patients receiving a potassium-sparing diuretic to prevent hypokalaemia owing to a medical history of this disease caused by use of a loop diuretic for fluid control, on the other hand, such a switchover to finerenone may lose maintenance of serum potassium. Safety information about co-administration of finerenone and a potassium-sparing diuretic is extremely limited. Based on information from experience with co-administration in Studies 16244 and 17530, co-administration of finerenone and a potassium-sparing diuretic does not have to be contraindicated, provided that serum potassium is strictly monitored and appropriate measures are taken according to the serum potassium level. On the other hand, such co-administration, which possibly increases the risk of hyperkalaemia, may be considered only when it is necessary for the treatment. The following cautionary statement should be provided: If the co-administration was necessary, the patient's condition should be closely monitored through measures such as more frequent monitoring of serum potassium. PMDA will make a final decision on it, taking account of comments raised at the Expert Discussion.

7.R.3.3 Blood pressure decreased

The mechanism of action of finerenone is likely to involve the risk of blood pressure decreased. PMDA asked the applicant to explain their view about whether a caution about the risk should be advised:

The applicant's explanation:
Tables 56 and 57 show incidences of events related to blood pressure decreased[25)] during the study drug treatment in subgroups by systolic blood pressure at baseline in Studies 16244 and 17530.

[25)] MedDRA PTs "Blood pressure decreased," "Hypotension," and "Orthostatic hypotension"

Table 56. Incidences of events related to blood pressure decreased in subgroups by baseline systolic blood pressure in the overall population (Study 16244, safety analysis population)

	Systolic blood pressure <100 mmHg		Systolic blood pressure ≥100 and <130 mmHg		Systolic blood pressure ≥130 and <160 mmHg		Systolic blood pressure ≥160 mmHg	
	Placebo (N = 16)	Finerenone (N = 9)	Placebo (N = 761)	Finerenone (N = 779)	Placebo (N = 1916)	Finerenone (N = 1897)	Placebo (N = 138)	Finerenone (N = 141)
All events related to blood pressure decreased[a]	12.5 (2)	11.1 (1)	6.0 (46)	8.9 (69)	3.0 (57)	3.9 (74)	2.2 (3)	3.5 (5)
Events leading to discontinuation	0 (0)	0 (0)	0 (0)	0.1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Serious events	0 (0)	0 (0)	0.3 (2)	0.5 (4)	0.2 (4)	0.4 (7)	0 (0)	0 (0)
Events leading to hospitalization	0 (0)	0 (0)	0.3 (2)	0.4 (3)	0.2 (4)	0.4 (7)	0 (0)	0 (0)
Events leading to death	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Incidence: % (n)

a MedDRA PTs "Blood pressure decreased," "Hypotension," and "Orthostatic hypotension"

Table 57. Incidences of events related to blood pressure decreased in subgroups by baseline systolic blood pressure in the overall population (Study 17530, safety analysis population)

	Systolic blood pressure <100 mmHg		Systolic blood pressure ≥100 and <130 mmHg		Systolic blood pressure ≥130 and <160 mmHg		Systolic blood pressure ≥160 mmHg	
	Placebo (N = 26)	Finerenone (N = 14)	Placebo (N = 1168)	Finerenone (N = 1173)	Placebo (N = 2351)	Finerenone (N = 2389)	Placebo (N = 113)	Finerenone (N = 107)
All events related to blood pressure decreaseds[a]	34.6 (9)	28.6 (4)	4.5 (53)	7.5 (88)	2.0 (48)	3.8 (91)	4.4 (5)	5.6 (6)
Events leading to discontinuation	0 (0)	7.1 (1)	0 (0)	0 (0)	<0.1 (1)	<0.1 (1)	0 (0)	0 (0)
Serious events	0 (0)	0 (0)	0.2 (2)	0 (0)	0 (0)	0.1 (3)	1.8 (2)	0 (0)
Events leading to hospitalization	0 (0)	0 (0)	0.2 (2)	0 (0)	0 (0)	0.1 (3)	1.8 (2)	0 (0)
Events leading to death	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Incidence: % (n)

a MedDRA PTs "Blood pressure decreased," "Hypotension," and "Orthostatic hypotension"

Both studies showed a higher trend of the incidence in the finerenone group than in the placebo group irrespective of systolic blood pressure at baseline as well as a higher trend of the incidence of events related to blood pressure decreased in the subgroups with lower systolic blood pressure at baseline in both groups. In addition, investigation of the events in subgroups by diastolic blood pressure at baseline showed similar trends. However, no events related to blood pressure decreased leading to death occurred, and most of the events were non-serious and mild or moderate in severity. The serious events in 3 patients in Study 16244 were assessed to be causally related to the study drug but resolved after discontinuation. Events that were causally related to the study drug and led to discontinuation occurred in 1 patient in the finerenone group in Study 16244 and 2 patients in the finerenone group in Study 17530, but these events were all mild or moderate in severity. In addition, no characteristics specific to the patients with events related to blood pressure decreased including blood pressure at baseline were found. Based on the above, finerenone has raised no safety concern about hypotension or an excessive hypotensive action, and the applicant considers it unnecessary to advise a caution.

PMDA's view:

The mechanism of action of finerenone is likely to involve the risk of decreased blood pressure, and the incidences of events related to blood pressure decreased tended to be higher in the finerenone group than in the placebo group in clinical studies. In view of the above, attention should be paid to blood pressure decreased during use of finerenone. On the other hand, these risks are clinically acceptable weighing the efficacy against them because these risks can be controlled if a caution is in place as done for general hypotensive drugs in view of seriousness and outcome of the events in clinical studies. In addition, as described in Section "7.R.4 Efficacy and safety by renal function" below, the incidence of events related to blood pressure decreased tended to be higher in subgroups with lower eGFR at baseline in Study 17530, but patients with eGFR <25 mL/min/1.73 m^2 are proposed to be subject to a caution requiring careful consideration about the appropriateness of use of finerenone. In view of the above, PMDA considers it unnecessary to advise an additional caution about blood pressure decreased in patients with renal impairment.

7.R.3.4 Use of finerenone in patients with hepatic impairment

The applicant's explanation about use of finerenone in patients with hepatic impairment:

AUC and C_{max} did not differ between subjects with mild hepatic impairment and subjects with normal hepatic function, and AUC in subjects with moderate hepatic impairment was 1.38 times higher than that in subjects with normal hepatic function but C_{max} did not greatly differ [see Section "6.R.2 Variations of exposure to finerenone in patients with hepatic impairment"]. Because the exposure did not greatly differ between subjects with normal hepatic function and subjects with mild hepatic impairment, the subjects in Studies 16244 and 17530 were sorted into a subgroup with hepatic function classified as probable[26)] Child-Pugh class A including normal and subgroup with hepatic function classified as probable[27)] or definite[28)] Child-Pugh class B, and comparisons of incidences of major adverse events during the study drug treatment and hyperkalaemia-related events[24)] were made between the subgroups (Tables 58 and 59).

[26)] Subjects with total serum bilirubin of <2 mg/dL and serum albumin of >3.5 g/dL at baseline

[27)] Subjects meeting either (a) or (b) below. (a) Subjects with total serum bilirubin of 2 to 3 mg/dL and serum albumin of >3.5 g/dL at baseline, (b) Subjects with total serum bilirubin of <2 mg/dL and serum albumin of 2.8 to 3.5 g/dL at baseline

[28)] Subjects meeting any of (a) to (c) below. (a) Subjects with total serum bilirubin of <2 mg/dL and serum albumin of <2.8 g/dL at baseline, (b) Subjects with total serum bilirubin of 2 to 3 mg/dL and serum albumin of ≤3.5 g/dL at baseline, and (c) Subjects with total serum bilirubin of >3 mg/dL

Table 58. Incidences of adverse events and hyperkalaemia-related events in subgroups by severity of hepatic impairment
(Study 16244, safety analysis population)

	Probable Child-Pugh class A (including normal hepatic function)		Probable or definite Child-Pugh class B	
	Placebo (N = 2662)	Finerenone (N = 2659)	Placebo[b] (N = 169)	Finerenone[c] (N = 168)
All adverse events	87.5 (2329)	87.3 (2322)	88.2 (149)	86.9 (146)
Events leading to discontinuation	5.7 (153)	7.1 (190)	8.9 (15)	10.1 (17)
Serious events	33.7 (897)	31.1 (828)	43.8 (74)	44.0 (74)
Serious events related to study drug	1.2 (31)	1.7 (45)	1.8 (3)	1.8 (3)
Serious events leading to discontinuation	2.6 (70)	2.6 (68)	4.7 (8)	4.2 (7)
Events leading to death	1.7 (46)	1.1 (29)	3.0 (5)	1.2 (2)
Hyperkalaemia-related events[a]	8.6 (228)	17.8 (473)	16.0 (27)	25.6 (43)
Hyperkalaemia-related events leading to hospitalization	0.3 (7)	1.5 (39)	0.6 (1)	0.6 (1)
Hyperkalaemia-related events leading to discontinuation	0.9 (23)	2.3 (61)	1.2 (2)	1.8 (3)

Incidence: % (n)
a MedDRA PTs "Hyperkalaemia" and "Blood potassium increased"
b Consisting of 164 subjects with probable Child-Pugh class B and 5 subjects with definite Child-Pugh class B
c Consisting of 164 subjects with probable Child-Pugh class B and 4 subjects with definite Child-Pugh class B

Table 59. Incidences of adverse events and hyperkalaemia-related events in subgroups by severity of hepatic impairment
(Study 17530, safety analysis population)

	Probable Child-Pugh class A (including normal hepatic function)		Probable or definite Child-Pugh class B	
	Placebo (N = 3566)	Finerenone (N = 3597)	Placebo[b] (N = 90)	Finerenone[c] (N = 84)
All adverse events	85.5 (3049)	85.0 (3057)	87.8 (79)	89.3 (75)
Events leading to discontinuation	4.9 (173)	5.6 (202)	11.1 (10)	6.0 (5)
Serious events	32.9 (1174)	31.4 (1128)	45.6 (41)	34.5 (29)
Serious events related to study drug	0.8 (27)	0.9 (34)	0 (0)	1.2 (1)
Serious events leading to discontinuation	2.0 (72)	1.9 (67)	4.4 (4)	3.6 (3)
Events leading to death	2.7 (98)	2.1 (76)	2.2 (2)	3.6 (3)
Hyperkalaemia-related events[a]	5.0 (179)	10.7 (386)	15.6 (14)	11.9 (10)
Hyperkalaemia-related events leading to hospitalization	<0.1 (2)	0.6 (20)	0 (0)	1.2 (1)
Hyperkalaemia-related events leading to discontinuation	0.3 (11)	1.2 (44)	2.2 (2)	2.4 (2)

Incidence: % (n)
a MedDRA PTs "Hyperkalaemia" and "Blood potassium increased"
b Consisting of 88 subjects with probable Child-Pugh class B and 2 subjects with definite Child-Pugh class B
c Consisting of 82 subjects with probable Child-Pugh class B and 2 subjects with definite Child-Pugh class B

In both studies, the incidence of all adverse events in the subgroup of subjects with probable Child-Pugh class A including normal hepatic function was comparable to that in the subgroup of subjects with probable or definite Child-Pugh class B irrespective of whether finerenone or placebo was administered. Serious adverse events occurred more frequently in the subgroup of subjects with probable or definite Child-Pugh class B than in the subgroup of subjects with probable Child-Pugh class A including normal hepatic function, but they occurred in both finerenone and placebo groups.

Based on the above, the applicant considers it unnecessary to adjust the dose for patients with mild hepatic impairment (Child-Pugh class A). In patients with moderate hepatic impairment (Child-Pugh class B), on the other hand, exposure to finerenone increased to a certain extent, and the incidence of hyperkalaemia-related events tended to be higher than that in patients with normal hepatic function or mild hepatic impairment (Child-Pugh class A). In view of the above, the applicant proposed to advise a caution requiring more frequent measurement of serum potassium rather than dose adjustment. In

patients with severe hepatic impairment (Child-Pugh class C), however, use of finerenone should be avoided, and thus the package insert provided a cautionary statement to the effect that use of finerenone in these patients should be avoided [see Section "6.R.2 Variations of exposure to finerenone in patients with hepatic impairment"].

PMDA's view:
A certain number of patients with mild or moderate hepatic impairment were enrolled in Studies 16244 and 17530, and incidences of adverse events in these patients did not greatly differ between the finerenone group and placebo group. In view of the above finding and the extent of an increase in exposure to finerenone in patients with moderate hepatic impairment, dose reduction of finerenone should not be considered in patients with mild or moderate hepatic impairment. The incidence of hyperkalaemia-related events, on the other hand, tended to increase with the dose of finerenone. Results from Tables 58 and 59 suggested that the incidence of hyperkalaemia-related events could be higher in patients with moderate hepatic impairment than in patients with normal hepatic function or mild hepatic impairment. In view of the above, PMDA considers the applicant's proposal appropriate to advise a caution requiring more frequent measurement of serum potassium in patients with moderate hepatic impairment. In patients with severe hepatic impairment, finerenone should be contraindicated because (a) finerenone has not been used in these patients, leaving the extent of an increase in exposure to finerenone unknown; (b) finerenone could further increase the risk of hyperkalaemia in these patients who may be in an extremely poor general condition and receive a potassium-sparing diuretic for treatment of ascites; and (c) the efficacy and safety of finerenone started at a lower dose than 10 mg once daily have not been evaluated, making it difficult to establish the starting regimen recommended for these patients. For cautionary statements for patients with hepatic impairment, PMDA will make a final conclusion, taking account of comments raised in the Expert Discussion.

