

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

215341Orig1s000

OTHER REVIEW(S)

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: July 6, 2021
Requesting Office or Division: Division of Cardiology and Nephrology (DCN)
Application Type and Number: NDA 215341
Product Name and Strength: Kerendia (finerenone) film-coated tablets, 10 mg and 20 mg
Applicant/Sponsor Name: Bayer Healthcare Pharmaceuticals, Inc. (Bayer)
OSE RCM #: 2020-2332-2
DMEPA Safety Evaluator: Mariette Aidoo, PharmD, MPH
DMEPA Team Leader: Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

Bayer submitted a response to recommendations for the container labels and carton labeling received on June 24, 2021 for Kerendia. We reviewed the response to determine if it is acceptable from a medication error perspective. The submission was in response to recommendations that we made during previous label and labeling reviews.^{a,b}

2 CONCLUSION

As previously noted, Bayer implemented our recommendations for the container label and we have no additional recommendations at this time. We previously noted the duplication of the (b) (4) heading on the back panel of the carton labeling. Bayer acknowledged our recommendation to delete the (b) (4) header to avoid redundancy. However, Bayer indicates that the "process of printing the cartons has already begun (due to the current packaging component lead times)" and thus proposes to implement the revised carton labeling (i.e. deleted header) by September 2021. We find this proposal acceptable and have no additional recommendations at this time.

^a Aidoo, M. Label and Labeling Review for Kerendia (NDA 215341). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 APR 13. RCM No.: 2020-2332.

^b Aidoo, M. Label and Labeling Review for Kerendia (NDA 215341). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 APR 13. RCM No.: 2020-2332-1

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/s/

MARIETTE A AIDOO
07/06/2021 01:41:19 PM

HINA S MEHTA
07/07/2021 09:39:35 AM

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: June 22, 2021

To: Anna Park
Regulatory Project Manager
Division of Cardiology and Nephrology (DCN)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Jessica Chung, PharmD, MS
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Samantha Bryant, PharmD, BCPS
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: (b) (4)

Drug Name (established name): KERENDIA (finerenone)

Dosage Form and Route: tablets, for oral use

Application Type/Number: NDA 215341

Applicant: Bayer HealthCare Pharmaceuticals, Inc.

1 INTRODUCTION

On November 6, 2020, Bayer HealthCare Pharmaceuticals, Inc. submitted for the Agency's review an original New Drug Application (NDA) 215341 for KERENDIA (finerenone) tablets for the proposed indication to (b) (4) (b) (4) reduce the risk of (b) (4) cardiovascular (b) (4) death, non-fatal myocardial infarction (b) (4) and hospitalization for heart failure in adult patients with chronic kidney disease (CKD) and type 2 diabetes (T2D). We note that the proposed proprietary name KERENDIA was found to be conditionally acceptable by the Division of Medication Error Prevention and Risk Management on April 5, 2021.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Cardiology and Nephrology (DCN) on November 13, 2020, for DMPP and OPDP to review the Applicant's proposed (b) (4) (b) (4) for KERENDIA (finerenone) tablets.

2 MATERIAL REVIEWED

- Draft KERENDIA (finerenone) (b) (4) received on November 9, 2020, and received by DMPP and OPDP on June 9, 2021.
- Draft KERENDIA (finerenone) Prescribing Information (PI) received on November 9, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 9, 2021.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APhont to make medical information more accessible for patients with vision loss. We reformatted the (b) (4) document using the Arial font, size 10.

(b) (4)

4 CONCLUSIONS

The (b) (4) is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review (b) (4) is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made (b) (4).

Please let us know if you have any questions.

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/s/

JESSICA M CHUNG
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06/22/2021 03:11:43 PM

BARBARA A FULLER
06/22/2021 03:13:14 PM

LASHAWN M GRIFFITHS
06/22/2021 03:14:01 PM

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: June 16, 2021

To: Anna Park, Regulatory Project Manager
Division of Cardiology and Nephrology, (DCN)

Michael Monteleone, Associate Director for Labeling, (DCN)

From: Samantha Bryant, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: James Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for KERENDIA (finerenone) tablets, for oral use

NDA: 215341

In response to DCN's consult request dated November 13, 2020, OPDP has reviewed the proposed product labeling (PI) (b) (4) and carton and container labeling for the original NDA submission for Kerendia.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DCN (Anna Park) on June 9, 2021, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed (b) (4) will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling received by electronic mail from DCN (Anna Park) on June 9, 2021, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Samantha Bryant at (301) 348-1711 or Samantha.Bryant@fda.hhs.gov.

31 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

SAMANTHA E BRYANT
06/16/2021 10:37:31 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Pediatrics and Maternal Health
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
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Division of Pediatric and Maternal Health Review

Date: 5/27/2021 **Date consulted:** 5/11/2021

From: Wenjie Sun, MD, Medical Officer, Maternal Health
Division of Pediatrics and Maternal Health (DPMH)

Through: Miriam Dinatale, DO, Team Leader, Maternal Health, DPMH
Lynne P. Yao, MD, OND, Division Director, DPMH

To: Division of Cardiology and Nephrology (DCN)

Drug: Kerendia (finerenone) tablets, for oral use

NDA: 215341

Applicant: Bayer HealthCare Pharmaceuticals Inc

Subject: New NDA

Proposed Indication: To reduce the risk of sustained eGFR decline, end-stage kidney disease, cardiovascular death, non-fatal myocardial infarction, and hospitalization for heart failure in adult patients with type 2 diabetes (T2D) (b) (4).

Materials

Reviewed:

- Applicant's submitted background package and proposed labeling for NDA 215341
- DCN consult form for DPMH, DARRTS Reference ID 4794235

Consult Question:

DHN is seeking assistance from DPMH regarding subsections (b) (4) 8.1, 8.2 and (b) (4) of the labeling. Specifically, DCN seeks the answer to the following question:

Whether the warnings and precautions (b) (4) is appropriate based on the level of concerns stemming from the nonclinical reproductive toxicology findings described below:

- In the embryo-fetal toxicity study in rats, finerenone resulted in reduced placental weights and signs of fetal toxicity, including reduced fetal weights and retarded ossification at the maternal toxic dose of 10 mg/kg/day corresponding to an AUC of 19 times that in humans. At 30 mg/kg/day, the incidence of visceral and skeletal variations was increased (slight edema, shortened umbilical cord, slightly enlarged fontanelle) and one fetus showed complex malformations including a rare malformation (double aortic arch) at an AUC of about 25 times that in humans. These findings coincide with maternal toxicity and reduced fetal weight, and the reduced ossifications are probably better described as a trend toward more variations (not malformations) with the dose. These were also observed in the historical control groups and could be spontaneous malformations. There were no embryofetal lethality or malformations, except one fetus in the rat study that showed a rare malformation. P/T usually does not put too much weight on a single incident of rare malformations in a single fetus at high exposure. No effects in the rabbit embryofetal study.
- Regarding post-natal toxicity through lactation: When rats were exposed during pregnancy and lactation in the pre- and postnatal developmental (PPND) toxicity study, increased postnatal pup mortality and other adverse effects (lower pup weight, delayed pinna unfolding) were observed at about 4 times the AUC expected in humans, coincide with reduced maternal body weight. In addition, the offspring showed slightly increased locomotor activity, but no other neurobehavioral changes starting at about 4 times the AUC expected in humans. The data from this PPND study seems to indicate a potential human risk given the mortality and CNS outcome and lower exposure multiples, (b) (4), although there were no data on the drug level in the milk in nonclinical studies.

INTRODUCTION AND BACKGROUND

On November 6, 2020, the applicant (Bayer HealthCare Pharmaceuticals Inc) submitted a new original NDA 215341 for finerenone tablets for approval. The Division of Cardiology and Nephrology (DCN) consulted the Division of Pediatric and Maternal Health (DPMH) on May 11, 2021, to assist with the Warnings and Precautions and Pregnancy and Lactation subsections of labeling.

Regulatory History

- On February 4, 2015, finerenone was granted Fast Track Designation.
- On November 6, 2020, the applicant submitted an original NDA for a new molecular entity, finerenone tablets. The proposed indication is to (b) (4) reduce the risk of (b) (4) cardiovascular (b) (4) death, non-fatal myocardial infarction (b) (4) and hospitalization for heart

failure in adult patients with type 2 diabetes (T2D) (b) (4). The application is under priority review with a PDUFA goal date of July 9, 2021.

- On May 11, 2021, DCN consulted DPMH to assist with the labeling.