7.R.4 Efficacy and safety by renal function

The applicant's explanation about the efficacy of finerenone in subgroups by renal function:
Tables 60 to 63 show incidences of the renal composite endpoint and cardiovascular composite endpoint in subgroups by renal function in Studies 16244 and 17530. Both studies excluded patients with eGFR <25 mL/min/1.73 m^2 at screening, but Study 16244 enrolled 69 patients with eGFR <25 mL/min/1.73 m^2 at baseline in the placebo group and 66 patients in the finerenone group, and Study 17530 enrolled 12 patients in the placebo group and 15 patients in the finerenone group. These patients were also subjected to the evaluation. The minimum eGFR at baseline was 15.8 mL/min/1.73 m^2 in both placebo group and finerenone group in Study 16244 as well as 17.6 mL/min/1.73 m^2 in the placebo group and 17.3 mL/min/1.73 m^2 in the finerenone group in Study 17530.

Table 60. Incidences of renal composite endpoint in subgroups by renal function (Study 16244, FAS)

Baseline eGFR (mL/min/1.73 m^2)	Overall population			Japanese population		
<25	Placebo (N = 69)	Finerenone (N = 66)	Hazard ratio [two-sided 95% CI][a]	Placebo (N = 5)	Finerenone (N = 3)	Hazard ratio [two-sided 95% CI][a]
Renal composite endpoint (first)	33.3 (23)	27.3 (18)	0.88 [0.48, 1.64]	20.0 (1)	33.3 (1)	1.89 [0.12, 30.5]
Renal failure	33.3 (23)	27.3 (18)	-	20.0 (1)	33.3 (1)	-
Sustained decrease of eGFR ≥40% from baseline	23.2 (16)	15.2 (10)	-	20.0 (1)	33.3 (1)	-
≥25 and <45	Placebo (N = 1505)	Finerenone (N = 1476)	Hazard ratio [two-sided 95% CI][a]	Placebo (N = 116)	Finerenone (N = 106)	Hazard ratio [two-sided 95% CI][a]
Renal composite endpoint (first)	22.5 (339)	20.0 (295)	0.86 [0.73, 1.00]	24.1 (28)	21.7 (23)	0.84 [0.48, 1.46]
Renal failure	12.0 (180)	11.1 (164)	-	11.2 (13)	13.2 (14)	-
Sustained decrease of eGFR ≥40% from baseline	21.7 (326)	18.9 (279)	-	23.3 (27)	21.7 (23)	-
≥45 and <60	Placebo (N = 928)	Finerenone (N = 972)	Hazard ratio [two-sided 95% CI][a]	Placebo (N = 63)	Finerenone (N = 82)	Hazard ratio [two-sided 95% CI][a]
Renal composite endpoint (first)	18.1 (168)	14.2 (138)	0.77 [0.61, 0.96]	15.9 (10)	18.3 (15)	0.85 [0.38, 1.93]
Renal failure	2.7 (25)	2.3 (22)	-	1.6 (1)	7.3 (6)	-
Sustained decrease of eGFR ≥40% from baseline	17.9 (166)	14.1 (137)	-	15.9 (10)	18.3 (15)	-
≥60	Placebo (N = 338)	Finerenone (N = 318)	Hazard ratio [two-sided 95% CI][a]	Placebo (N = 23)	Finerenone (N = 17)	Hazard ratio [two-sided 95% CI][a]
Renal composite endpoint (first)	20.7 (70)	16.7 (53)	0.78 [0.55, 1.12]	21.7 (5)	17.6 (3)	1.18 [0.27, 5.11]
Renal failure	2.1 (7)	1.3 (4)	-	0 (0)	0 (0)	-
Sustained decrease of eGFR ≥40% from baseline	20.4 (69)	16.7 (53)	-	21.7 (5)	17.6 (3)	-

Incidence: % (n)

-; Not calculated. Of components of the renal composite endpoint, renal death was omitted because the concerned event occurred only in 2 patients each in the placebo group and finerenone group in the overall population.

a Stratified Cox proportional hazards model using the dose group as a factor and the region (North America, Europe, Asia, Latin America, or others), type of albuminuria at screening visit (high albuminuria or very high albuminuria), and eGFR at screening visit (≥25 mL/min/1.73 m^2 and <45 mL/min/1.73 m^2, ≥45 mL/min/1.73 m^2 and <60 mL/min/1.73 m^2, or ≥60 mL/min/1.73 m^2) as stratification factors

Table 61. Incidences of renal composite endpoint in subgroups by renal function (Study 17530, FAS)

Baseline eGFR (mL/min/1.73 m^2)	Overall population			Japanese population		
<25	Placebo (N = 12)	Finerenone (N = 15)	Hazard ratio [two-sided 95% CI][a]	Placebo (N = 1)	Finerenone (N = 1)	Hazard ratio [two-sided 95% CI][a]
Renal composite endpoint (first)	0 (0)	13.3 (2)	-	0 (0)	0 (0)	-
Renal failure	0 (0)	13.3 (2)	-	0 (0)	0 (0)	-
Sustained decrease of eGFR ≥40% from baseline	0 (0)	0 (0)	-	0 (0)	0 (0)	-
≥25 and <45	Placebo (N = 610)	Finerenone (N = 641)	Hazard ratio [two-sided 95% CI][a]	Placebo (N = 37)	Finerenone (N = 36)	Hazard ratio [two-sided 95% CI][a]
Renal composite endpoint (first)	8.4 (51)	7.8 (50)	0.92 [0.62, 1.37]	8.1 (3)	8.3 (3)	1.00 [0.20, 5.08]
Renal failure	3.4 (21)	2.5 (16)	-	0 (0)	5.6 (2)	-
Sustained decrease of eGFR ≥40% from baseline	7.9 (48)	7.0 (45)	-	8.1 (3)	8.3 (3)	-
≥45 and <60	Placebo (N = 789)	Finerenone (N = 745)	Hazard ratio [two-sided 95% CI][a]	Placebo (N = 75)	Finerenone (N = 67)	Hazard ratio [two-sided 95% CI][a]
Renal composite endpoint (first)	8.5 (67)	9.8 (73)	1.25 [0.88, 1.77]	1.3 (1)	9.0 (6)	5.33 [0.64, 44.3]
Renal failure	0.8 (6)	0.9 (7)	-	0 (0)	1.5 (1)	-
Sustained decrease of eGFR ≥40% from baseline	8.4 (66)	9.4 (70)	-	1.3 (1)	9.0 (6)	-
≥60 and <90	Placebo (N = 1600)	Finerenone (N = 1631)	Hazard ratio [two-sided 95% CI][a]	Placebo (N = 137)	Finerenone (N = 141)	Hazard ratio [two-sided 95% CI][a]
Renal composite endpoint (first)	13.4 (214)	10.8 (176)	0.80 [0.65, 0.98]	10.9 (15)	8.5 (12)	0.80 [0.37, 1.71]
Renal failure	1.7 (27)	1.2 (19)	-	0.7 (1)	0.7 (1)	-
Sustained decrease of eGFR ≥40% from baseline	13.1 (209)	10.7 (174)	-	10.9 (15)	8.5 (12)	-
≥90	Placebo (N = 654)	Finerenone (N = 654)	Hazard ratio [two-sided 95% CI][a]	Placebo (N = 3)	Finerenone (N = 5)	Hazard ratio [two-sided 95% CI][a]
Renal composite endpoint (first)	9.6 (63)	7.5 (49)	0.78 [0.53, 1.14]	0 (0)	20.0 (1)	-
Renal failure	1.2 (8)	0.3 (2)	-	0 (0)	0 (0)	-
Sustained decrease of eGFR ≥40% from baseline	9.5 (62)	7.5 (49)	-	0 (0)	20.0 (1)	-

Incidence: % (n)

-: Not calculated. Of components of the renal composite endpoint, renal death was omitted because the concerned event occurred only in 2 patients in the placebo group in the overall population.

a Stratified Cox proportional hazards model using the dose group as a factor and the region (North America, Europe, Asia, Latin America, or others), type of albuminuria at screening visit (high albuminuria or very high albuminuria), eGFR at screening visit (≥25 mL/min/1.73 m^2 and <45 mL/min/1.73 m^2, ≥45 mL/min/1.73 m^2 and <60 mL/min/1.73 m^2, or ≥60 mL/min/1.73 m^2), and presence or absence of a medical history of cardiovascular diseases as stratification factors

Table 62. Incidences of cardiovascular composite endpoint in subgroups by renal function (Study 16244, FAS)

Baseline eGFR (mL/min/1.73 m^2)	Overall population			Japanese population		
<25	Placebo (N = 69)	Finerenone (N = 66)	Hazard ratio [two-sided 95% CI][a]	Placebo (N = 5)	Finerenone (N = 3)	Hazard ratio [two-sided 95% CI][a]
Cardiovascular composite endpoint (first)	27.5 (19)	12.1 (8)	0.40 [0.18, 0.92]	40.0 (2)	0 (0)	-
Cardiovascular death	14.5 (10)	7.6 (5)	-	20.0 (1)	0 (0)	-
Non-fatal myocardial infarction	0 (0)	3.0 (2)	-	0 (0)	0 (0)	-
Hospitalization for cardiac failure	7.2 (5)	6.1 (4)	-	0 (0)	0 (0)	-
Non-fatal stroke	5.8 (4)	1.5 (1)	-	20.0 (1)	0 (0)	-
≥25 and <45	Placebo (N = 1505)	Finerenone (N = 1476)	Hazard ratio [two-sided 95% CI][a]	Placebo (N = 116)	Finerenone (N = 106)	Hazard ratio [two-sided 95% CI][a]
Cardiovascular composite endpoint (first)	14.9 (224)	14.4 (212)	0.95 [0.78, 1.14]	6.0 (7)	9.4 (10)	1.56 [0.59, 4.10]
Cardiovascular death	5.0 (76)	5.4 (79)	-	1.7 (2)	1.9 (2)	-
Non-fatal myocardial infarction	3.5 (52)	2.0 (30)	-	0.9 (1)	0.9 (1)	-
Hospitalization for cardiac failure	5.6 (85)	5.9 (87)	-	0.9 (1)	4.7 (5)	-
Non-fatal stroke	2.8 (42)	3.0 (45)	-	2.6 (3)	2.8 (3)	-
≥45 and <60	Placebo (N = 928)	Finerenone (N = 972)	Hazard ratio [two-sided 95% CI][a]	Placebo (N = 63)	Finerenone (N = 82)	Hazard ratio [two-sided 95% CI][a]
Cardiovascular composite endpoint (first)	13.6 (126)	10.9 (106)	0.78 [0.60, 1.01]	4.8 (3)	2.4 (2)	0.45 [0.07, 2.71]
Cardiovascular death	4.5 (42)	3.1 (30)	-	1.6 (1)	0 (0)	-
Non-fatal myocardial infarction	2.8 (26)	3.0 (29)	-	1.6 (1)	0 (0)	-
Hospitalization for cardiac failure	5.4 (50)	3.3 (32)	-	0 (0)	0 (0)	-
Non-fatal stroke	3.2 (30)	3.4 (33)	-	1.6 (1)	2.4 (2)	-
≥60	Placebo (N = 338)	Finerenone (N = 318)	Hazard ratio [two-sided 95% CI][a]	Placebo (N = 23)	Finerenone (N = 17)	Hazard ratio [two-sided 95% CI][a]
Cardiovascular composite endpoint (first)	15.1 (51)	12.6 (40)	0.85 [0.56, 1.28]	4.3 (1)	17.6 (3)	4.40 [0.45, 43.2]
Cardiovascular death	6.5 (22)	4.1 (13)	-	0 (0)	5.9 (1)	-
Non-fatal myocardial infarction	2.7 (9)	2.5 (8)	-	4.3 (1)	0 (0)	-
Hospitalization for cardiac failure	6.5 (22)	5.0 (16)	-	0 (0)	0 (0)	-
Non-fatal stroke	3.3 (11)	3.5 (11)	-	0 (0)	11.8 (2)	-

Incidence: % (n)

-: Not calculated

a Stratified Cox proportional hazards model using the dose group as a factor and the region (North America, Europe, Asia, Latin America, or others), type of albuminuria at screening visit (high albuminuria or very high albuminuria), and eGFR at screening visit (≥25 mL/min/1.73 m^2 and <45 mL/min/1.73 m^2, ≥45 mL/min/1.73 m^2 and <60 mL/min/1.73 m^2, or ≥60 mL/min/1.73 m^2) as stratification factors

Table 63. Incidences of cardiovascular composite endpoint in subgroups by renal function (Study 17530, FAS)

Baseline eGFR (mL/min/1.73 m^2)	Overall population			Japanese population		
<25	Placebo (N = 12)	Finerenone (N = 15)	Hazard ratio [two-sided 95% CI][a]	Placebo (N = 0)	Finerenone (N = 0)	Hazard ratio [two-sided 95% CI][a]
Cardiovascular composite endpoint (first)	33.3 (4)	20.0 (3)	0.62 [0.10, 3.83]	0 (0)	0 (0)	-
Cardiovascular death	16.7 (2)	6.7 (1)	-	0 (0)	0 (0)	-
Non-fatal myocardial infarction	8.3 (1)	0 (0)	-	0 (0)	0 (0)	-
Hospitalization for cardiac failure	16.7 (2)	13.3 (2)	-	0 (0)	0 (0)	-
Non-fatal stroke	0 (0)	6.7 (1)	-	0 (0)	0 (0)	-
≥25 and <45	Placebo (N = 610)	Finerenone (N = 641)	Hazard ratio [two-sided 95% CI][a]	Placebo (N = 37)	Finerenone (N = 36)	Hazard ratio [two-sided 95% CI][a]
Cardiovascular composite endpoint (first)	17.5 (107)	17.0 (109)	0.95 [0.73, 1.25]	2.7 (1)	5.6 (2)	-
Cardiovascular death	6.9 (42)	7.8 (50)	-	0 (0)	0 (0)	-
Non-fatal myocardial infarction	4.6 (28)	3.7 (24)	-	0 (0)	0 (0)	-
Hospitalization for cardiac failure	5.7 (35)	5.5 (35)	-	0 (0)	0 (0)	-
Non-fatal stroke	2.3 (14)	2.3 (15)	-	2.7 (1)	5.6 (2)	-
≥45 and <60	Placebo (N = 789)	Finerenone (N = 745)	Hazard ratio [two-sided 95% CI][a]	Placebo (N = 75)	Finerenone (N = 67)	Hazard ratio [two-sided 95% CI][a]
Cardiovascular composite endpoint (first)	15.3 (121)	12.2 (91)	0.81 [0.61, 1.06]	10.7 (8)	7.5 (5)	0.70 [0.22, 2.22]
Cardiovascular death	5.8 (46)	5.4 (40)	-	2.7 (2)	0 (0)	-
Non-fatal myocardial infarction	3.2 (25)	3.9 (29)	-	1.3 (1)	3.0 (2)	-
Hospitalization for cardiac failure	4.8 (38)	2.7 (20)	-	2.7 (2)	1.5 (1)	-
Non-fatal stroke	4.1 (32)	2.6 (19)	-	5.3 (4)	3.0 (2)	-
≥60 and <90	Placebo (N = 1600)	Finerenone (N = 1631)	Hazard ratio [two-sided 95% CI][a]	Placebo (N = 137)	Finerenone (N = 141)	Hazard ratio [two-sided 95% CI][a]
Cardiovascular composite endpoint (first)	13.4 (214)	12.5 (204)	0.94 [0.78, 1.14]	6.6 (9)	3.5 (5)	0.53 [0.18, 1.58]
Cardiovascular death	6.1 (97)	5.2 (85)	-	0.7 (1)	1.4 (2)	-
Non-fatal myocardial infarction	2.0 (32)	2.3 (37)	-	0.7 (1)	0.7 (1)	-
Hospitalization for cardiac failure	3.8 (61)	3.1 (50)	-	1.5 (2)	0.7 (1)	-
Non-fatal stroke	3.3 (52)	3.5 (57)	-	3.6 (5)	0.7 (1)	-
≥90	Placebo (N = 654)	Finerenone (N = 654)	Hazard ratio [two-sided 95% CI][a]	Placebo (N = 3)	Finerenone (N = 5)	Hazard ratio [two-sided 95% CI][a]
Cardiovascular composite endpoint (first)	11.0 (72)	7.8 (51)	0.67 [0.46, 0.96]	0 (0)	0 (0)	-
Cardiovascular death	4.0 (26)	2.8 (18)	-	0 (0)	0 (0)	-
Non-fatal myocardial infarction	2.4 (16)	2.0 (13)	-	0 (0)	0 (0)	-
Hospitalization for cardiac failure	4.1 (27)	1.5 (10)	-	0 (0)	0 (0)	-
Non-fatal stroke	2.0 (13)	2.4 (16)	-	0 (0)	0 (0)	-

Incidence: % (n)

-: Not calculated

a Stratified Cox proportional hazards model using the dose group as a factor and the region (North America, Europe, Asia, Latin America, or others), type of albuminuria at screening visit (high albuminuria or very high albuminuria), eGFR at screening visit (≥25 mL/min/1.73 m^2 and <45 mL/min/1.73 m^2, ≥45 mL/min/1.73 m^2 and <60 mL/min/1.73 m^2, or ≥60 mL/min/1.73 m^2), and presence or absence of a medical history of cardiovascular diseases as stratification factors

In terms of the renal composite endpoint, the hazard ratio of finerenone to placebo was less than 1 in all of the subgroups by renal function in the overall population in Study 16244, indicating that the efficacy of finerenone could be expected irrespective of baseline eGFR. In the overall population in Study 17530, the hazard ratio was greater than 1 in the subgroup with baseline eGFR ≥45 and <60 mL/min/1.73 m^2. Both studies, however, showed no consistent declining trend of the efficacy of finerenone with worsening of the renal function. In terms of the cardiovascular composite endpoint,

the hazard ratio of finerenone to placebo was less than 1 in all of the subgroups by renal function in the overall population in both studies, indicating that the efficacy of finerenone could be expected irrespective of baseline eGFR. In the Japanese population, the hazard ratio was greater than 1 in a part of the subgroups in both studies, but there are limitations in interpreting the results due to the small sample size in the subgroups. The Japanese population has not shown a trend clearly different from that in the overall population. In addition, comparisons of incidences of the renal composite endpoint and cardiovascular composite endpoint in Studies 16244 and 17530 were made among subgroups by severity of CKD classified according to the Evidence-based Clinical Practice Guideline for CKD 2018, but no large differences were observed in efficacy of finerenone between any combination of the subgroups.

Based on the above, the efficacy of finerenone can be expected irrespective of renal function at baseline.

Tables 64 and 65 show incidences of major adverse events during the study drug treatment in subgroups by renal function in Studies 16244 and 17530.

Table 64. Incidences of major adverse events in each of the subgroups by baseline renal function (Study 16244, safety analysis population)

Baseline eGFR ($mL/min/1.73 m^2$)		Overall population		Japanese population	
		Placebo	Finerenone	Placebo	Finerenone
<25	All adverse events	94.2 (65/69)	90.9 (60/66)	100 (5/5)	100 (3/3)
	Adverse events leading to death	2.9 (2/69)	3.0 (2/66)	20.0 (1/5)	0 (0/3)
	Serious adverse events	52.2 (36/69)	34.8 (23/66)	60.0 (3/5)	66.7 (2/3)
	Adverse events leading to discontinuation	11.6 (8/69)	18.2 (12/66)	20.0 (1/5)	66.7 (2/3)
	Hyperkalaemia-related events[a]	13.0 (9/69)	21.2 (14/66)	20.0 (1/5)	33.3 (1/3)
	Events related to renal function aggravated[b]	18.8 (13/69)	28.8 (19/66)	20.0 (1/5)	0 (0/3)
	Events related to blood pressure decreased[c]	8.7 (6/69)	4.5 (3/66)	0 (0/5)	0 (0/3)
≥25 and <45	All adverse events	88.9 (1333/1449)	88.2 (1299/1473)	96.5 (110/114)	98.1 (104/106)
	Adverse events leading to death	1.8 (27/1449)	1.0 (15/1473)	4.4 (5/114)	0 (0/106)
	Serious adverse events	35.3 (529/1449)	31.8 (468/1473)	28.9 (33/114)	18.9 (20/106)
	Adverse events leading to discontinuation	6.3 (95/1449)	8.2 (121/1473)	8.8 (10/114)	6.6 (7/106)
	Hyperkalaemia-related events[a]	10.6 (159/1449)	22.1 (325/1473)	18.4 (21/114)	20.8 (22/106)
	Events related to renal function aggravated[b]	18.0 (270/1449)	18.2 (268/1473)	7.9 (9/114)	12.3 (13/106)
	Events related to blood pressure decreased[c]	4.0 (60/1449)	5.6 (83/1473)	1.8 (2/114)	7.5 (8/106)
≥45 and <60	All adverse events	86.2 (798/926)	86.8 (843/971)	98.4 (62/63)	97.6 (80/82)
	Adverse events leading to death	1.9 (18/926)	1.2 (12/971)	4.8 (3/63)	1.2 (1/82)
	Serious adverse events	33.2 (307/926)	32.6 (317/971)	33.3 (21/63)	25.6 (21/82)
	Adverse events leading to discontinuation	5.0 (46/926)	6.0 (58/971)	11.1 (7/63)	6.1 (5/82)
	Hyperkalaemia-related events[a]	6.3 (58/926)	14.7 (143/971)	3.2 (2/63)	14.6 (12/82)
	Events related to renal function aggravated[b]	13.0 (120/926)	15.7 (152/971)	7.9 (5/63)	11.0 (9/82)
	Events related to blood pressure decreased[c]	3.8 (35/926)	5.0 (49/971)	1.6 (1/63)	4.9 (4/82)
≥60	All adverse events	83.7 (282/337)	83.9 (266/317)	95.7 (22/23)	94.1 (16/17)
	Adverse events leading to death	1.2 (4/337)	0.6 (2/317)	0 (0/23)	0 (0/17)
	Serious adverse events	29.4 (99/337)	29.7 (94/317)	30.4 (7/23)	23.5 (4/17)
	Adverse events leading to discontinuation	5.6 (19/337)	5.0 (16/317)	4.3 (1/23)	17.6 (3/17)
	Hyperkalaemia-related events[a]	8.6 (29/337)	10.7 (34/317)	8.7 (2/23)	11.8 (2/17)
	Events related to renal function aggravated[b]	10.7 (36/337)	14.2 (45/317)	4.3 (1/23)	11.8 (2/17)
	Events related to blood pressure decreased[c]	2.1 (7/337)	4.4 (14/317)	8.7 (2/23)	5.9 (1/17)

Incidence: % (number of patients with event/number of patients analyzed)

a MedDRA PTs “Hyperkalaemia” and “Blood potassium increased”

b MedDRA PTs “Prerenal failure,” “Postrenal failure,” “Blood creatinine increased,” “Glomerular filtration rate decreased,” “Acute kidney injury,” “Renal failure,” and “Renal dysfunction,” and MedDRA Lowest Level Term (MedDRA LLT) “Acute prerenal failure”

c MedDRA PTs “Blood pressure decreased,” “Hypotension,” and “Orthostatic hypotension”

Table 65. Incidences of major adverse events in each of the subgroups by baseline renal function (Study 17530, safety analysis population)