Drug Characteristics¹

Drug Class ²	Selective mineralocorticoid receptor (MR) antagonist
Proposed Mechanism of action	(b) (4) Finerenone has a high potency and selectivity for the MR (b) (4).
Proposed Dose and Administration ³	The recommended starting dosage is 10 mg or 20 mg orally taken once daily based on estimated glomerular filtration rate (eGFR) and serum potassium thresholds. Increase dosage after 4 weeks to the target dose of 20 mg once daily, based on eGFR and serum potassium thresholds.
Metabolism ³	Finerenone is primarily metabolized by CYP3A4 (90%) and to a lesser extent by CYP2C8 (10%) to inactive metabolites. About 80% of the administered dose was excreted in urine (<1% as unchanged) and approximately 20% in feces (<0.2% as unchanged).
Molecular weight ³	378.43 g/mol
Half life ³	2-3 hours
Protein Binding ³	91.7%
Bioavailability ³	43.5%.
Proposed Serious Adverse Reactions ⁴	Hyperkalemia

REVIEW

PREGNANCY

Type II Diabetes, diabetic nephropathy, and Pregnancy⁵

An estimated 14.9 million women in the United States have diabetes mellitus.⁵ In the US, about 1 to 2% of pregnant women have pregestational diabetes mellitus.⁵ Diabetic nephropathy is estimated to occur in 5 to 10% of diabetic pregnancies. Renal failure develops in 25% to 30% of

¹ Based on Applicant's Proposed Labeling with DCN Review Team Input.

² Based on labeling proposed by the DCN review team.

³ Based on discussion with DCN Clinical Pharmacology Team.

⁴ Based on discussion with DCN Pharmacology Toxicology Team and Clinical Team.

⁵ ACOG Practice Bulletin Number 201 Pregestational Diabetes Mellitus. Green Journal 2018;132(5):e228-248

females with insulin-dependent diabetes mellitus with a peak incidence after approximately 16 years of disease.^{5,6,7}

Most studies have failed to demonstrate permanent deterioration in renal function associated with pregnancy in women with mild-to-moderate diabetic nephropathy.^{8,9} However, progression to end stage renal disease has been reported in women with serum creatinine levels exceeding 1.5 mg/dL or severe proteinuria (more than 3g per 24 hours) at baseline.^{10,11}

Overall perinatal mortality rate in pregnancies complicated by pregestational diabetes mellitus decreased markedly in the twentieth century.¹² Major congenital anomalies are the leading cause of perinatal mortality in pregnancies complicated by pregestational diabetes mellitus (due to uncontrolled serum glucose), and they occur in 6-12% of infants of women with diabetes.^{13,14,15} Women with preexisting diabetic nephropathy (Class F) are at significantly higher risk for several adverse obstetric complications, including hypertensive disorders, uteroplacental insufficiency, and iatrogenic preterm birth because of worsening renal function.^{16,17,18} Additionally, pregestational diabetes is a risk factor for acute myocardial infarction.^{16,19}

Management of patients with diabetic nephropathy during pregnancy involves a multidisciplinary team approach with baseline evaluation of renal function by serum creatinine and assessment of urinary protein excretion (urine protein-to-creatinine ratio or 24-hour protein excretion) with follow up at regular intervals throughout pregnancy. Monthly growth ultrasound

⁶ Quinn M, Angelico MC, Warram JH, et al. Familial factors determine the development of diabetic nephropathy in patients with IDDM. *Diabetologia*. 1996; 39:940.

⁷ Landon MB. Diabetic Nephropathy and pregnancy. *Clinical Obstetrics and Gynecology* 2007;50(4):998-1006.

⁸ Rossing K, Jacobsen P, Hommel E, Mathiesen E, Svenningsen A, Rossing P, et al. Pregnancy and progression of diabetic nephropathy. *Diabetologia* 2002; 45:36-41.

⁹ Young EC, Pires ML, Marques LP, de Oliveira JE, Zajdenverg L. Effects of pregnancy on the onset and progression of diabetic nephropathy and of diabetic nephropathy on pregnancy outcomes. *Diabetes Metab Syndr* 2011; 5:137-42.

¹⁰ Purdy LP, Hantsch CE, Molitch ME, Metzger BE, Phelps RL, Dooley SL, et al. Effect of pregnancy on renal function in patients with moderate-to-severe diabetic renal insufficiency. *Diabetes Care* 1996; 19:1067-74.

¹¹ Gordon M, Landon MB, Samuels P, Hissrich S, Gabbe SG. Perinatal outcome and long-term follow-up associated with modern management of diabetic nephropathy. *Obstet Gynecol* 1996; 87:401-9.

¹² Feig DS, Hwee J, Shah BR, Booth GL, Bierman AS, Lipscombe LL. Trends in incidence of diabetes in pregnancy and serious perinatal outcomes: a large, population-based study in Ontario, Canada, 1996-2010. *Diabetes Care* 2014; 37:1590-6.

¹³ Kitzmiller JL, Buchanan TA, Kjos S, Combs CA, Ratner RE. Pre-conception care of diabetes, congenital malformations, and spontaneous abortions. *Diabetes Care* 1996; 19:514-41.

¹⁴ Agha MM, Glazier RH, Moineddin R, Booth G. Congenital abnormalities in newborns of women with pregestational diabetes: a time-trend analysis, 1994 to 2009. *Birth Defects Res A Clin Mol Teratol* 2016; 106:831-9.

¹⁵ Leirgul E, Brodwall K, Greve G, Vollset SE, Holmstrom H, Tell GS, et al. Maternal diabetes, birth weight, and neonatal risk of congenital heart defects in Norway, 1994-2009. *Obstet Gynecol* 2016; 128:1116-25.

¹⁶ Ekblom P, Damm P, Feldt-Rasmussen B, Feldt-Rasmussen U, Molvig J, Mathiesen ER. Pregnancy outcome in type 1 diabetic women with microalbuminuria. *Diabetes Care* 2001; 24:1739-44.

¹⁷ Combs CA, Rosenn B, Kitzmiller JL, Khoury JC, Wheeler BC, Miodovnik M. Early-pregnancy proteinuria in diabetes related to preeclampsia. *Obstet Gynecol* 1993; 82:802-7.

¹⁸ Khoury JC, Miodovnik M, LeMasters G, Sibai B. Pregnancy outcome and progression of diabetic nephropathy. What's next? *J Matern Fetal Neonatal Med* 2002; 11:238-44.

¹⁹ Gordon MC, Landon MB, Boyle J, Stewart KS, Gabbe SG. Coronary artery disease in insulin-dependent diabetes mellitus of pregnancy (class H): a review of the literature. *Obstet Gynecol Surv* 1996;51:437-44.

and antenatal testing initiated at 32 weeks' gestation until delivery is often used.⁵ Low dose aspirin (81 mg/day) is recommended to start between 12 weeks and 28 weeks of gestation and continued until delivery. Management is often on screening for development of complications. Early delivery is often recommended due to worsening renal disease or obstetric complications.

Nonclinical Experience

In the embryo-fetal toxicity study in rats, finerenone resulted in reduced placental weights and signs of fetal toxicity, including reduced fetal weights and retarded ossification at the maternal toxic dose of 10 mg/kg/day corresponding to an exposure ($AUC_{unbound}$) 18 times that in humans. At 30 mg/kg/day, the incidence of visceral and skeletal variations was increased (slight edema, shortened umbilical cord, slightly enlarged fontanelle) and one fetus showed complex malformations including a rare malformation (double aortic arch) at an exposure of about 25 times that in humans.

In the embryo-fetal toxicity study in rabbits, finerenone did not show any signs of teratogenicity up to 2.5 mg/kg/day. The doses free of any findings (low dose in rats, high dose in rabbits) provided safety margins at exposures 10 to 12 times the AUC in humans.

When rats were exposed during pregnancy and lactation in the pre- and postnatal developmental toxicity study, increased pup mortality and other adverse effects (lower pup weight, delayed pinna unfolding) were observed at about 4 times the $AUC_{unbound}$ expected in humans. In addition, the offspring showed slightly increased locomotor activity, but no other neurobehavioral changes starting at about 4 times the $AUC_{unbound}$ expected in humans. The dose free of findings provided a safety margin of about 2 times the $AUC_{unbound}$ expected in humans.

The reader is referred to the Nonclinical comments within the integrated review.

Review of Clinical Trials

There were no pregnant people enrolled in the clinical trials.

Review of Literature

DPMH's Review of Literature

DPMH conducted a literature review in Embase, Pubmed, Micromedex,²⁰ and ReproTox.²¹

Embase and Pubmed were searched for “finerenone” and “pregnancy,” “finerenone” or “finerenone” and “fetal malformations/congenital malformations/birth defects/stillbirth/spontaneous abortion/miscarriage.”

- There is no published literature on finerenone use in pregnancy.

Micromedex²⁰ and ReproTox²¹ contain no information on finerenone.

Reviewer comment:

There are no data on the use of finerenone in human pregnancy. In nonclinical rat and rabbit study, no adverse effects were observed on fetal growth or development 10 and 12 times the

²⁰ Truven Health Analytics information, <http://www.micromedexsolutions.com/>. Accessed 5/12/2021

²¹ Reprotox Website: www.Reprotox.org. REPROTOX dytem was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed 5/12/2021.

human dose (by AUC), respectively. In patients with CKD, the maximum dose of 20mg is based on serum potassium level. This was confirmed in discussion with the Clinical Pharmacology Team. Therefore, a study evaluating the pharmacokinetics of finerenone during pregnancy is not necessarily needed, because dosing is based on titration to a clinical marker (i.e., potassium level).

LACTATION

Nonclinical Experience

When rats were exposed during pregnancy and lactation in the pre- and postnatal developmental toxicity study, increased pup mortality and other adverse effects (lower pup weight, delayed pinna unfolding) were observed at about 4 times the AUC_{unbound} expected in humans. Since finerenone was measured in rat pup serum, it is likely that finerenone was secreted in rat milk.