Baseline eGFR ($mL/min/1.73 m^2$)		Overall population		Japanese population	
		Placebo	Finerenone	Placebo	Finerenone
<25	All adverse events	91.7 (11/12)	93.3 (14/15)	100 (1/1)	100 (1/1)
	Adverse events leading to death	8.3 (1/12)	6.7 (1/15)	0 (0/1)	0 (0/1)
	Serious adverse events	50.0 (6/12)	33.3 (5/15)	0 (0/1)	0 (0/1)
	Adverse events leading to discontinuation	0 (0/12)	13.3 (2/15)	0 (0/1)	0 (0/1)
	Hyperkalaemia-related events[a]	16.7 (2/12)	26.7 (4/15)	0 (0/1)	0 (0/1)
	Events related to renal function aggravated[b]	25.0 (3/12)	6.7 (1/15)	0 (0/1)	0 (0/1)
	Events related to blood pressure decreased[c]	16.7 (2/12)	26.7 (4/15)	0 (0/1)	0 (0/1)
≥25 and <45	All adverse events	87.1 (529/607)	87.8 (561/639)	97.3 (36/37)	97.2 (35/36)
	Adverse events leading to death	2.8 (17/607)	3.0 (19/639)	0 (0/37)	0 (0/36)
	Serious adverse events	38.2 (232/607)	38.0 (243/639)	51.4 (19/37)	27.8 (10/36)
	Adverse events leading to discontinuation	7.6 (46/607)	9.7 (62/639)	13.5 (5/37)	19.4 (7/36)
	Hyperkalaemia-related events[a]	9.2 (56/607)	20.7 (132/639)	8.1 (3/37)	25.0 (9/36)
	Events related to renal function aggravated[b]	12.7 (77/607)	16.9 (108/639)	0 (0/37)	16.7 (6/36)
	Events related to blood pressure decreased[c]	5.8 (35/607)	8.5 (54/639)	5.4 (2/37)	8.3 (3/36)
≥45, <60	All adverse events	88.6 (697/787)	87.6 (652/744)	96.0 (72/75)	98.5 (66/67)
	Adverse events leading to death	2.9 (23/787)	2.6 (19/744)	4.0 (3/75)	1.5 (1/67)
	Serious adverse events	37.7 (297/787)	34.0 (253/744)	36.0 (27/75)	34.3 (23/67)
	Adverse events leading to discontinuation	5.6 (44/787)	7.9 (59/744)	6.7 (5/75)	6.0 (4/67)
	Hyperkalaemia-related events[a]	6.2 (49/787)	12.9 (96/744)	5.3 (4/75)	10.4 (7/67)
	Events related to renal function aggravated[b]	11.3 (89/787)	13.0 (97/744)	1.3 (1/75)	4.5 (3/67)
	Events related to blood pressure decreased[c]	3.9 (31/787)	5.8 (43/744)	4.0 (3/75)	7.5 (5/67)
≥60 and <90	All adverse events	85.8 (1371/1598)	85.2 (1389/1631)	98.5 (134/136)	95.8 (136/142)
	Adverse events leading to death	2.7 (43/1598)	2.0 (32/1631)	0.7 (1/136)	2.1 (3/142)
	Serious adverse events	32.4 (518/1598)	30.2 (492/1631)	31.6 (43/136)	30.3 (43/142)
	Adverse events leading to discontinuation	4.8 (76/1598)	4.0 (66/1631)	6.6 (9/136)	2.1 (3/142)
	Hyperkalaemia-related events[a]	4.4 (70/1598)	8.8 (143/1631)	3.7 (5/136)	9.9 (14/142)
	Events related to renal function aggravated[b]	8.9 (143/1598)	9.6 (156/1631)	5.9 (8/136)	3.5 (5/142)
	Events related to blood pressure decreased[c]	2.4 (38/1598)	4.2 (69/1631)	0.7 (1/136)	4.9 (7/142)
≥90	All adverse events	79.8 (521/653)	79.2 (518/654)	100 (3/3)	80.0 (4/5)
	Adverse events leading to death	2.5 (16/653)	1.2 (8/654)	0 (0/3)	0 (0/5)
	Serious adverse events	24.8 (162/653)	25.2 (165/654)	33.3 (1/3)	20.0 (1/5)
	Adverse events leading to discontinuation	2.6 (17/653)	2.8 (18/654)	0 (0/3)	0 (0/5)
	Hyperkalaemia-related events[a]	2.5 (16/653)	3.2 (21/654)	0 (0/3)	0 (0/5)
	Events related to renal function aggravated[b]	6.0 (39/653)	6.1 (40/654)	0 (0/3)	0 (0/5)
	Events related to blood pressure decreased[c]	1.4 (9/653)	2.9 (19/654)	0 (0/3)	0 (0/5)

Incidence: % (number of patients with event/number of patients analyzed)

a MedDRA PTs “Hyperkalaemia” and “Blood potassium increased”

b MedDRA PTs “Prerenal failure,” “Postrenal failure,” “Blood creatinine increased,” “Glomerular filtration rate decreased,” “Acute kidney injury,” “Renal failure,” and “Renal dysfunction,” and MedDRA LLT “Acute prerenal failure”

c MedDRA PTs “Blood pressure decreased,” “Hypotension,” and “Orthostatic hypotension”

In both studies, incidences of events related to renal function aggravated[29)] tended to increase with decreasing eGFR in the placebo group and finerenone group. The events were sorted according to time of occurrence for evaluation. In the overall population in Study 16244, 2.4% (69 of 2831) of patients in the placebo group and 4.5% (126 of 2827) of patients in the finerenone group experienced the events by Month 4, while 13.8% (390 of 2831) of patients and 14.1% (399 of 2827) of patients, respectively, experienced the events after Month 4. In the overall population in Study 17530, 1.5% (56 of 3658) of patients in the placebo group and 2.0% (73 of 3683) of patients in the finerenone group experienced the events by Month 4, and 8.4% (309 of 3658) of patients and 9.4% (347 of 3683) of patients, respectively, experienced the events after Month 4. In the finerenone group, the events tended to occur more frequently during an early period of the treatment, and the most commonly reported adverse event was glomerular filtration rate decreased.[30)] The trend specific to the finerenone group is considered largely attributable to the decrease in eGFR resulted from the mechanism of action of finerenone. In addition, incidences of hyperkalaemia-related events[24)] and events related to blood pressure decreased[25)] tended to increase with decreasing eGFR. In view of the above results and limited safety information in patients with eGFR <25 mL/min/1.73 m^2, the package insert provided a cautionary statement that "Finerenone should be administered while closely monitoring the patient's condition, as a decrease in eGFR may occur during an early period of the treatment" and "Finerenone should be started in patients with eGFR <25 mL/min/1.73 m^2 only when its use is considered unavoidable for the treatment." Furthermore, concerning hyperkalaemia-related events, hyperkalaemia can be controlled by advising the caution that patients at a high risk of hyperkalaemia including patients with low eGFR should be more frequently tested for serum potassium [see Section "7.R.3.1 Hyperkalaemia"]. In the Japanese population, a subgroup analysis by renal function has limitations owing to the small sample size, making it difficult to find a certain trend as done in the overall population, but the Japanese population has no basis supporting a trend remarkably different from that in the overall population.

PMDA's view:

Concerning whether severity of renal impairment impacts the efficacy of finerenone, the hazard ratio for the renal composite endpoint was greater than 1 in the subgroup with eGFR (mL/min/1.73 m^2) ≥45 and <60 in the overall population in Study 17530, but a relationship between the severity of renal impairment and incidence of the renal composite endpoint did not show any certain trend. In addition, the hazard ratio for the cardiovascular composite endpoint was less than 1 irrespective of severity of renal impairment. In the Japanese population, the hazard ratios for the renal and cardiovascular composite endpoints was greater than 1 in a part of the subgroups, but in these subgroups, the number of patients with the renal composite endpoint did not substantially differ between the placebo group and finerenone group, and none of the common combinations of the subgroups in the studies showed a consistent decline of the efficacy. Based on the above, the efficacy of finerenone can be expected in Japanese patients irrespective of severity of renal impairment as well. Concerning the effect of severity of renal impairment on the safety of finerenone, in the overall population in Studies 16244 and 17530, none of the adverse events showed the ratio of the incidence in the finerenone group to that in the placebo group remarkably increased with worsening of the renal function, but incidences of all

29) MedDRA PTs "Prerenal failure," "Postrenal failure," "Blood creatinine increased," "Glomerular filtration rate decreased," "Acute kidney injury," "Renal failure," and "Renal dysfunction," and MedDRA LLT "Acute prerenal failure"

30) MedDRA PT "Glomerular filtration rate decreased"

hyperkalaemia-related events, events related to renal function aggravated, and events related to blood pressure decreased tended to increase with decreasing eGFR at baseline. In addition to cautions provided in Sections "7.R.3.1 Hyperkalaemia" and "7.R.3.3 Blood pressure decreased," cautions about a decrease in eGFR during an early period of the treatment and for patients with eGFR <25 mL/min/1.73 m^2 proposed by the applicant were largely acceptable. Use of finerenone in patients with end-stage renal disease (ESRD) and patients on maintenance dialysis is reviewed in Section "7.R.5 Indication and eligible patients." A final decision on the appropriateness of the above conclusion of PMDA will be made, taking account of comments raised at the Expert Discussion.

7.R.5 Indication and eligible patients

The applicant's explanation about indication of and patients eligible for finerenone:

The efficacy and safety of finerenone were demonstrated by Studies 16244 and 17530 in patients with type 2 diabetes mellitus and a diagnosis of diabetic kidney disease who had received the standard of care with an ACE inhibitor or ARB. Studies 16244 and 17530 separately enrolled patients with type 2 diabetes mellitus and a diagnosis of diabetic kidney disease in accordance with the different inclusion criteria for eGFR and UACR. Accordingly, Study 16244 was conducted in patients with CKD at a relatively late stage, while Study 17530 was conducted in patients with CKD in a wide range of severity including relatively mild disease [see Sections "7.3.1 Global phase III study (a)" and "7.3.2 Global phase III study (b)"]. As described above, these studies used partially different inclusion criteria for eGFR and UACR but targeted the same disease, and thus the proposed indication of finerenone was "Chronic kidney disease associated with type 2 diabetes mellitus," which appropriately reflected the disease demonstrated to respond to finerenone with acceptable safety.

PMDA asked the applicant to explain whether finerenone may be indicated in other patient populations than those in Studies 16244 and 17530.

The applicant's explanation about use in other patient populations:

(a) Patients with nondiabetic kidney diseases

Patients with a diagnosis of an "evident nondiabetic kidney disease" (IgA nephropathy, polycystic kidney, etc.) excluded from Studies 16244 and 17530 are supposed to receive the treatment appropriate for the kidney disease. Once type 2 diabetes mellitus, however, additionally develop in these patients, involvement of the diabetes mellitus in progression of the kidney disease cannot be ruled out, and they may benefit from finerenone. Therefore, patients with a diagnosis of an "evident nondiabetic kidney disease" who additionally develop type 2 diabetes mellitus and meet the clinical diagnosis criteria for CKD are considered potentially eligible for finerenone.

(b) Use of ACE inhibitor or ARB

In Studies 16244 and 17530, the efficacy and safety of finerenone were demonstrated in patients with CKD associated with type 2 diabetes mellitus who were receiving an ACE inhibitor or ARB at an optimized dose. In patients untreated with an ACE inhibitor or ARB, on the other hand, the efficacy and safety of finerenone have not been evaluated. It is, however, considered desirable to provide an option of potentially effective finerenone to patients untreated with an ACE inhibitor or ARB as well because hyperactivation of MR plays an independent role in progression of CKD and onset of

cardiovascular diseases (*Nat Rev Nephrol*. 2013;9:86-98); finerenone is inferred to exert organ protection through the mechanism of action independent of ACE inhibitors and ARBs; and clinical settings are supposed to involve patients who cannot use an ACE inhibitor or ARB or optimize the dose because of various adverse drug reactions.

(c) eGFR and albuminuria

The subgroup analysis by eGFR at baseline in Studies 16244 and 17530 showed almost consistent results on the efficacy [see Section "7.R.4 Efficacy and safety by renal function"]. According to the subgroup analysis by UACR at baseline, the hazard ratio was greater than 1 in the subgroup with UACR (mg/g) ≥30 and <300 in Study 17530, but no consistent trend in both studies was observed, for example, the effect of finerenone in delaying the occurrence of the renal composite endpoint did not decline with decreasing or increasing UACR. The hazard ratio of finerenone to placebo for the effect of finerenone in delaying the occurrence of the cardiovascular composite endpoint was less than 1, irrespective of UACR in both studies (Tables 66 and 67). Based on the above, benefits of finerenone can be promising irrespective of eGFR or UACR.

Table 66. Incidences of renal composite endpoint in subgroups by baseline UACR (Studies 16244 and 17530, FAS)

	Study 16244			Study 17530		
Baseline UACR (mg/g)	Placebo	Finerenone	Hazard ratio [two-sided 95% CI][a]	Placebo	Finerenone	Hazard ratio [two-sided 95% CI][a]
<30	16.7 (2/12)	0 (0/11)	-	3.1 (3/98)	3.7 (4/109)	0.58 [0.09, 3.57]
≥30 and <300	6.0 (20/335)	5.4 (19/350)	0.92 [0.49, 1.72]	7.3 (124/1688)	8.4 (145/1726)	1.16 [0.91, 1.47]
≥300	23.2 (578/2493)	19.6 (485/2470)	0.83 [0.73, 0.93]	14.3 (268/1878)	10.9 (201/1851)	0.74 [0.62, 0.90]

Incidence: % (number of patients with event/number of patients analyzed)
-: Not calculated
a Stratified Cox proportional hazards model using the dose group as a factor and UACR at baseline (<30 mg/g, ≥30 mg/g and <300 mg/g, or ≥300 mg/g) and an interaction between the dose group and baseline UACR as stratification factors

Table 67. Incidences of cardiovascular composite endpoint in subgroups by baseline UACR (Studies 16244 and 17530, FAS)

	Study 16244			Study 17530		
Baseline UACR (mg/g)	Placebo	Finerenone	Hazard ratio [two-sided 95% CI][a]	Placebo	Finerenone	Hazard ratio [two-sided 95% CI][a]
<30	16.7 (2/12)	0 (0/11)	-	13.3 (13/98)	9.2 (10/109)	0.67 [0.27, 1.66]
≥30 and <300	12.2 (41/335)	9.7 (34/350)	0.76 [0.48, 1.20]	14.9 (251/1688)	13.1 (226/1726)	0.87 [0.73, 1.04]
≥300	15.1 (377/2493)	13.4 (332/2470)	0.87 [0.75, 1.01]	13.5 (254/1878)	12.0 (222/1851)	0.90 [0.75, 1.08]

Incidence: % (number of patients with event/number of patients analyzed)
-: Not calculated
a Stratified Cox proportional hazards model using the dose group as a factor and UACR at baseline (<30 mg/g, ≥30 mg/g and <300 mg/g, or ≥300 mg/g) and an interaction between the dose group and baseline UACR as stratification factors

(d) Patients with end-stage renal disease and on maintenance dialysis

The subgroup analysis by eGFR at baseline in Studies 16244 and 17530, which included patients with eGFR ≥25 mL/min/1.73 m^2, showed almost consistent results on the efficacy irrespective of eGFR [see Section "7.R.4 Efficacy and safety by renal function"]. Finerenone has not been started in patients with end-stage renal disease (ESRD) or on maintenance dialysis. However, the most frequent cause of

death in patients on long-term dialysis is cardiovascular death (*Journal of Japanese Society for Dialysis Therapy.* 2020;53:579-632), and thus medical needs for controlling occurrence of cardiovascular system events is high in patients on dialysis. In Studies 16244 and 17530, a safety risk raised from continued use of finerenone in patients who experienced "renal failure" was controlled, indicating potential efficacy [see Section "7.R.6 Meaning of continued use of finerenone in patients whose disease has progressed to end-stage renal disease after the start of finerenone"]. Based on the above, the applicant considers it appropriate to give patients with ESRD or on maintenance dialysis a chance to start finerenone according to their individual status based on the judgement of the physician.

PMDA's view:
Concerning (a), it is hard to determine that finerenone would benefit patients who have received a diagnosis of "evident non-diabetic kidney disease" and additionally developed type 2 diabetes mellitus based on results in Studies 16244 and 17530 which excluded patients with "evident non-diabetic kidney disease." If a patient with a pre-existing "evident non-diabetic kidney disease" and concurrent type 2 diabetes mellitus presents progression of the renal disorder, healthcare professionals in clinical practice would have difficulty in determining whether the progression of the renal disorder is due to non-diabetic causes or type 2 diabetes mellitus, and it cannot be ruled out that the concurrent diabetes mellitus has contributed to the progression of the renal disorder, which is non-diabetic though. Accordingly, patients eligible for finerenone may be defined as those with "chronic kidney disease associated with type 2 diabetes mellitus" irrespective of the cause of CKD including diabetes mellitus but the package insert should provide information that Studies 16244 and 17530 excluded patients with a diagnosis of "evident non-diabetic kidney disease" irrespective of additional presence of type 2 diabetes mellitus.

Concerning (b), patients receiving an ACE inhibitor or ARB were included in Studies 16244 and 17530, which provided pivotal data demonstrating the efficacy and safety of finerenone, and thus use of the ACE inhibitor or ARB should take precedence over finerenone basically; finerenone should be administered as an add-on drug to patients receiving the ACE inhibitor or ARB. On the other hand, clinical settings are supposed to involve patients who cannot use an ACE inhibitor or ARB because of the renal impairment or tolerability problem, and PMDA considers it also possible to give patients untreated with an ACE inhibitor or ARB a chance to start finerenone because, based on its mechanism of action, finerenone is expected to exert cardiorenal protection in patients in whom neither ACE inhibitor nor ARB is available as well; and the patients ineligible for ACE inhibitors and ARBs have further limited treatment options. In addition, the criteria for ACE inhibitors and ARBs applied to the clinical studies should be provided as information about patient characteristics that increase eligibility for finerenone.

Concerning (c), eGFR and UACR in patients eligible for finerenone should be within ranges specified in Studies 16244 and 17530 which evaluated the efficacy and safety. For albuminuria, some patients without albuminuria were enrolled in Studies 16244 and 17530 because the inclusion criteria did not refer to this condition, but experience with finerenone in these patients was limited. The concerned population is considered to have a lower risk of the renal composite endpoint than one of patients with albuminuria. The balance of benefits and risks associated with use of finerenone in the concerned

population may be different from that in the study populations. Based on the above, the inclusion criteria for UACR in the clinical studies should be provided in the package insert as information about patient characteristics that increase eligibility for finerenone. Because analyses suggested that finerenone delayed the occurrence of the cardiovascular composite endpoint in patients with eGFR <25 mL/min/1.73 m^2, such patient population do not have to be uniformly deemed ineligible, but renal impairment is potentially worsened during treatment with finerenone. Not only the caution presented in Section "7.R.4 Efficacy and safety by renal function" should be advised, but also the package insert should include information stated in the protocols of Studies 16244 and 17530, in which patients with eGFR <25 mL/min/1.73 m^2 were specified as part of the exclusion criteria. In (d) patients with ESRD or on maintenance dialysis, on the other hand, finerenone can no longer exert one of the expected effects to delay progression to ESRD. In addition, finerenone was not started in such patients in the clinical studies. It is therefore difficult to evaluate the efficacy of finerenone in patients with ESRD or on maintenance dialysis based on results in patients with eGFR <25 mL/min/1.73 m^2 and patients who progressed to "renal failure" during use of finerenone. The risk of hyperkalaemia-related events[24)] associated with finerenone increased with decreasing renal function, and a decrease in eGFR that resulted from the mechanism of action of finerenone was also observed during an early period of the treatment [see Section "7.R.4 Efficacy and safety by renal function"]. In view of the above and according to the applicant's explanation, finerenone is not expected to be effective in patients with ESRD or on maintenance dialysis with an acceptable risk, and safety concerns are raised. Patients with ESRD or on maintenance dialysis therefore should be deemed to be ineligible for finerenone.

Based on the above, the Indication and Precautions Concerning Indication sections should be as shown below, but for the details, PMDA will make a final conclusion, taking account of comments raised in the Expert Discussion.

Indication

Chronic kidney disease associated with type 2 diabetes mellitus (with exception of patients who have end-stage renal disease or are undergoing dialysis)

Precautions Concerning Indication

- Finerenone should be administered to patients who are receiving an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker, except for patients who are not eligible for an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker.
- Finerenone may cause a decrease in eGFR and worsen the renal function. Finerenone should be started in patients with eGFR <25 mL/min/1.73 m^2 only when its use is considered unavoidable for the treatment by weighing risks and benefits.
- Eligible patients must be selected by physicians with a full understanding of the information presented in the "Clinical Studies" section and characteristics of the patients enrolled in clinical studies (primary disease, concomitant drugs, renal function, albuminuria, etc.).

7.R.6 Meaning of continued use of finerenone in patients whose disease has progressed to end-stage renal disease after the start of finerenone

One of the objectives of use of finerenone is to prevent progression to end-stage renal disease (ESRD). PMDA asked the applicant to explain the meaning of continued use of finerenone in patients whose disease has progressed to ESRD after the start of finerenone.

The applicant's explanation:

In Studies 16244 and 17530, all of the randomized patients (including patients who experienced the primary or secondary efficacy endpoint) continued use of the study drug unless safety reasons justifying discontinuation were recognized. Tables 68 and 69 show incidences of the cardiovascular composite endpoint and all-cause death after occurrence of "renal failure" in patients who did not continue the study drug after the occurrence and patients who continued the study drug after that.

Table 68. Incidences of cardiovascular composite endpoint and all-cause death in patients who did not continue the study drug after occurrence of "renal failure" and patients who continued the study drug after that (Study 16244, FAS)

	Patients who did not continue the study drug		Patients who continued the study drug	
	Placebo (N = 134)	Finerenone (N = 134)	Placebo (N = 101)	Finerenone (N = 74)
Cardiovascular composite endpoint (first occurrence)	26.9 (36)	32.1 (43)	15.8 (16)	17.6 (13)
Cardiovascular death	6.0 (8)	6.0 (8)	3.0 (3)	6.8 (5)
Non-fatal myocardial infarction	5.2 (7)	4.5 (6)	3.0 (3)	0 (0)
Hospitalization for cardiac failure	17.9 (24)	22.4 (30)	8.9 (9)	9.5 (7)
Non-fatal stroke	2.2 (3)	3.7 (5)	4.0 (4)	1.4 (1)
All-cause deaths	12.7 (17)	15.7 (21)	5.9 (6)	9.5 (7)

Incidence: % (n). Events after occurrence of renal failure were included in the tabulation. The treatment period after occurrence of renal failure in patients who continued the study drug (mean ± SD) was 200.4 ± 172.0 days in the placebo group and 213.7 ± 172.2 days in the finerenone group.

Table 69. Incidences of cardiovascular composite endpoint and all-cause death in patients who did not continue the study drug after occurrence of "renal failure" and patients who continued the study drug after that (Study 17530, FAS)

	Patients who did not continue the study drug		Patients who continued the study drug	
	Placebo (N = 38)	Finerenone (N = 32)	Placebo (N = 24)	Finerenone (N = 14)
Cardiovascular composite endpoint (first occurrence)	39.5 (15)	34.4 (11)	58.3 (14)	14.3 (2)
Cardiovascular death	10.5 (4)	21.9 (7)	16.7 (4)	7.1 (1)
Non-fatal myocardial infarction	7.9 (3)	3.1 (1)	12.5 (3)	7.1 (1)
Hospitalization for cardiac failure	15.8 (6)	18.8 (6)	41.7 (10)	7.1 (1)
Non-fatal stroke	7.9 (3)	3.1 (1)	4.2 (1)	0 (0)
All-cause deaths	21.1 (8)	34.4 (11)	25.0 (6)	14.3 (2)

Incidence: % (n). Events after occurrence of renal failure were included in the tabulation. The treatment period after occurrence of renal failure in patients who continued the study drug (mean ± SD) was 302.5 ± 311.5 days in the placebo group and 288.1 ± 274.8 days in the finerenone group.

In patients who continued the study drug, the incidence of the cardiovascular composite endpoint was higher in the finerenone group than in the placebo group in Study 16244, while it was lower in the finerenone group than in the placebo group in Study 17530. In both studies, however, the incidence of the cardiovascular composite endpoint in the placebo group differed between patients who continued the study drug and patients who did not, and factors other than the study drug were potentially involved, and thus it is considered difficult to perform appropriate evaluation.

Tables 70 and 71 show the incidences of adverse events and hyperkalaemia-related events[24)] after occurrence of “renal failure” in patients who did not continue the study drug after the occurrence and patients who continued the study drug after that.

Table 70. Incidences of adverse events and hyperkalaemia-related events in patients who did not continue the study drug after occurrence of “renal failure” and patients who continued the study drug after that (Study 16244, FAS)

	Patients who did not continue the study drug		Patients who continued the study drug	
	Placebo (N = 134)	Finerenone (N = 134)	Placebo (N = 101)	Finerenone (N = 74)
All adverse events	70.9 (95)	68.7 (92)	68.3 (69)	71.6 (53)
Adverse events related to the study drug	2.2 (3)	0 (0)	5.9 (6)	6.8 (5)
Adverse events leading to discontinuation	3.0 (4)	0.7 (1)	7.9 (8)	8.1 (6)
Serious adverse events	43.3 (58)	43.3 (58)	40.6 (41)	37.8 (28)
Adverse events leading to death	5.2 (7)	7.5 (10)	2.0 (2)	4.1 (3)
Hyperkalaemia-related events[a]	12.7 (17)	9.0 (12)	7.9 (8)	14.9 (11)
Serious hyperkalaemia-related events	0.7 (1)	2.2 (3)	1.0 (1)	1.4 (1)
Hyperkalaemia-related events leading to death	0 (0)	0.7 (1)	0 (0)	0 (0)

Incidence: % (n). Only adverse events after occurrence of renal failure were included in the tabulation. The treatment period after occurrence of renal failure in patients who continued the study drug (mean ± SD) was 200.4 ± 172.0 days in the placebo group and 213.7 ± 172.2 days in the finerenone group.

a MedDRA PTs “Hyperkalaemia” and “Blood potassium increased”

Table 71. Incidences of adverse events and hyperkalaemia-related events after occurrence of “renal failure” in patients who did not continue the study drug after the occurrence and patients who continued the study drug after that (Study 17530, FAS)

	Patients who did not continue the study drug		Patients who continued the study drug	
	Placebo (N = 38)	Finerenone (N = 32)	Placebo (N = 24)	Finerenone (N = 14)
All adverse events	68.4 (26)	50.0 (16)	62.5 (15)	64.3 (9)
Adverse events related to the study drug	2.6 (1)	0 (0)	8.3 (2)	7.1 (1)
Adverse events leading to discontinuation	0 (0)	0 (0)	8.3 (2)	0 (0)
Serious adverse events	52.6 (20)	25.0 (8)	50.0 (12)	28.6 (4)
Adverse events leading to death	7.9 (3)	3.1 (1)	8.3 (2)	7.1 (1)
Hyperkalaemia-related events[a]	2.6 (1)	6.3 (2)	12.5 (3)	28.6 (4)
Serious hyperkalaemia-related events	0 (0)	3.1 (1)	0 (0)	0 (0)
Hyperkalaemia-related events leading to death	0 (0)	0 (0)	0 (0)	0 (0)

Incidence: % (n). Only adverse events after occurrence of renal failure were included in the tabulation. The treatment period after occurrence of renal failure in patients who continued the study drug (mean ± SD) was 302.5 ± 311.5 days in the placebo group and 288.1 ± 274.8 days in the finerenone group.

a MedDRA PTs “Hyperkalaemia” and “Blood potassium increased”

In patients who continued the study drug in both studies, the incidence of all adverse events in the placebo group was comparable to that in the finerenone group, and the incidence of hyperkalaemia-related events was higher in the finerenone group than in the placebo group, but the incidence of serious or fatal hyperkalaemia-related events did not differ between the groups. In patients whose disease has progressed to ESRD or a condition in need of dialysis after the start of finerenone, the risk of hyperkalaemia-related events can be controlled by including in the package insert the cautionary statement “If eGFR decreases to <15 mL/min/1.73 m^2 during use of finerenone, the appropriateness of continued use should be considered with attention paid to the serum potassium level. The risk of hyperkalaemia may increase.” Based on the above, continued use of finerenone in patients whose disease has progressed to ESRD or a condition in need of dialysis has acceptable safety and may reduce the occurrence of cardiovascular system events and death. The applicant, therefore,

considers it meaningful to continue finerenone after the disease has progressed to ESRD or a condition in need of dialysis.