The reader is referred to the Nonclinical comments within the integrated review.

Review of Clinical Trials

There were no lactating people in any of the clinical trials.

Review of Literature

DPMH's Review of Literature

A search was performed using the sources noted below, and the following findings were retrieved:

A search in PubMed and Embase was performed using the search terms “finerenone” AND “lactation” and “finerenone” AND “breastfeeding.”

- No articles were found on the use of finerenone during lactation.

LactMed,²² Briggs,²³ and Hale²⁴ contain no information on finerenone.

Reviewer comment:

It is not known if finerenone is present in human breastmilk. There are no data on the effect of finerenone on the breastfed child or the effect on milk production.

Based on pre- and postnatal animal study, finerenone is likely present in animal milk. Although no direct measurement of finerenone in rat milk was obtained, concentration of finerenone in the plasma concentration in the F1 generation was directly proportional to maternal dose measured on post-natal day 21. The terminal half-life of finerenone is only 2-3 hours. Finerenone detected in rat pup serum is likely from ingestion of breastmilk. Therefore, this reviewer concludes that

²² <http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm>. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed data base provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfeeding infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility. Accessed 5/12/2021.

²³ Briggs GG, Freeman RK. Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. 10th Ed. 2015. Online, accessed 5/12/2021.

²⁴ Hale, Thomas. Hale's Medications and Mother's Milk 2019. Springer Publishing Company, New York, NY. Accessed 5/12/2021.

finerenone is likely present in rat milk. This was confirmed in discussion with DCN Pharmacology Toxicology Team. When a drug is present in animal milk, it is likely to be present in human milk.

Adverse effects, including increased pup mortality, lower pup weight, and delayed pinna unfolding, were observed in rats during the pre- and postnatal developmental toxicity study at about 4 times the AUC_{unbound} expected in humans. Specifically, four pups from two litters exposed to 10 mg/kg/day (AUC_{unbound} of 19 times that in humans) and four pups from four litters exposed to 3 mg/kg/day were found dead or missing (presumed cannibalized). In discussion with DCN Pharmacology Toxicology Team, the no observed adverse effect level (NOAEL) is considered 3 mg/kg/day for dams. Due to pre- and postnatal deaths, the NOAEL for the F1 generation into adulthood is considered 1 mg/kg/day. Because drug concentration in animal milk does not directly correlate to drug concentration in human milk, we cannot establish the NOAEL dose in humans based on the animal findings.

The reader is referred to the Discussion and Conclusion section at the end of this review for DPMH's opinion of the data submission and recommendations.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

Finerenone was non-genotoxic.

In 2-year carcinogenicity studies, finerenone did not show a carcinogenic potential in male and female rats as well as female mice. In male mice, finerenone resulted in an increase in Leydig cell adenoma at doses representing 26 times the AUC_{unbound} in humans. A dose representing 17 times the AUC_{unbound} in humans did not cause any tumors. Based on the known sensitivity of rodents to develop these tumors and the pharmacology-based mechanism at suprathreshold doses as well as adequate safety margins, the increase in Leydig cell tumors in male mice is not clinically relevant. No human data on the effect of Kerendia on fertility are available. Animal studies with finerenone did not indicate a risk of impaired male fertility. A fertility study in rats with finerenone indicated impaired female fertility at 20 times AUC to the maximum human exposure. The dose free of findings provided a safety margin of about 10 times the exposure expected in humans.

The reader is referred to the Nonclinical comments within the integrated review.

Review of Clinical Trials

There are no specific reports of fertility issues noted in any of the clinical trials.

Review of Literature

DPMH's Review of Literature

DPMH conducted a published literature review by using the sources noted below, and the following findings were retrieved:

DPMH conducted a published literature review on PubMed and Embase using term “finerenone” and “fertility,” “finerenone” AND “reproduction,” “finerenone” AND “contraception.” No relevant articles were retrieved.

ReproTox²⁵ contains no information on finerenone.

Reviewer comment:

There are no data on the effect of finerenone on fertility in humans. In animal reproduction studies, finerenone does not affect fertility at clinical doses. The reader is referred to the Discussion and Conclusion section at the end of this review for DPMH’s opinion of the data, submission and recommendations.

DISCUSSION AND CONCLUSIONS

Pregnancy

There are no data on the use of finerenone in human pregnancy. In embryo-fetal development studies in pregnant rats and rabbits, no adverse effects were observed on fetal growth or development at 10 and 12 times the human dose (by AUC), respectively. Therefore, DPMH does not recommend a statement regarding embryofetal toxicity under Warning and Precautions based on the animal findings above.

Pregestational diabetes mellitus in pregnancy is observed in 1 to 2% of all pregnancies.⁵ Diabetic nephropathy complicates approximately 5%-10% of insulin-dependent diabetic pregnancies.⁵ Based on the total number of pregnancies per year in the US,²⁶ which is 6,369,000 pregnancies, the estimated number of pregnant patients with pregestational diabetes who would be affected by diabetic nephropathy would be 3,184 to 12,738 pregnancies per year. Although animal reproduction studies did not show any specific safety concerns at the clinical doses, there are no human data on the use of finerenone in pregnancy. Therefore, since there is the potential for use of finerenone in females of reproductive potential and during pregnancy, DPMH recommends a postmarketing pregnancy registry and complementary pregnancy study to obtain information about the use of finerenone in pregnancy.

Lactation

There are no data on the presence of finerenone in human milk, the effects of the drug on the breastfed infant, or on milk production. Finerenone is likely present in rat milk. When a drug is present in rat milk, it is likely to be present in human milk.

Adverse effects, including increased pup mortality, were observed in rats during the pre- and postnatal developmental toxicity study at about 4 times the AUC_{unbound} expected in humans. Because drug concentration in animal milk does not directly correlate to drug concentration in human milk, we cannot establish the NOAEL dose in humans based on animal finding. Since we know that the drug will likely be present in human milk and since there were reports of pup mortality in rats exposed to finerenone during lactation, DPMH recommends no breastfeeding during treatment with finerenone. This recommendation will appear under Highlights Use in Specific Populations, and Patient Counseling Information.

²⁵ ReproTox. Accessed 5/12/2021.

²⁶ Curtin SC et al. Pregnancy Rates for U.S. Women Continue to Drop. NCHS Fata Brief No. 136. 2013

Finerenone is likely to be used in females of reproductive potential and during lactation. There is no information on presence of finerenone in human milk, and the information that we have in rats is concerning for infant harm. Therefore, DPMH recommends a post-marketing milk-only lactation study (that may be open to enrollment of healthy volunteers) to determine if finerenone will be present in human milk and if so, how much. Because DPMH recommends not breastfeeding during treatment with finerenone, recruiting patients who are taking finerenone for diabetic nephropathy will not be feasible; therefore, consideration should be made for recruitment of healthy volunteers who are no longer breastfeeding their infants but choose to provide breastmilk samples for the study.

Females and Males of Reproductive Potential

There are no reports of finerenone adversely affecting human fertility. Based on animal studies, maralixibat has no effect on male fertility. Finerenone impairs female fertility at 20 times AUC to the maximum human exposure. These data will be presented under subsection 13.1. There are no data to suggest finerenone interacts with systemic hormonal contraceptive.

Additionally, in animal reproduction studies, finerenone administered in pregnancy did not result in embryotoxicity or structural malformation at 10-13X for AUC_{unbound}. Therefore, this reviewer does not agree with the applicant proposed labeling (b) (4). DPMH recommends omitting subsection 8.3.

LABELING RECOMMENDATIONS

DPMH proposes deleting the applicant's proposed language in subsection (b) (4) and proposes edits to subsections 8.1, 8.2, and 17 of labeling for the new NDA and in compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

-----USE IN SPECIFIC POPULATION-----

- Lactation: Breastfeeding not recommended (8.2)

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on KERENDIA use during pregnancy to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Animal studies have shown developmental toxicity at exposures (b) (4). (see Data).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth

defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

(b) (4)

Data

Animal Data

In the embryo-fetal toxicity study in rats, finerenone resulted in reduced placental weights and signs of fetal toxicity, including reduced fetal weights and retarded ossification at the maternal toxic dose of 10 mg/kg/day corresponding to an $AUC_{unbound}$ of (b) (4) times that in humans. At 30 mg/kg/day, the incidence of visceral and skeletal variations was increased (slight edema, shortened umbilical cord, slightly enlarged fontanelle) and one fetus showed complex malformations including a rare malformation (double aortic arch) at an $AUC_{unbound}$ of about 25 times that in humans. The doses free of any findings (low dose in rats, high dose in rabbits) provide safety margins of 10 to (b) (4) times for the $AUC_{unbound}$ expected in humans.