PMDA's view:
Studies 16244 and 17530 do not show any consistent trend of reducing the occurrence of cardiovascular composite endpoint and all-cause deaths in patients who continued finerenone after occurrence of "renal failure." On the other hand, the incidence of hyperkalaemia-related events tended to increase with decreasing renal function [see Section "7.R.4 Efficacy and safety by renal function"], raising a concern that continued use of finerenone after progression to ESRD or a condition in need of dialysis may increase the risk of hyperkalaemia-related events. Therefore, the following caution should be provided: If the disease progresses to ESRD or a condition in need of dialysis, physicians should basically discontinue finerenone considering the patient's condition. A final decision on the above conclusion of PMDA will be made, taking account of comments raised at the Expert Discussion.

7.R.7 Dosage and administration

The applicant's explanation about the initial and target doses of finerenone as well as dose-adjustment method:
The dosage regimens in Studies 16244 and 17530 were established based on results in the foreign phase II study (Study 16243) in patients with type 2 diabetes mellitus and a diagnosis of diabetic nephropathy who were receiving the standard of care with an ACE inhibitor or ARB.

(a) Initial and target doses
In Study 16243, the ratio of UACR on Day 90 to that at baseline, the primary endpoint, decreased with the dose of finerenone [see Section "7.2.2 Foreign phase II study"]. At all the doses of finerenone studied (1.25-20 mg once daily), the safety and tolerability were favorable, but very high albuminuria was observed at 20 mg, and especially in the population with eGFR <60 mL/min/1.73 m^2, risks of hyperkalaemia and a decrease in eGFR during an early period of the treatment tended to be high. In the concerned population, the dose of 20 mg once daily was deemed to be the maximum dose. In addition, the Japanese phase II study (Study 16816) was conducted in a similar design to that of Study 16243 and presented results on the efficacy and safety of finerenone similar to those in Study 16243 [see Section "7.2.1 Japanese phase II study"]. Based on the above results, the initial dose of finerenone was adjusted according to eGFR at screening. In Studies 16244 and 17530, the initial dose of finerenone was 20 mg once daily in patients with eGFR ≥60 mL/min/1.73 m^2 and 10 mg once daily in patients with eGFR <60 mL/min/1.73 m^2, and the target dose was 20 mg once daily.

(b) Dose adjustment method
Based on results from the above study according to Study 16243, patients starting finerenone 10 mg once daily in Studies 16244 and 17530 were deemed to be eligible for dose increase to 20 mg once daily when the serum potassium level was ≤4.8 mmol/L and a decrease in eGFR from the previous scheduled visit was <30% at a visit of Month 1 or later. Throughout the subsequent study period, serum potassium and eGFR were measured at scheduled visits, and the dose of finerenone was adjusted according to the criterion on serum potassium in specified the protocols. Unless there were

safety problems, the investigators were instructed to increase finerenone to the maximum dose of 20 mg once daily.

Studies 16244 and 17530 were conducted in accordance with the setting in the above (a) and (b) and demonstrated the efficacy of finerenone with a favorable safety profile. The dosage and administration should be specified based on the protocols of these studies. The proposed Dosage and Administration was "The usual adult dosage is 20 mg of finerenone administered orally once daily." A statement that finerenone should be started at 10 mg in patients with eGFR <60 mL/min/1.73 m^2 was initially included in the Precautions Concerning Dosage and Administration section. In Study 16244, however, only a small proportion (7.6%) of the patients started finerenone 20 mg once daily, and thus the proposed Dosage and Administration should be modified to "The usual adult dosage is 20 mg of finerenone administered orally once daily. For patients with eGFR <60 mL/min/1.73 m^2, finerenone should be started at 10 mg once daily." Rules for dose adjustment of finerenone and resumption after interruption should be provided according to the protocols of these studies to raise caution.

PMDA asked the applicant to explain the efficacy in subgroups by maintenance dose of finerenone.

The applicant's explanation:
Tables 72 to 75 show incidences of the renal composite endpoint and cardiovascular composite endpoint in subgroups by maintenance dose in Studies 16244 and 17530.

Table 72. Incidences of renal composite endpoint in subgroups by maintenance dose (Study 16244, FAS)

	Overall population			Japanese population		
Maintenance dose[a] 10 mg	Placebo (N = 767)	Finerenone (N = 1140)	Hazard ratio [two-sided 95% CI][b]	Placebo (N = 24)	Finerenone (N = 52)	Hazard ratio [two-sided 95% CI][b]
Renal composite endpoint (first occurrence)	26.5 (203)	22.4 (255)	0.762 [0.632, 0.920]	25.0 (6)	32.7 (17)	1.021 [0.397, 2.631]
Renal failure	12.5 (96)	10.5 (120)	-	12.5 (3)	21.2 (11)	-
Sustained decrease of eGFR ≥40% from baseline	25.4 (195)	21.1 (240)	-	25.0 (6)	32.7 (17)	-
Maintenance dose[a] 20 mg	Placebo (N = 2063)	Finerenone (N = 1686)	Hazard ratio [two-sided 95% CI][b]	Placebo (N = 181)	Finerenone (N = 156)	Hazard ratio [two-sided 95% CI][b]
Renal composite endpoint (first occurrence)	19.2 (396)	14.7 (248)	0.753 [0.642, 0.882]	21.0 (38)	16.0 (25)	0.760 [0.458, 1.260]
Renal failure	6.7 (139)	5.2 (87)	-	6.6 (12)	6.4 (10)	-
Sustained decrease of eGFR ≥40% from baseline	18.5 (381)	14.1 (238)	-	20.4 (37)	16.0 (25)	-

Incidence: % (n)
-: Not calculated. Of components of the renal composite endpoint, renal death was omitted because the concerned event occurred only in 2 patients each in the placebo group and finerenone group in the overall population.
a The dose used for the longest period during the study
b Stratified Cox proportional hazards model using the dose group as a factor and the region (North America, Europe, Asia, Latin America, or others), type of albuminuria at screening visit (high albuminuria or very high albuminuria), and eGFR at screening visit (≥25 mL/min/1.73 m^2 and <45 mL/min/1.73 m^2, ≥45 mL/min/1.73 m^2 and <60 mL/min/1.73 m^2, or ≥60 mL/min/1.73 m^2) as stratification factors

Table 73. Incidences of renal composite endpoint in subgroups by maintenance dose (Study 17530, FAS)

	Overall population			Japanese population		
Maintenance dose[a] 10 mg	Placebo (N = 415)	Finerenone (N = 640)	Hazard ratio [two-sided 95% CI][b]	Placebo (N = 13)	Finerenone (N = 13)	Hazard ratio [two-sided 95% CI][b]
Renal composite endpoint (first occurrence)	13.5 (56)	13.0 (83)	0.815 [0.578, 1.151]	7.7 (1)	7.7 (1)	-
Renal failure	2.7 (11)	1.7 (11)	-	0 (0)	0 (0)	-
Sustained decrease of eGFR ≥40% from baseline	13.0 (54)	12.2 (78)	-	7.7 (1)	7.7 (1)	-
Maintenance dose[a] 20 mg	Placebo (N = 3244)	Finerenone (N = 3041)	Hazard ratio [two-sided 95% CI][b]	Placebo (N = 240)	Finerenone (N = 237)	Hazard ratio [two-sided 95% CI][b]
Renal composite endpoint (first occurrence)	10.4 (338)	8.8 (267)	0.836 [0.712, 0.982]	7.5 (18)	8.9 (21)	1.183 [0.630, 2.221]
Renal failure	1.5 (50)	1.2 (35)	-	0.4 (1)	1.7 (4)	-
Sustained decrease of eGFR ≥40% from baseline	10.2 (330)	8.5 (260)	-	7.5 (18)	8.9 (21)	-

Incidence: % (n)

-: Not calculated. Of components of the renal composite endpoint, renal death was omitted because the concerned event occurred only in 2 patients in the placebo group in the overall population.

a The dose used for the longest period during the study

b Stratified Cox proportional hazards model using the dose group as a factor and the region (North America, Europe, Asia, Latin America, or others), type of albuminuria at screening visit (high albuminuria or very high albuminuria), eGFR at screening visit (≥25 mL/min/1.73 m^2 and <45 mL/min/1.73 m^2, ≥45 mL/min/1.73 m^2 and <60 mL/min/1.73 m^2, or ≥60 mL/min/1.73 m^2), and presence or absence of a medical history of cardiovascular diseases as stratification factors

Table 74. Incidences of cardiovascular composite endpoint in subgroups by maintenance dose (Study 16244, FAS)

	Overall population			Japanese population		
Maintenance dose[a] 10 mg	Placebo (N = 767)	Finerenone (N = 1140)	Hazard ratio [two-sided 95% CI][b]	Placebo (N = 24)	Finerenone (N = 52)	Hazard ratio [two-sided 95% CI][b]
Cardiovascular composite endpoint (first)	19.0 (146)	15.8 (180)	0.792 [0.636, 0.987]	12.5 (3)	7.7 (4)	0.480 [0.097, 2.386]
Cardiovascular death	8.2 (63)	5.4 (62)	-	4.2 (1)	0 (0)	-
Non-fatal myocardial infarction	3.8 (29)	3.0 (34)	-	0 (0)	1.9 (1)	-
Hospitalization for cardiac failure	5.3 (41)	6.3 (72)	-	0 (0)	3.8 (2)	-
Non-fatal stroke	4.3 (33)	3.8 (43)	-	8.3 (2)	1.9 (1)	-
Maintenance dose[a] 20 mg	Placebo (N = 2063)	Finerenone (N = 1686)	Hazard ratio [two-sided 95% CI][b]	Placebo (N = 181)	Finerenone (N = 156)	Hazard ratio [two-sided 95% CI][b]
Cardiovascular composite endpoint (first)	13.2 (272)	11.0 (185)	0.817 [0.678, 0.986]	5.5 (10)	7.1 (11)	1.287 [0.546, 3.034]
Cardiovascular death	4.2 (86)	3.8 (64)	-	1.7 (3)	1.9 (3)	-
Non-fatal myocardial infarction	2.8 (58)	2.1 (35)	-	1.7 (3)	0 (0)	-
Hospitalization for cardiac failure	5.9 (121)	3.9 (66)	-	0.6 (1)	1.9 (3)	-
Non-fatal stroke	2.6 (53)	2.8 (47)	-	1.7 (3)	3.8 (6)	-

Incidence: % (n)

-: Not calculated

a The dose used for the longest period during the study

b Stratified Cox proportional hazards model using the dose group as a factor and the region (North America, Europe, Asia, Latin America, or others), type of albuminuria at screening visit (high albuminuria or very high albuminuria), and eGFR at screening visit (≥25 mL/min/1.73 m^2 and <45 mL/min/1.73 m^2, ≥45 mL/min/1.73 m^2 and <60 mL/min/1.73 m^2, or ≥60 mL/min/1.73 m^2) as stratification factors

Table 75. Incidences of cardiovascular composite endpoint in subgroups by maintenance dose (Study 17530, FAS)

	Overall population			Japanese population		
Maintenance dose[a] 10 mg	Placebo (N = 415)	Finerenone (N = 640)	Hazard ratio [two-sided 95% CI][b]	Placebo (N = 13)	Finerenone (N = 13)	Hazard ratio [two-sided 95% CI][b]
Cardiovascular composite endpoint (first)	24.3 (101)	19.1 (122)	0.751 [0.576, 0.979]	23.1 (3)	23.1 (3)	0.721 [0.111, 4.703]
Cardiovascular death	11.6 (48)	8.3 (53)	-	15.4 (2)	7.7 (1)	-
Non-fatal myocardial infarction	4.1 (17)	5.6 (36)	-	0 (0)	0 (0)	-
Hospitalization for cardiac failure	8.4 (35)	6.1 (39)	-	7.7 (1)	0 (0)	-
Non-fatal stroke	3.9 (16)	2.7 (17)	-	7.7 (1)	15.4 (2)	-
Maintenance dose[a] 20 mg	Placebo (N = 3244)	Finerenone (N = 3041)	Hazard ratio [two-sided 95% CI][b]	Placebo (N = 240)	Finerenone (N = 237)	Hazard ratio [two-sided 95% CI][b]
Cardiovascular composite endpoint (first)	12.8 (416)	11.0 (335)	0.853 [0.739, 0.985]	6.3 (15)	3.8 (9)	0.601 [0.263, 1.374]
Cardiovascular death	5.1 (165)	4.6 (140)	-	0.4 (1)	0.4 (1)	-
Non-fatal myocardial infarction	2.6 (84)	2.2 (67)	-	0.8 (2)	1.3 (3)	-
Hospitalization for cardiac failure	3.9 (128)	2.6 (78)	-	1.3 (3)	0.8 (2)	-
Non-fatal stroke	2.9 (94)	3.0 (91)	-	3.8 (9)	1.3 (3)	-

Incidence: % (n)
-: Not calculated
a The dose used for the longest period during the study
b Stratified Cox proportional hazards model using the dose group as a factor and the region (North America, Europe, Asia, Latin America, or others), type of albuminuria at screening visit (high albuminuria or very high albuminuria), eGFR at screening visit (≥25 mL/min/1.73 m^2 and <45 mL/min/1.73 m^2, ≥45 mL/min/1.73 m^2 and <60 mL/min/1.73 m^2, or ≥60 mL/min/1.73 m^2), and presence or absence of a medical history of cardiovascular diseases as stratification factors

In the overall population and Japanese population, patients receiving finerenone 20 mg as the maintenance dose accounted for 59.7% (1686 of 2826) of patients and 75.0% (156 of 208) of patients, respectively, in Study 16244 and for 82.6% (3041 of 3681) of patients and 94.8% (237 of 250) of patients, respectively, in Study 17530. An analysis in subgroups by maintenance dose revealed that finerenone delayed the occurrence of the renal composite endpoint and cardiovascular composite endpoint, irrespective of maintenance dose, in the overall population in both Studies 16244 and 17530. In the Japanese population, the hazard ratio was greater than 1 for the renal composite endpoint in the subgroups with the maintenance dose of 10 mg in Study 16244 and with the maintenance dose of 20 mg in Study 17530 as well as for the cardiovascular composite endpoint in the subgroup with the maintenance dose of 20 mg in Study 16244, but there are limitations in interpreting the results due to variations in patient characteristics, such as baseline eGFR, between the groups and the small sample size. As described above, the variations in patient characteristics might have impacted the efficacy, but the efficacy of finerenone is unlikely to differ depending on the maintenance dose because clinically meaningful exposure to finerenone did not differ between Japanese and non-Japanese patients [see Section “6.R.1 Difference in PK between Japanese and non-Japanese subjects”].

PMDA’s view:

In Studies 16244 and 17530, patients with eGFR ≥60 mL/min/1.73 m^2 received finerenone 20 mg once daily and patients with eGFR <60 mL/min/1.73 m^2 started finerenone 10 mg once daily in consideration of risks of hyperkalaemia and a decrease in eGFR, followed by dose increase to 20 mg once daily according to serum potassium and eGFR. The concerned dosage regimen is considered reasonable to some extent in view of results on the safety and pharmacodynamic action (change in

UACR) in the Japanese and foreign phase II studies. In Studies 16244 and 17530 where the dosage regimens were established based on the above studies, proportions of patients in the subgroups by maintenance dose did not substantially differ between the overall population and Japanese population, and the efficacy and safety of finerenone were demonstrated. Thus, in principle, the initial dose, maximum dose, and dose adjustment method should be established based on the protocols of these studies. The efficacy was demonstrated to some extent even in the subgroups of patients who received finerenone 10 mg once daily as the maintenance dose in both studies, and thus PMDA considers it meaningful to administer finerenone 10 mg once daily to patients in whom dose increase to the target dose of 20 mg once daily is difficult.

Based on the above review results, the Dosage and Administration and Precautions Concerning Dosage and Administration sections in the package insert should be as shown below, but for the details, PMDA will make a final conclusion, taking account of comments raised in the Expert Discussion.

Dosage and Administration
The usual adult dosage is 20 mg of finerenone administered orally once daily. The starting dose should be determined as shown below:
eGFR ≥60 mL/min/1.73 m^2: 20 mg
eGFR <60 mL/min/1.73 m^2: 10 mg. The dose may be increased to 20 mg approximately 4 weeks after the start of treatment, based on serum potassium and estimated glomerular filtration rate (eGFR).

Precautions Concerning Dosage and Administration
Serum potassium and eGFR should be measured 4 weeks after start or re-start of the treatment or dose increase and then periodically. The dose should be adjusted according to the table shown below.

Serum potassium level (mEq/L)	Dose adjustment
≤4.8	20 mg once daily: Unchanged 10 mg once daily: Increase to 20 mg once daily (unless eGFR decrease from the previous measurement by >30%)
>4.8 and ≤5.5	Unchanged
>5.5	Interruption

When the serum potassium level decreases to ≤5.0 mEq/L after dose interruption, finerenone may be resumed at 10 mg once daily.

7.R.8 Post-marketing investigations
The applicant's explanation about post-marketing investigations:
In view of the mechanism of action of finerenone and the incidences of hyperkalaemia in Studies 16244 and 17530, patient characteristics (e.g., age, medical history, concomitant drugs) and clinical laboratory values (e.g., serum potassium, eGFR) involved in the occurrence of hyperkalaemia in clinical practice will be collected so that a post-marketing database survey can be performed to identify risk factors for hyperkalaemia. In addition, incidences of renal events will be investigated in a post-marketing surveillance.

PMDA's view:

In the post-marketing setting, finerenone may be used in patients with high serum potassium levels, severe renal impairment, or receiving a potassium-sparing diuretic who were excluded from clinical studies and in whom drugs with a similar mechanism of action are contraindicated. However, the safety information in these patients is limited. In view of the above, the applicant should implement a post-marketing surveillance to collect information about the occurrence of hyperkalaemia associated with finerenone in clinical use. In light of the incidences of the renal composite endpoint in the Japanese population in Studies 16244 and 17530, it is appropriate to investigate the incidences of renal events. A final decision on the appropriateness of the post-marketing investigations and a survey method will be made, taking account of comments raised at the Expert Discussion, including the identification of safety specifications and the appropriateness of risk classification, the pharmacovigilance activities, and risk minimization activities, in accordance with the "Risk Management Plan Guidance" (PFSB/SD Notification No. 0411-1 and PFSB/ELD Notification No. 0411-2 dated April 11, 2012).

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The inspection is currently ongoing, and the results of the inspection and the conclusion of PMDA will be reported in Review report (2).

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The inspection is currently ongoing, and the results of the inspection and the conclusion of PMDA will be reported in Review report (2).

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that finerenone has efficacy in the treatment of CKD associated with type 2 diabetes mellitus and that finerenone has acceptable safety in view of its benefits. Finerenone is an MR antagonist and it is meaningful to provide access to finerenone for use in clinical settings as a new option for the treatment of CKD associated with type 2 diabetes mellitus. In addition, PMDA considers it necessary to further examine the efficacy of finerenone in Japanese patients, indication, dosage and administration, cautionary statements in the package insert, and post-marketing investigations.

PMDA has concluded that finerenone may be approved if finerenone is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

January 18, 2022

Product Submitted for Approval

Brand Name	Kerendia Tablets 10 mg Kerendia Tablets 20 mg
Non-proprietary Name	Finerenone
Applicant	Bayer Yakuhin, Ltd.
Date of Application	November 26, 2020

List of Abbreviations
See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Clinical positioning

Diabetes mellitus is one of the major causes of onset and progression of CKD. The Japanese and foreign guidelines recommend the use of an ACE inhibitor or ARB as the standard of care in patients with CKD associated with type 2 diabetes mellitus. The clinical positioning of finerenone in such a situation was examined at the Expert Discussion. The expert advisors raised comments that the standard of care including an ACE inhibitor or ARB would not adequately delay the progression of CKD in some patients, and thus it would be meaningful to provide access to a therapeutic option with the novel mechanism of action for use in clinical practice. The expert advisors supported the following PMDA's conclusion presented in Section "7.R.1 Clinical positioning" in the Review Report (1): Based on results in Studies 16244 and 17530, it is meaningful to provide access to finerenone for use in clinical practice as a therapeutic option with the novel mechanism of action, which is added to standard of care for CKD associated with type 2 diabetes mellitus.

1.2 Efficacy

The expert advisors supported PMDA's conclusion that the clinically meaningful efficacy of finerenone was demonstrated in patients with CKD associated with type 2 diabetes mellitus, based on the following findings: In the overall population in Studies 16244 and 17530, the superiority of finerenone to placebo was demonstrated in terms of the respective primary endpoints (renal composite

endpoint in Study 16244 and cardiovascular composite endpoint in Study 17530), and the results for components of the primary endpoint in each study supported the efficacy of finerenone.

The expert advisors commented that the hazard ratio of finerenone to placebo for "renal failure," a component of the renal composite endpoint, in Studies 16244 and 17530 was greater than 1 in the Japanese population, unlike the overall population, with the cause for such a trend remaining to be identified, and thus it is unavoidable to say that the efficacy of finerenone in Japanese is unknown.

On the other hand, the following comments were raised by the expert advisors:
(i) Based on the review results presented by PMDA [see Section "7.R.2.3 Efficacy of finerenone in Japanese patients" in the Review Report (1)], PMDA's conclusion is appropriate that the clinical benefits of finerenone in the overall population observed in Studies 16244 and 17530 can be promising in the Japanese population as well, because the hazard ratios of finerenone to placebo for the primary endpoints in Studies 16244 and 17530 were less than 1 in the Japanese population, as in the overall population, although the limited numbers of Japanese patients and events preclude interpreting the results in the Japanese population for the component of the renal composite endpoint (primary endpoint) in Study 16244 and for the renal composite endpoint (secondary endpoint) in Study 17530; and (ii) study results have indicated that the effect of finerenone in delaying the occurrence of the cardiovascular composite endpoint can be promising in Japanese patients as well, supporting its usefulness in the treatment of CKD.

PMDA provided the following explanation:
The effect of finerenone in delaying the occurrence of the renal composite endpoint is applicable to Japanese patients, based on the comprehensive review of the findings showing that the hazard ratio of finerenone to placebo for the primary endpoint of Study 16244 is less than 1 in the Japanese population as in the overall population and of the following results presented in Section "7.R.2.3 Efficacy of finerenone in Japanese patients" in the Review Report (1):

(a) There are limitations in evaluating individual components of the renal composite endpoint in the Japanese population with small sample size for any consistent trend;
(b) The pharmacodynamic action (change in UACR) did not differ between Japanese and non-Japanese patients; and
(c) No differences between Japanese and non-Japanese populations potentially affecting the efficacy were presented in any of the intrinsic and extrinsic ethnic factors.

In addition to the above PMDA's explanation, the following results were obtained: In Study 17530, the hazard ratio of finerenone to placebo for the cardiovascular composite endpoint, the primary endpoint, was less than 1 in the Japanese population as in the overall population; and the hazard ratios of finerenone to placebo for all-cause deaths in both Studies 16244 and 17530 were less than 1 in the Japanese population as in the overall population.

In view of the above findings and results, the expert advisors reached the conclusion that in Studies 16244 and 17530, the efficacy observed in the Japanese population was consistent with that in the

overall population and that the clinical benefits of finerenone could be promising in the Japanese patients with CKD associated with type 2 diabetes mellitus as well.

The expert advisor raised the following comment:
The efficacy of finerenone was demonstrated only in patients concomitantly receiving an ACE inhibitor or ARB at the maximum tolerated dose. The efficacy of finerenone in patients concomitantly receiving an ACE inhibitor or ARB at a dose lower than the maximum tolerated dose remained unknown.

PMDA's conclusion:
Finerenone should be mainly recommended to a population of patients receiving an ACE inhibitor or ARB at the maximum tolerated dose as specified in the protocol of the clinical studies, but based on the efficacy data in subgroups by dose of an ACE inhibitor or ARB [see Tables 47 and 48 in the Review Report (1)], the treatment with an ACE inhibitor or ARB at the maximum tolerated dose is not a precondition for the efficacy of finerenone. The Clinical Studies section should include information that patients receiving an ACE inhibitor or ARB at the maximum tolerated dose were enrolled. In addition, the Precautions Concerning Indication section should include a statement that eligible patients must be selected by physicians with a full understanding of the characteristics of patients enrolled in clinical studies.

The expert advisors finally supported the conclusion.

1.3 Safety

The expert advisor raised the following comment:
Whether finerenone is contraindicated in patients with a serum potassium level >5.5 mmol/L should be considered, because finerenone was interrupted in patients with an increase in serum potassium to >5.5 mmol/L in accordance with the criteria for dose-adjustment of finerenone in Studies 16244 and 17530.