When rats were exposed during pregnancy and lactation in the pre- and postnatal developmental toxicity study, increased pup mortality and other adverse effects (lower pup weight, delayed pinna unfolding) were observed at about 4 times the $AUC_{unbound}$ expected in humans. In addition, the offspring showed slightly increased locomotor activity, but no other neurobehavioral changes starting at about 4 times the $AUC_{unbound}$ expected in humans. The dose free of findings provided a safety margin of about 2 times for the $AUC_{unbound}$ expected in humans. (b) (4)

8.2 Lactation

Risk Summary

There are no data on the presence of finerenone or its metabolite in human milk, the effects on the breastfed infant or the effects on milk production. In a pre- and postnatal developmental toxicity study in rats, increased pup mortality and lower pup weight were observed at about 4 times the $AUC_{unbound}$ expected in humans. These findings suggest that finerenone is present in rat milk [see *Use in Specific Populations* (8.1)]. When a drug is present in animal milk, it is likely that the drug will be present in human milk. Because of (b) (4)

(b) (4)

avoid breastfeeding during treatment and for 1 day after treatment.

17 PATIENT COUNSELING INFORMATION

(b) (4)

Advise women that breastfeeding is not recommended at the time of treatment with KERENDIA and for 1 day after treatment [*see Use in Specific Populations (8.2)*].

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/s/

WENJIE SUN
05/27/2021 11:10:16 AM

MIRIAM C DINATALE
05/27/2021 11:15:32 AM

LYNNE P YAO
05/27/2021 12:32:23 PM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 21, 2021
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 215341
Product Name and Strength:	Kerendia (finerenone) film-coated tablets, 10 mg and 20 mg
Applicant/Sponsor Name:	Bayer Healthcare Pharmaceuticals, Inc. (Bayer)
OSE RCM #:	2020-2332-1
DMEPA Safety Evaluator:	Mariette Aidoo, PharmD, MPH
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on May 11, 2021 for Kerendia. We reviewed the revised container labels and carton labeling for Kerendia (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

We note our recommendation to consider reorienting the linear barcode to a vertical position was not implemented as the Applicant stated the bottles are square allowing the barcode to be placed on a flat surface (i.e. not a curvature). We find this proposal acceptable. The Applicant implemented our recommendations for the container labeling and we have no additional recommendations at this time.

The revised carton labeling is unacceptable from a medication error perspective given the redundancy of a dosage statement.

We recommend the following be implemented prior to approval of this NDA:

^a Aidoo, M. Label and Labeling Review for Kerendia (NDA 215341). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 APR 13. RCM No.: 2020-2332.

- A. As currently displayed on the carton labeling there is a (b) (4) heading which is followed by the each tablet contains statement on the back panel. To avoid redundancy given a dosage statement is already present under "Recommended dosage: See prescribing information." we recommend deleting the heading (b) (4) (b) (4) .

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

MARIETTE A AIDOO
05/21/2021 02:49:36 PM

HINA S MEHTA
05/21/2021 05:48:32 PM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	April 13, 2021
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 215341
Product Name, Dosage Form, and Strength:	Kerendia (finerenone) film-coated tablets, 10 mg and 20 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Bayer Healthcare Pharmaceuticals, Inc. (Bayer)
FDA Received Date:	November 9, 2020, November 30, 2020
OSE RCM #:	2020-2332
DMEPA Safety Evaluator:	Mariette Aidoo, PharmD, MPH
DMEPA Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

Bayer Healthcare Pharmaceuticals, Inc. (Bayer) submitted a New Drug Application for Kerendia (finerenone) tablets under NDA 215341. Kerendia is being proposed to (b) (4) reduce the risk of (b) (4) cardiovascular (b) (4) death, non-fatal myocardial infarction (b) (4) and hospitalization for heart failure in adult patients with chronic kidney disease (CKD) and type 2 diabetes. We evaluated the proposed Prescribing Information (PI), (b) (4) carton labeling, and container labels for areas of vulnerability that could lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Bayer submitted a 505(b)(1) New Drug Application for Kerendia (finerenone), a new molecular entity classified as a nonsteroidal mineralocorticoid receptor (MR) antagonist. Kerendia (finerenone) is being proposed for an indication to (b) (4) reduce the risk of (b) (4) cardiovascular (b) (4) death, non-fatal myocardial infarction (b) (4) and hospitalization for heart failure in adult patients with chronic kidney disease (CKD) and type 2 diabetes.

We performed a risk assessment of the proposed prescribing information (PI), (b) (4) carton labeling, and container labels for Kerendia to determine whether there are deficiencies that may lead to medication errors and other areas of improvement. (b) (4)

(b) (4) Our review of the proposed Kerendia PI, carton labeling, and container labels

identified areas of vulnerability that may lead to medication errors. For the Division we recommend inclusion of route of administration and clarity on cautionary statement in the Prescribing Information. For the Applicant we recommend revision to the recommended dosage statement, clarity on expiration date format, and prominence of net quantity statement.

4 CONCLUSION & RECOMMENDATIONS

(b) (4). We conclude that the proposed Kerendia Prescribing Information, carton labeling and container labels may be improved to promote the safe use of this product from a medication error perspective. We provide specific recommendations in Section 4.1 for the Division and 4.2 for the Applicant below.

4.1 RECOMMENDATIONS FOR DIVISION OF CARDIOLOGY AND NEPHROLOGY (DCN)

A. Highlights of Prescribing Information

1. Revise first bullet under Dosage and Administration for clarity and to add the route of administration. Revise to "The recommended starting dosage is 10 mg or 20 mg orally once daily based on estimated glomerular filtration rate (eGFR) and serum potassium thresholds. (2.1)".
2. We recommend adding a space between the strength and mg unit in Dosage Form and Strengths. Revise from "10mg" to "10 mg".

B. Full Prescribing Information

1. Dosage and Administration Section

- a. Revise (b) (4)

- b. Consider including the route of administration "orally" after the dose throughout Section 2.2 of the PI.

Revise the dosing statements in Section 2.2 to read:

(b) (4)

2. How Supplied/Storage and Handling

- a. (b) (4)

(b) (4)

(b) (4). Consider revising the temperature statement to "Store at 20°C to 25°C (68°F to 77°F); excursions are permitted from 15°C to 30°C (59°F to 86°F) [see *USP Controlled Room Temperature*].".

4.2 RECOMMENDATIONS FOR BAYER HEALTHCARE PHARMACEUTICALS, INC. (BAYER)

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Sample and Commercial Container labels & Carton Labeling)

1. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the location and format you intend to use for the lot number and expiration date. We recommend that the human-readable expiration date on the drug package label include a year, month, and non-zero day. We recommend that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. We recommend that a hyphen or a space be used to separate the portions of the expiration date.⁵
2. We recommend adding a space between the strength and mg unit on the principle display panel (PDP) for readability. For example, revise from "10mg" to "10 mg".
3. We recommend increasing the prominence of the word 'tablet' in the established name.
4. The net quantity statement appears prominent in large bold font. Decrease the prominence by reducing the font for the net quantity statement.
5. The statement "(b) (4)" is not required to be displayed. We recommend removal of the "(b) (4)" statement.
6. As currently presented the storage information is not consistent among all labels and labeling. We recommend revising the storage information for consistency among all labels and labeling.

⁵ Guidance for Industry: Product Identifiers Under the Drug Supply Chain Security Act Questions and Answers. 2018. Available from <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM621044.pdf>

7. To ensure consistency with the Prescribing Information, revise the statement, "(b) (4)." to read "Recommended Dosage: See prescribing information."

B. Commercial Container Labels

1. Consider reorienting the linear barcode to a vertical position to improve the scannability of the barcode. Barcodes placed in a horizontal position may not scan due to bottle curvature.^a

C. Commercial Carton Labeling

1. In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act. The Act requires manufacturers and repackagers, respectively, to affix or imprint a human-readable and machine-readable (2D data matrix barcode) product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. We note the human-readable product identifier is available, but it is unclear if the machine-readable product identifier will be included on your product's labeling. The draft guidance is available from:
<https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf>.

^a Neuenschwander M. et al. Practical guide to bar coding for patient medication safety. Am J Health Syst Pharm. 2003 Apr 15;60(8):768-79.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Kerendia received on November 9, 2020 from Bayer Healthcare Pharmaceuticals, Inc. (Bayer).

Table 2. Relevant Product Information for Kerendia	
Initial Approval Date	N/A
Active Ingredient	finerenone
Indication	To (b) (4) reduce the risk of (b) (4) cardiovascular (b) (4) death, non-fatal myocardial infarction (b) (4) and hospitalization for heart failure in adult patients with chronic kidney disease (CKD) and type 2 diabetes (T2D).
Route of Administration	oral
Dosage Form	film-coated tablets
Strength	10 mg and 20 mg
Dose and Frequency	<ul style="list-style-type: none"> Initiate treatment at 10 mg or 20 mg taken once daily based on estimated glomerular filtration rate (eGFR) and serum potassium thresholds. Increase dosage after 4 weeks to the target dose of 20 mg once daily, based on eGFR and serum potassium thresholds. Tablets may be taken with or without food.
How Supplied	<ul style="list-style-type: none"> - Bottle of 30 tablets - Bottle of 90 tablets
Storage	Store at 25°C (77°F); excursions are permitted from 15°C to 30°C (59°F to 86°F) [see <i>USP Controlled Room Temperature</i>].
Container Closure	White high-density polyethylene (HDPE) bottle with white (b) (4) screw caps.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On March 11, 2021, we searched for previous DMEPA reviews relevant to this current review using the terms, kerendia. Our search identified no previous reviews, and we considered our previous recommendations to see if they are applicable for this current review.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^b along with postmarket medication error data, we reviewed the following Kerendia labels and labeling submitted by Bayer Healthcare Pharmaceuticals, Inc. (Bayer).