PMDA's conclusion:
In the clinical studies of finerenone, the inclusion criteria required the serum potassium level ≤4.8 mmol/L during the run-in period and at screening visit, but some of the enrolled patients had a serum potassium level >4.8 mmol/L at baseline. Although the safety data from these patients [see Tables 54 and 55 in the Review Report (1)] raised no clinically unacceptable safety concerns in patients with serum potassium levels >4.8 and ≤5.0 mmol/L or patients with serum potassium levels>5.0 mmol/L, the protocol specified that finerenone treatment had to be interrupted in patients with an increase in serum potassium levels to >5.5 mmol/L, and thus experience with the use of finerenone in patients with such serum potassium levels is very limited. In light of this fact, finerenone should be contraindicated in patients who have serum potassium levels >5.5 mmol/L at the start of treatment.

The expert advisors supported PMDA's conclusion.

In addition to the above, the expert advisors supported PMDA's conclusion on the safety of finerenone and necessary cautions in Sections "7.R.3.2 Concomitant use with potassium-sparing diuretics" to "7.R.3.4 Use of finerenone in patients with hepatic impairment" in the Review Report (1).

In view of the above discussion, PMDA requested the applicant to include the relevant cautionary statements in the package insert and confirmed that appropriate actions were taken.

1.4 Patients eligible for finerenone and indication

The expert advisor raised the following comment:
The efficacy of finerenone in patients with non-diabetic CKD or CKD without albuminuria (UACR <30 mg/g), who were excluded from the clinical studies, remains unclear.

PMDA's conclusion:
(a) In patients with non-diabetic CKD (such as IgA nephropathy and polycystic kidney) who have concurrent type 2 diabetes mellitus, healthcare professionals in clinical practice would have difficulty in determining whether the progression of the renal disorder is due to non-diabetic causes or type 2 diabetes mellitus, and thus finerenone should be indicated for the treatment of "chronic kidney disease associated with type 2 diabetes mellitus"; and (b) patients with UACR <30 mg/g were enrolled in the clinical studies, although the number of such patients was limited, and the efficacy of finerenone in these patients was not substantially different from that in patients with high albuminuria or very high albuminuria, requiring no restrictions for UACR. Finerenone, on the other hand, should be mainly recommended to a population of patients with diabetic kidney disease and UACR ≥30 mg/g, and thus the package insert should include appropriate advice, i.e., the Precautions Concerning Indication section should include a cautionary statement that eligible patients must be selected by physicians with a full understanding of the characteristics of patients enrolled in clinical studies, and the Clinical Studies section should include the inclusion criteria for UACR in the clinical studies and information that patients with non-diabetic CKD (such as IgA nephropathy and polycystic kidney) were excluded from the clinical studies.

The expert advisors supported PMDA's conclusion.

In view of the above discussion at the Expert Discussion, PMDA has concluded that the indication and related cautionary statements in the package insert should be as follows:

Indication
Chronic kidney disease associated with type 2 diabetes mellitus (with exception of patients who have end-stage renal disease or are undergoing dialysis)

Precautions Concerning Indication
- Finerenone should be administered to patients who are receiving an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker, except for patients who are not eligible for these drugs.
- Finerenone may cause a decrease in eGFR. Use of finerenone in patients with eGFR <25 mL/min/1.73 m^2 should be carefully considered by weighing its risks and benefits.

- Eligible patients must be selected by physicians with a full understanding of the information presented in the "17. Clinical Studies" section and the characteristics of patients enrolled in clinical studies (primary disease, concomitant drugs, renal function, albuminuria, etc.).

1.5 Meaning of continued use of finerenone in patients whose disease has progressed to end-stage renal disease after the start of finerenone

In view of the efficacy results in patients whose disease has progressed to end-stage renal disease (ESRD) after the start of finerenone in Studies 16244 and 17530 and the incidences of hyperkalaemia-related events in subgroups by renal function, PMDA concluded that a caution should be advised that finerenone should be discontinued in patients whose disease has progressed to ESRD or a condition in need of dialysis. The expert advisors supported PMDA's conclusions above and in Section "7.R.6 Meaning of continued use of finerenone in patients whose disease has progressed to ESRD after the start of finerenone" in the Review Report (1).

1.6 Dosage and administration

The expert advisors supported PMDA's conclusions described in Section "7.R.7 Dosage and administration" in the Review Report (1), including the conclusion that the initial dose, maximum dose, and dose adjustment method should be established in accordance with the protocols of Studies 16244 and 17530.

In view of the above, PMDA has concluded that the dosage and administration and related cautionary statements in the package insert should be as follows:

Dosage and Administration

The usual adult dosage is 20 mg of finerenone administered orally once daily. The starting dose should be determined as shown below:

eGFR ≥60 mL/min/1.73 m^2: 20 mg

eGFR <60 mL/min/1.73 m^2: 10 mg. The dose may be increased to 20 mg approximately 4 weeks after the start of treatment, based on serum potassium and estimated glomerular filtration rate (eGFR).

Precautions Concerning Dosage and Administration

Serum potassium and eGFR should be measured 4 weeks after the start or re-start of the treatment or dose increase and then periodically. The dose should be adjusted according to the table shown below.

Serum potassium level (mEq/L)	Dose adjustment
≤4.8	20 mg once daily: Unchanged 10 mg once daily: Increase to 20 mg once daily (unless eGFR decrease by >30% compared to the previous measurement)
>4.8 and ≤5.5	Unchanged
>5.5	Discontinuation

When the serum potassium level decreases to ≤5.0 mEq/L after dose discontinuation, finerenone may be resumed at 10 mg once daily.

1.7 Risk management plan (draft)

In view of the discussions presented in Section "7.R.8 Post-marketing investigations" in the Review Report (1) and comments from the expert advisers at the Expert Discussion, PMDA has concluded that the risk management plan (draft) for finerenone should include the safety specifications presented in Table 76 and that the applicant should conduct additional pharmacovigilance activities and additional risk minimization activities presented in Table 77. In addition, in light of the incidences of the renal composite endpoint in the Japanese population in Studies 16244 and 17530, PMDA has concluded that the applicant should investigate the incidences of renal failure in the post-marketing setting through post-marketing database surveillance. The optimal method for pharmacovigilance activities using medical information databases should be further investigated by taking account of the feasibility.

Table 76. Safety and efficacy specifications in the risk management plan (draft)

Safety specifications		
Important identified risks	Important potential risks	Important missing information
• Hyperkalaemia	• Function kidney decreased	Not applicable
Efficacy specifications		
Not applicable		

Table 77. Summary of additional pharmacovigilance activities and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance • Post-marketing database surveillance (hyperkalaemia) • Post-marketing database surveillance (function kidney decreased)	• Disseminate information based on early post-marketing phase vigilance • Organize and disseminate materials for healthcare professionals • Organize and disseminate materials for patients

2. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

2.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

2.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.1.6) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

3. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication and the dosage and administration shown below, with the following condition. The product is a drug with a new active ingredient, and thus the re-examination period is 8 years. The product is

not classified as a biological product or a specified biological product. The drug substance is classified as a powerful drug. The drug product is not classified as a poisonous drug or a powerful drug.

Indication

Chronic kidney disease associated with type 2 diabetes mellitus (with exception of patients who have end-stage renal disease or are undergoing dialysis)

Dosage and Administration

The usual adult dosage is 20 mg of finerenone administered orally once daily. The starting dose should be determined as shown below:

eGFR ≥60 mL/min/1.73 m^2: 20 mg

eGFR <60 mL/min/1.73 m^2: 10 mg. The dose may be increased to 20 mg approximately 4 weeks after the start of treatment, based on serum potassium and estimated glomerular filtration rate (eGFR).

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

Appendix

List of Abbreviations

A→B	From the apical surface to the basolateral surface
ACE	Angiotensin-converting enzyme
ADAMTS-1	A disintegrin and metallopeptidase with thrombospondin motif 1
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AR	Androgen receptor
ARB	Angiotensin receptor blocker
ASC2	Activating signal co-integrator 2
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
AUC/D	Dose-corrected AUC
AUC_{0-t}	AUC from time zero to time of the last quantifiable concentration
AUC_{τ}	AUC during a dosing interval
$AUC_{0-\infty}$	AUC from time zero to time of infinity
BA	Bioavailability
B→A	From the basolateral surface to the apical surface
BCRP	Breast cancer resistance protein
BE	Bioequivalence
BE Guidelines for Different Strengths	"Guideline for Bioequivalence Studies for Different Strengths of Oral Solid Dosage Forms" (PMSB/ELD Notification No. 64 dated February 14, 2000, partially revised by PFSB/ELD Notification No. 0229-10 dated February 29, 2012)
BE Guidelines for Formulation Change	"Guideline for Bioequivalence Studies for Formulation Changes of Oral Solid Dosage Forms" (PMSB/ELD Notification No. 64 dated February 14, 2000, partially revised by PFSB/ELD Notification No. 0229-10 dated February 29, 2012)
BMI	Body mass index
BSEP	Bile salt export pump
CEC	Clinical Endpoint Committee
CI	Confidence interval
CKD	Chronic kidney disease
CKD-EPI	Chronic kidney disease epidemiology collaboration
CL	Total body clearance
CL_{cr}	Creatinine clearance
CL/F	Apparent total body clearance
C_{max}	Maximum plasma concentration
C_{max}/D	Dose-corrected C_{max}
CQA	Critical quality attribute
CYP	Cytochrome P450
DOCA	Desoxycorticosterone acetate
dp/dt_{max}	Maximum rate of pressure rise
dp/dt_{min}	Minimum rate of pressure drop
d8-TCA	d8-taurocholic acid
EC_{50}	50% effective concentration
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
ERα	Estrogen receptor α
ERβ	Estrogen receptor β
ESRD	End-stage renal disease
FAS	Full Analysis set
FDA	Food and Drug Administration
Finerenone	Finerenone

GC	Gas chromatography
GGT	γ-glutamyl transpeptidase
GR	Glucocorticoid receptor
hCav1.2	Human voltage-gated (L-type) calcium channel/current isoform 1.2
HEK	Human embryonic kidney
hERG	Human ether-a-go-go related gene
hNav1.5	Human sodium channel/current isoform 1.5
HPLC	High performance liquid chromatography
IC_{20}	20% inhibition concentration
IC_{50}	50% inhibitory concentration
ICH Q1E guideline	"Guideline on Evaluation of Stability Data" (PFSB/ELD Notification No. 0603004 dated June 3, 2003)
IR	Infrared absorption spectroscopy
Kerendia	Kerendia Tablets
KIM-1	Kidney injury molecule-1
LC-MS/MS	Liquid chromatography and tandem mass spectrometry
LDL	Low density lipoprotein
LLC-PK	Lilly laboratory culture porcine kidney
MATE	Multidrug and toxin extrusion
MCP-1	Monocyte chemoattractant protein-1
MDCK	Madin-Darby canine kidney
MDRD	Modification of diet in renal disease
MedDRA PT	MedDRA Preferred Term
MedDRA LLT	MedDRA Lowest Level Term
MMP-2	Matrix metalloproteinase-2
MPP^+	1-methyl-4-phenylpyridinium
MR	Mineralocorticoid receptor
mRNA	Messenger ribonucleic acid
MS	Mass spectrum
MWF	Munich Wistar Frömter
NCoR1	Nuclear receptor corepressor 1
NGAL	Neutrophil gelatinase-associated lipocalin
NMR	Nuclear magnetic resonance spectroscopy
NO	Nitric oxide
NT-proBNP	N-terminal pro-B type natriuretic peptide
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
OPN	Osteopontin
PAH	p-aminohippuric acid
PAI-1	Plasminogen activator inhibitor-1
P_{app}	Apparent permeability coefficient
PBPK	physiologically-based pharmacokinetics
PCR	Polymerase chain reaction
PD	Pharmacodynamics
PE	Polyethylene
PEG	Polyethylene glycol
PGC-1α	Peroxisome proliferator-activated receptor γ coactivator 1α
P-gp	P-glycoprotein
PhIP	2-Amino-1-methyl-6-phenylimidazo[4,5-b]pyridine
PK	Pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	Population pharmacokinetics
PR	Progesterone receptor

proBNP	Prohormone of brain natriuretic peptide
PTP	Press through packaging
PTZ	Pentylenetetrazole
PVC	Polyvinyl chloride
PVDC	Polyvinylidene chloride
QTc	Corrected QT interval
QTcF	Fridericia-corrected QT Interval
RH	Relative humidity
SD	Sprague-Dawley
SGLT	Sodium-glucose cotransporter
SHRSP	Stroke-prone spontaneous hypertensive rat
SRC1	Steroid receptor coactivator-1
TIF1α	Transcriptional intermediary factor 1α
TIMP-1	Tissue inhibitor of matrixmetalloproteinase-1
t_{max}	Time to reach maximum plasma concentration
Tnnt2	Cardiac troponin T (troponin T type 2)
TNX	Teneicin-X
TRAP220	RNA polymerase II transcription subunit 1
$t_{1/2}$	Elimination half-life
UACR	Urine albumin-to-creatinine ratio
UGT	Uridine diphosphate-glucuronosyltransferase
UV-A	Ultraviolet A
UV/VIS	Ultraviolet-visible spectrophotometry
V_c/F	Apparent central volume of distribution
V_{ss}	Volume of distribution at steady state