- Container label received on November 9, 2020
- Professional Sample Container Labeling received on November 9, 2020
- Carton labeling received on November 30, 2020
- Professional Sample Carton Labeling received on November 30, 2020
- Prescribing Information (Image not shown) received on November 9, 2020, available from <\\CDSESUB1\evsprod\nda215341\0001\m1\us\114-labeling\draft\annotated\annotated-draft-labeling-text-06nov2020.pdf>

G.2 Label and Labeling Images



^b Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

MARIETTE A AIDOO
04/13/2021 05:05:25 PM

HINA S MEHTA
04/15/2021 12:16:27 PM

Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA 215341
Submission Number	001 / New NDA
Submission Date	11/6/2020
Date Consult Received	11/18/2020
Drug Name	Finerenone
Indication	To (b) (4) reduce the risk of (b) (4) CV (b) (4) death, non-fatal MI (b) (4) and hospitalization for heart failure in adult patients with CKD and T2D
Therapeutic dose	Up to 20 mg once daily (titrated)
Clinical Division	DCN

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This review responds to your consult dated 11/18/2020 regarding the sponsor's QT evaluation. We reviewed the following materials:

- Sponsor's clinical study protocol # 15113 (SN0001; [link](#));
- Sponsor's clinical study report # 15113 (SN0001; [link](#));
- Sponsor's statistical analysis plan # 15113 (SN0001; [link](#));
- Sponsor's proposed product label (SN0001; [link](#)); and
- Highlights of clinical pharmacology and cardiac safety (SN0001; [link](#)).

1 SUMMARY

No significant QTc prolongation effect of finerenone was detected in this QT assessment.

The effect of finerenone was evaluated in the thorough QT study (Study # 15113). This was a Phase-1, randomized, double-blinded, double-dummy, placebo- and positive-controlled, 4-way crossover study. The highest dose that was evaluated was 80 mg as a single dose, which covers the worst case exposure scenario (CYP3A inhibition, Section 3.1). Assay sensitivity was established using moxifloxacin. The data were analyzed using by-time analysis as the primary analysis, which did not suggest that finerenone is associated with significant QTcF prolonging effect (refer to Section 4.3) – see Table 1 for overall results.

The findings of this analysis are further supported by the available nonclinical data (Section 3.1.2) and exposure-response analysis (Section 4.5) and categorical analysis (Section 4.4).

Table 1: The Point Estimates and the 90% CIs (FDA Analysis)

ECG Parameter	Treatment	Time (hours)	$\Delta\Delta\text{QTcF}$ (msec)	90% CI (msec)
QTc	Finerenone 20 mg IR	6.0	1.3	(-0.7 to 3.2)
QTc	Finerenone 80 mg IR	0.8	1.7	(-0.6 to 4.1)

For further details on the FDA analysis, please see Section 4.

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

Not applicable.

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

Not applicable.

2.2 PROPOSED LABEL

Below are proposed edits to the label submitted to SDN001 ([link](#)) from the IRT. Our changes are highlighted ([addition](#), [deletion](#)). Please note, that this is a suggestion only and that we defer final labeling decisions to the Division.

<p>12.2 Pharmacodynamics</p> <p><u>Cardiac Electrophysiology</u></p> <p>(b) (4)</p> <p>At a dose 3 times the maximum approved recommended dose, <Tradename> does not prolong the QT interval to any clinically relevant extent.</p> <p><i>We propose to use labeling language for this product consistent with the “Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format” guidance.</i></p>
--

3 SPONSOR’S SUBMISSION

3.1 OVERVIEW

3.1.1 Clinical

Bayer HealthCare Pharmaceuticals Inc. is developing finerenone to (b) (4) (b) (4) reduce the risk of (b) (4) cardiovascular (b) (4) death, non-fatal myocardial infarction (b) (4) and hospitalization for heart failure in adult patients with chronic kidney disease and type 2 diabetes. Finerenone (MW: 378.43 g/mol) is an antagonist (nonsteroidal) of the

mineralocorticoid receptor that attenuates inflammation and fibrosis mediated by mineralocorticoid receptor overactivation.

The product (Kerendia) is formulated as immediate-release tablet formulation containing 10 and 20 mg finerenone (b) (4) for oral administration. The proposed starting dose is 20 mg once daily ($\text{eGFR} \geq 60 \text{ mL/min/1.73m}^2$) or 10 mg once daily ($\text{eGFR} \geq 25$ to $< 60 \text{ mL/min/1.73m}^2$) which is determined after measuring eGFR. The maximum proposed (targeted) therapeutic dose is 20 mg once daily (titrated based on serum potassium levels). The peak concentrations of $\sim 160 \text{ ng/mL}$ (T_{max} : 0.5 to 1.25 h; half-life: ~ 2 to 3 h) are expected at steady-state with the anticipated therapeutic dose (POP-PK). No significant accumulation is expected at steady state with the proposed maximum therapeutic dose ($C_{\text{max Racc}}$: ~ 0.9 to 1.48). The maximum tolerated dose is not established, and the maximum studied dose is 80 mg as a single dose (C_{max} 597 to 657 $\mu\text{g/L}$; healthy subjects, Study # 13784) and 40 mg once daily for 10 days (C_{max} : 259 to 519 $\mu\text{g/L}$).

The human mass balance study indicates that $\sim 80\%$ (0.825% unchanged) of the drug is excreted in urine, and $\sim 21\%$ (0.184% unchanged) in feces (Study # 14502). The studies indicate that finerenone is extensively metabolized (mainly by CYP3A4) forming 4 major (M-1a; M-1b, naphthyridine; M-2a, hydroxy naphthyridine; and M-3a, carboxy naphthyridine) metabolites. Concomitant administration of finerenone with erythromycin resulted in increased exposures of finerenone (C_{max} : $\sim 88\%$; Study # 14504). Similarly, concomitant administration of finerenone with verapamil resulted in increased exposures of finerenone (C_{max} : $\sim 122\%$; Study # 16910). The sponsor proposed contraindication for concomitant administration of finerenone with strong CYP3A4 inhibitors. In addition, the product is not recommended in patients with $\text{eGFR} < 25 \text{ mL/min/1.73 m}^2$ or severe hepatic impairment.

The sponsor conducted thorough QT study to characterize the QT effects of finerenone using by-time as a primary analysis (Study # 15113). This was a single-center, randomized, double-blinded, double-dummy, placebo- and positive- (moxifloxacin) controlled, 4-way crossover study evaluating the effect of single doses (20 mg as a therapeutic dose and 80 mg as a supratherapeutic dose) of finerenone on the QTc interval in healthy subjects. The peak concentration (C_{max} : $\sim 597 \text{ ng/mL}$) observed with highest dose studied (i.e., 80 mg single dose) is expected to offer only ~ 3.7 -fold margin over the therapeutic exposures (C_{max} : $\sim 160 \text{ ng/mL}$) associated with the maximum proposed dose at the steady-state (See Appendix).

3.1.2 Nonclinical Safety Pharmacology Assessments

Refer to the sponsor's highlights of clinical pharmacology and clinical safety and sponsor's non-clinical overview ([m2.4](#)).

Finerenone inhibits the hERG K^+ current in vitro with low potency ($\text{IC}_{20} \sim 22 \mu\text{mol/L}$). This IC_{20} (equivalent to 8.325 mg/L) is 56 and 14-fold higher than the measured C_{max} at 20 mg and 80 mg doses in the tQT study in man. No inhibition of the hERG K^+ current was determined in vitro when the plasma-metabolites of finerenone M-1, M-2, and M-3 were investigated at concentrations higher than their expected C_{max} following a dose of 80 mg finerenone (Study # A53161).

In conscious telemetry device-implanted dogs, single administration of finerenone (1, 3 and 10 mg/kg) did not affect blood pressure and heart rate during a 16 h observation time period (Study # PH-35861). QRS and QT intervals, and QTc values remained unaffected. Atrioventricular conduction was slightly accelerated (PQ interval shortening by 5 to 10%) at ≥ 3 mg/kg (corresponding to finerenone C_{max} 27- and 7-fold higher than measured in man at 20 mg and 80 mg, respectively, in the tQT (Study # 15113).

Finerenone C_{max} values of 1.4, 4, and 13.9 mg/L were determined in satellite animals at these doses. The finerenone C_{max} values are 0.150 and 0.597 mg/L in healthy subjects at 20 mg and 80 mg doses in the tQT study, and 0.160 mg/L in CKD / T2D patients (pop PK analysis in FIDELIO-DKD). Taking these findings together, there were no effects observed on QRS, QT, and QTc in dogs at 93 and 23 fold higher finerenone C_{max} than expected following 20 mg and 80 mg doses administered in healthy subjects, and 87 fold higher C_{max} compared to CKD / T2D patients treated with 20 mg.

3.2 SPONSOR'S RESULTS

3.2.1 By-Time Analysis

Finerenone excluded the 10 msec threshold at both the therapeutic and supratherapeutic dose levels for $\Delta\Delta\text{QTcF}$.

Sponsor also presented by-time analysis for other intervals (HR, PR and QRS). Sponsor used ANCOVA method to analyze the data. Please see Section 5 for details.

Reviewer's comment: FDA reviewer used linear mixed model to analyze the data which incorporates correlations across QTcF at different timepoints. FDA reviewer's analysis results are similar to the sponsor's results. Please see Section 4.3 for details.

3.2.1.1 Assay Sensitivity

Assay sensitivity was established by the moxifloxacin arm.

Reviewer's comment: FDA reviewer's analysis results also show that assay sensitivity was established by the moxifloxacin arm. Please see Sections 3.2.1 and 4.5 for additional details.

3.2.1.1.1 QT Bias Assessment

Not applicable.

3.2.2 Categorical Analysis

There were no significant outliers per the sponsor's analysis for QTc (i.e., > 500 msec or > 60 msec over baseline).

Reviewer's comment: FDA reviewer's analysis results are similar to the sponsor's QTcF results. FDA reviewer could not locate categorical analysis results for PR, HR and QRS. One subject in finerenone 20 mg IR group experienced HR greater than 100 beats/min. Please see Section 4.4 for details.

3.2.3 Exposure-Response Analysis

The sponsor used by-time analysis as primary analysis and did not performed PK/PD analysis to exploring the relationship between concentration of finerenone and QTcF.

Reviewer's comment: Please see Section 4.5 for reviewer's exposure-response analysis.

3.2.4 Safety Analysis

All 60 subjects who received any study medication were included in the safety analysis.

In total, 24 out of 60 subjects (40.0%) had at least one treatment-emergent AE (TEAE): 10 subjects after 20 mg finerenone; 7 subjects after 80 mg finerenone; 11 subjects after placebo and 14 subjects after moxifloxacin. The maximum intensity of the TEAEs was mild in 20 subjects (33.3%) and moderate in 4 subjects (6.7%). 19 subjects had at least one TEAE assessed as being related to study drug. There were no serious adverse events and no deaths. One subject was prematurely discontinued due to a TEAE ((b) (6), Vision blurred).

Reviewer's comment: None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e., unexplained syncope, significant ventricular arrhythmias or sudden cardiac death) occurred in this study.

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis, which is acceptable as no large increases or decreases in heart rate (i.e. $|\text{mean}| < 10$ beats/min) were observed (see Section 4.3.2).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Overall ECG acquisition and interpretation in this study appears acceptable.

4.2.2 QT Bias Assessment

Not Applicable.

4.3 BY-TIME ANALYSIS

The analysis population used for the by-time analysis included all subjects with a baseline and at least one post-dose ECG.

The statistical reviewer used linear mixed model to analyze the drug effect by time for each biomarker (e.g., ΔQTcF , ΔHR) independently. The default model includes treatment, sequence, period, time (as a categorical variable), and treatment-by-time interaction as fixed effects and baseline as a covariate. The default model also includes subject as a random effect and an unstructured covariance matrix to explain the associated between repeated measures within period.

4.3.1 QTc

Figure 1 displays the time profile of $\Delta\Delta\text{QTcF}$ for different treatment groups. The maximum $\Delta\Delta\text{QTcF}$ values by treatment are shown in Table 2.

Figure 1: Mean and 90% CI of $\Delta\Delta\text{QTcF}$ Timecourse (unadjusted CIs).

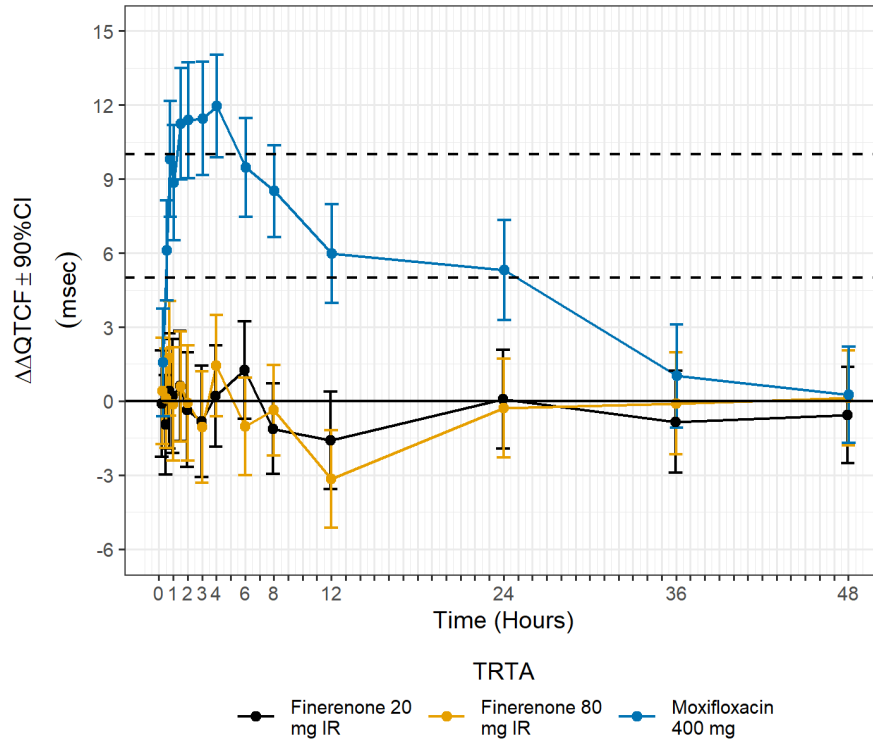


Table 2: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for $\Delta\Delta\text{QTcF}$

Actual Treatment	Nact / Npbo	Time (hours)	$\Delta\Delta\text{QTcF}$ (msec)	90.0% CI (msec)
Finerenone 80 mg IR	59 / 60	0.8	1.7	(-0.6 to 4.1)
Finerenone 20 mg IR	59 / 60	6.0	1.3	(-0.7 to 3.2)

4.3.1.1 Assay sensitivity

Assay sensitivity was assessed using by-time analysis. The statistical reviewer used the same linear mixed model as treatment arms to analyze the moxifloxacin effect by time for each biomarker (e.g., ΔQTcF , ΔHR) independently. The time-course of changes in $\Delta\Delta\text{QTcF}$ is shown in Figure 1 and shows the expected time-profile with a mean effect of > 5 msec after Bonferroni adjustment for 4 time points (Table 3).

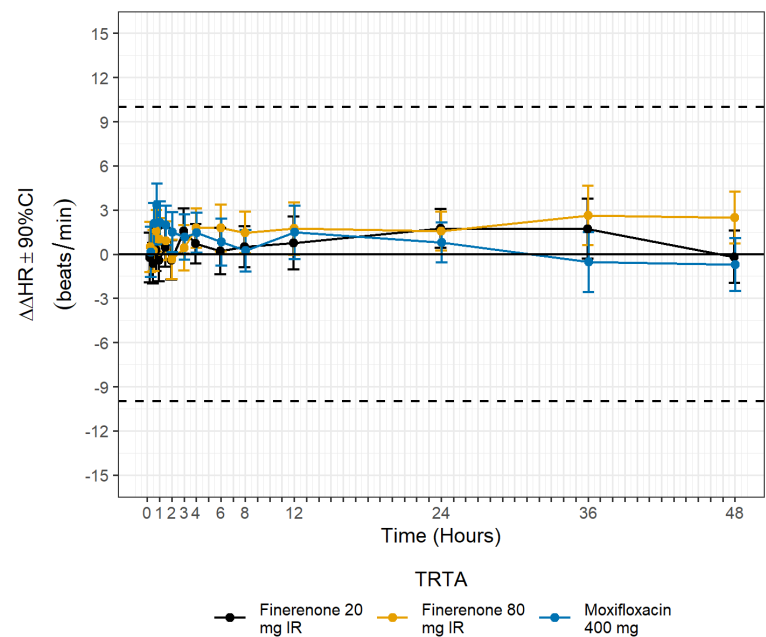
Table 3: The Point Estimates and the 90% CIs Corresponding to the Largest Lower Bounds for $\Delta\Delta\text{QTcF}$

Actual Treatment	Nact / Npbo	Time (hours)	$\Delta\Delta\text{QTcF}$ (msec)	90.0% CI (msec)	97.5% CI (msec)
Moxifloxacin 400 mg	57 / 60	4.0	12.0	(9.9 to 14.0)	(9.1 to 14.8)

4.3.2 HR

Figure 2 displays the time profile of $\Delta\Delta\text{HR}$ for different treatment groups.

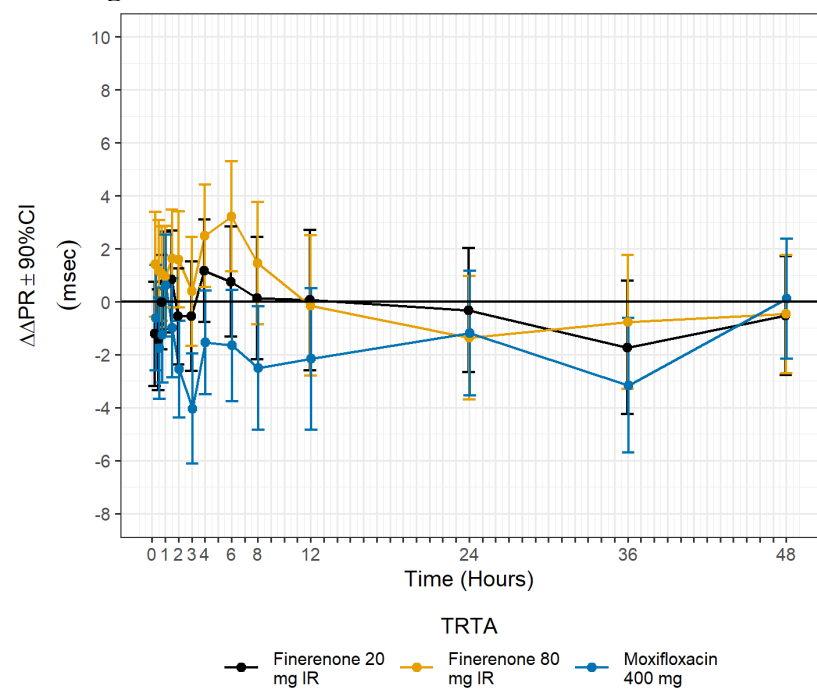
Figure 2: Mean and 90% CI of $\Delta\Delta\text{HR}$ Timecourse



4.3.3 PR

Figure 3 displays the time profile of $\Delta\Delta\text{PR}$ for different treatment groups.

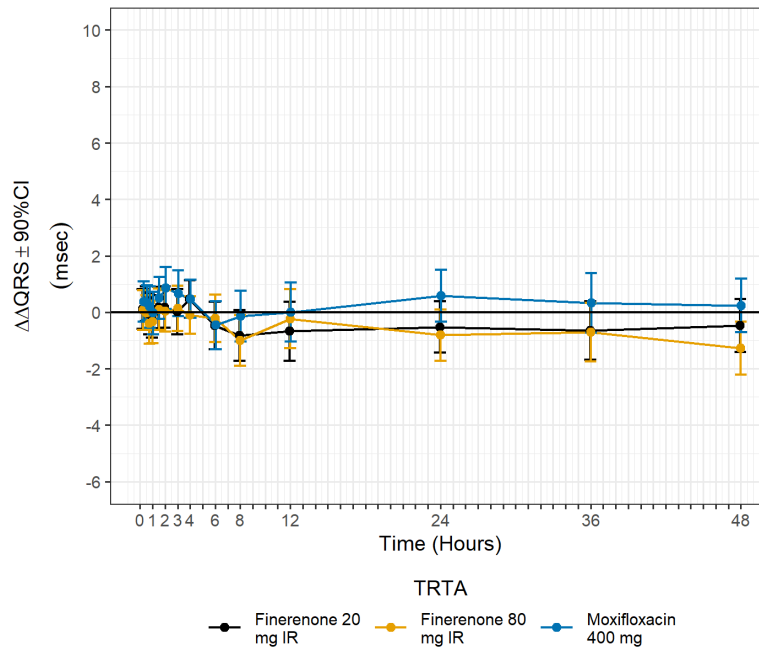
Figure 3: Mean and 90% CI of $\Delta\Delta\text{PR}$ Timecourse



4.3.4 QRS

Figure 4 displays the time profile of $\Delta\Delta$ QRS for different treatment groups.

Figure 4: Mean and 90% CI of $\Delta\Delta$ QRS Timecourse



4.4 CATEGORICAL ANALYSIS

Categorical analysis was performed for different ECG measurements either using absolute values, change from baseline or a combination of both. The analysis was conducted using the safety population and includes both scheduled and unscheduled ECGs.

4.4.1 QTc

None of the subjects experienced QTcF greater than 480 msec and/or none of the subjects experienced Δ QTcF greater than 60 msec in both dose levels of finerenone.

4.4.2 HR

Table 4 lists the categorical analysis results for maximum HR (<100 beats/min and >100 beats/min). One subject experienced HR greater than 100 beats/min in finerenone 20 mg IR dose level.

Table 4: Categorical Analysis for HR (maximum)

Actual Treatment	Total (N)		Value ≤ 100 beats/min		Value > 100 beats/min	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Finerenone 20 mg IR	59	822	58 (98.3%)	821 (99.9%)	1 (1.7%)	1 (0.1%)
Finerenone 80 mg IR	59	826	59 (100.0%)	826 (100.0%)	0 (0%)	0 (0%)
Placebo	60	835	60 (100.0%)	835 (100.0%)	0 (0%)	0 (0%)

4.4.3 PR

None of the subjects experienced PR>220 msec & percentage change from baseline above 25%.

4.4.4 QRS

None of the subjects experienced QRS greater than 120 msec in both dose levels of finerenone.

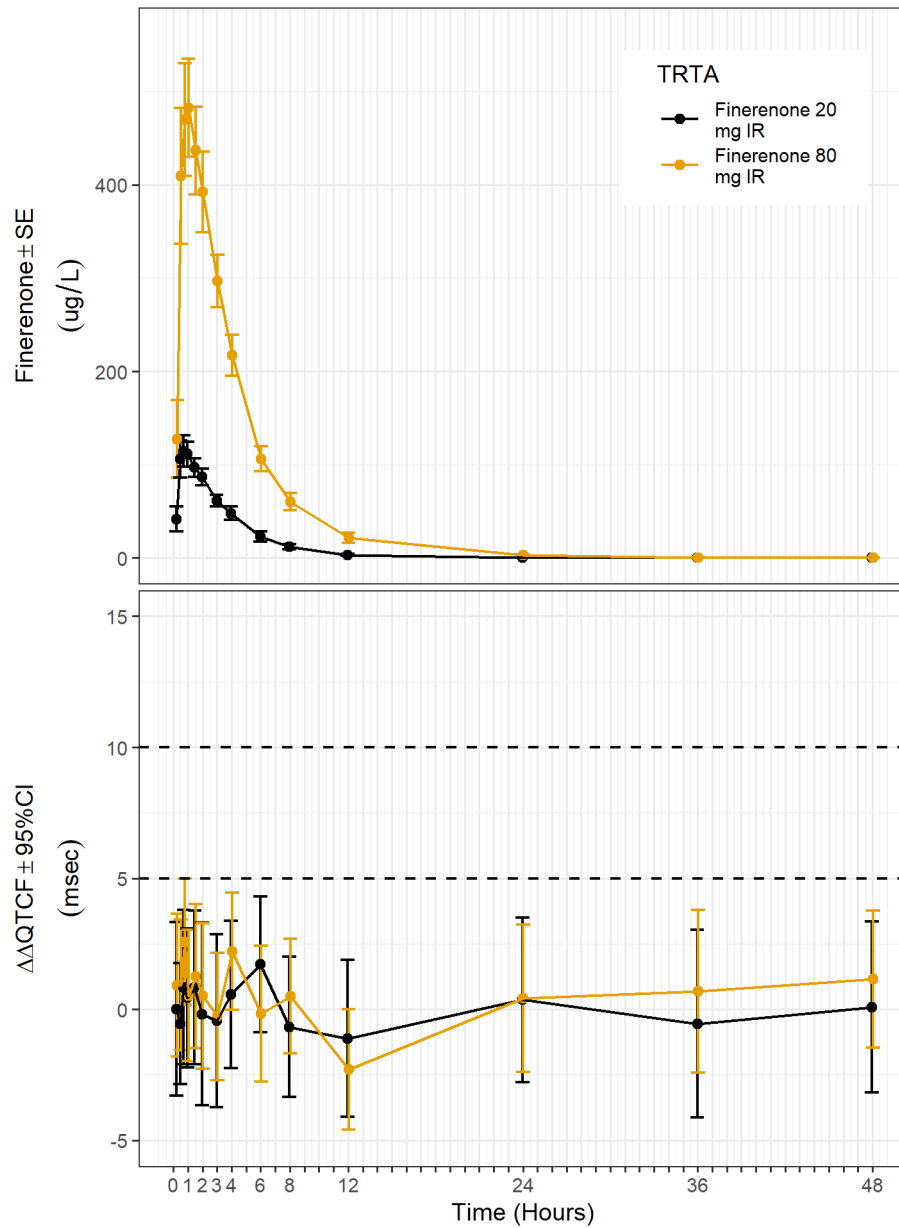
4.5 EXPOSURE-RESPONSE ANALYSIS

The objective of the clinical pharmacology analysis was to assess the relationship between plasma concentration of finerenone (and its M1, M2, and M3 metabolites) and Δ QTcF. Exposure response analysis was conducted using all subjects with baseline and at a least one postbaseline ECG with time-matched PK.

Prior to evaluating the relationship between finerenone (and its metabolites) concentration and QTc using a linear model, the three key assumptions of the model were evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 bpm increase or decrease in mean HR); 2) delay between finerenone concentration and Δ QTc and 3) presence of non-linear relationship.

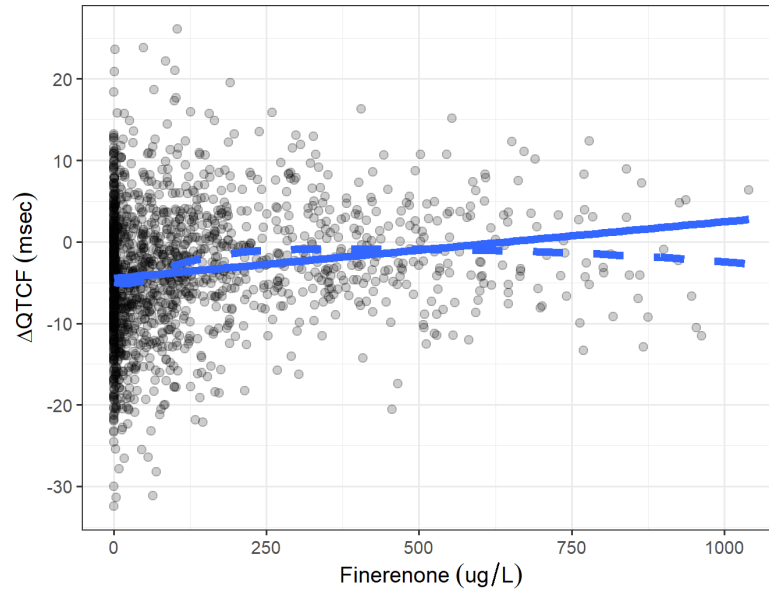
An evaluation of the time-course of finerenone concentration and changes in Δ QTcF is shown in Figure 5. There was no apparent correlation between the time at maximum effect on Δ QTcF and peak concentrations of finerenone indicating no significant hysteresis. Figure 2 shows the time-course of Δ HR, which shows an absence of significant Δ HR changes and the maximum change in heart rate is considerably below 10 bpm (Sections 4.3.2 and 4.4.2).

Figure 5: Time course of finerenone concentration (top) and QTcF (bottom)



After confirming the absence of significant heart rate changes or delayed QTc changes, the relationship between finerenone concentration and ΔQTcF was evaluated to determine if a linear model would be appropriate. Figure 6 shows the relationship between finerenone concentration and ΔQTc and supports the use of a linear model.

Figure 6: Assessment of linearity of concentration-QTcF relationship



Finally, the linear model was applied to the data and the goodness-of-fit plot is shown in Figure 7. Predictions from the concentration-QTc model are provide in Table 5.

Figure 7: Goodness-of-fit plot for QTcF

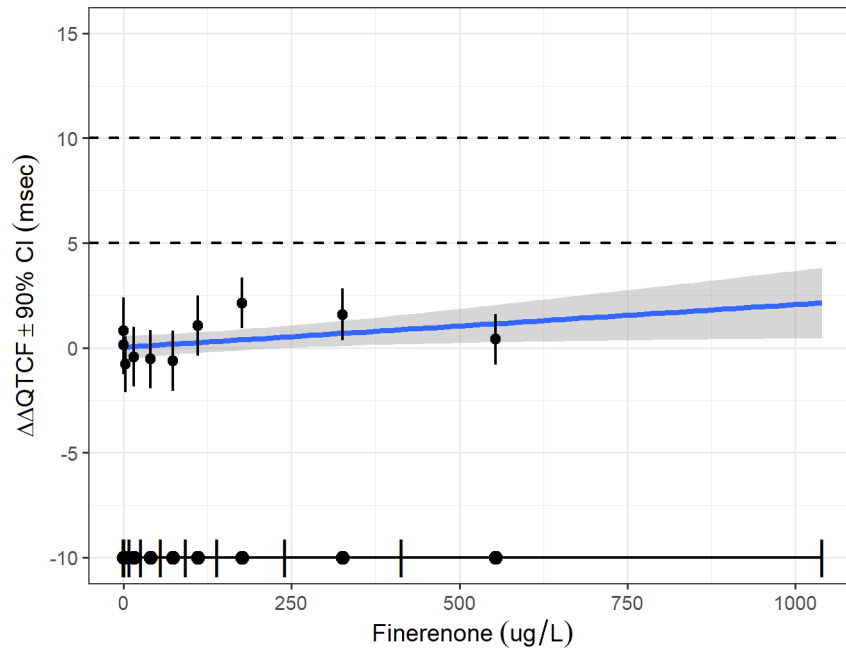


Table 5: Predictions from concentration-QTcF model

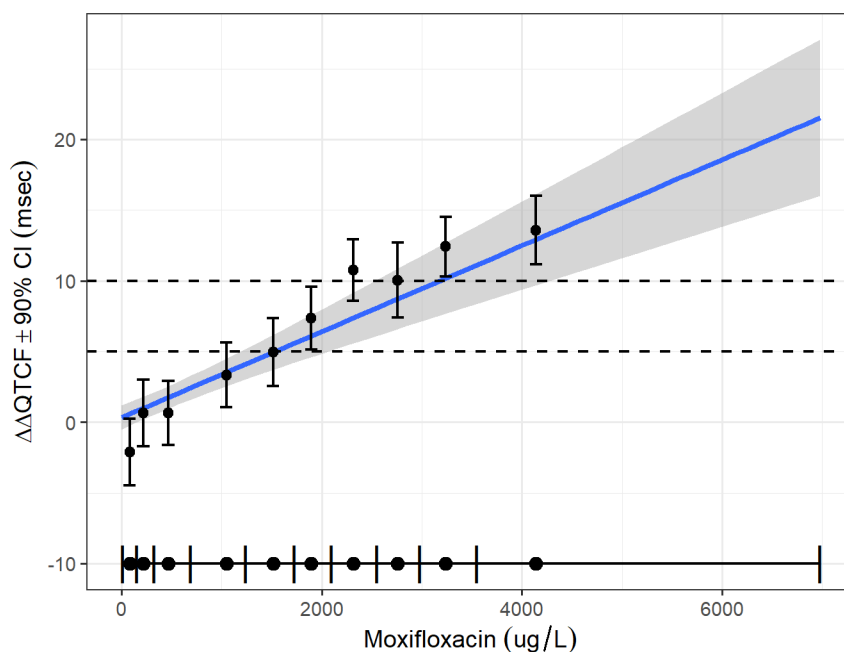
Actual Treatment	Finerenone (ug/L)	$\Delta\Delta\text{QTcF}$ (msec)	90.0% CI (msec)
Finerenone 20 mg IR	150.0	0.3	(-0.2 to 0.8)
Finerenone 80 mg IR	596.9	1.2	(0.3 to 2.2)

4.5.1.1 Assay sensitivity

To demonstrate assay sensitivity, the sponsor included oral moxifloxacin 400 mg as a positive control to detect small increases from baseline for QTcF in this study. Assay sensitivity was primarily established using by time analysis (Section 4.3.1.1).

In addition, the sponsor determined moxifloxacin concentrations in plasma. The PK profile in the moxifloxacin group are generally consistent with the ascending, peak, and descending phases of historical data (*data not shown*). Concentration-response analysis of moxifloxacin data indicated a positive slope in the relationship between ΔQTcF and the plasma concentration of moxifloxacin. The lower limit of the two-sided 90% confidence interval at the observed mean peak concentrations of moxifloxacin is above 5 ms. Therefore, assay sensitivity is established.

Figure 8: Goodness-of-fit plot for $\Delta\Delta\text{QTcF}$ for moxifloxacin



The goodness-of-fit plot for moxifloxacin is shown in Figure 8 and the predicted QTc at the geometric mean Cmax is listed in Table 6.

Table 6: Predictions from concentration-QTcF model for moxifloxacin

Actual Treatment	Moxifloxacin (μg/L)	$\Delta\Delta\text{QTcF}$ (msec)	90.0% CI (msec)
Moxifloxacin 400mg	3,525.3	11.1	(8.3 to 13.8)

5 APPENDIX

5.1 EVALUATION OF CLINICAL QT ASSESSMENT PLAN

1. Product Information								
Generic Name		Finerenone			Brand Name		Kerendia	
Drug class		Non-steroidal Mineralocorticoid Receptor Antagonist						
Combination product		No						
Indication		To (b) (4) reduce the risk of (b) (4) CV (b) (4) death, non-fatal MI (b) (4) and hospitalization for heart failure in adult patients with CKD and T2D						
Therapeutic Dose		Titrated up to 20 mg once daily (See Section 3.1.1)						
Maximum Tolerated Dose		Not established (See Section 3.1.1)						
Dosage Form		Immediate-release tablet formulation			Route of Administration		Oral	
2. Clinical Cardiac Safety								
Refer to the sponsor’s highlights of clinical pharmacology and clinical safety.								
3. QT Studies								
3.1 Primary Studies								
Protocol number / Population	ECG Quality		Arms		Sample size		ECG & PK assessments	
	Assessment	Ok?	Arms	High dose covers?	No subjects	Ok?	Timing	Ok?
Protocol number: 15113/PH-38555	Central read? Yes Blinded? Yes	Yes	Highest dose: 80 mg	Above therapeutic	60	Yes	Baseline: Pre-dose baseline Timing: .2,.5, 75,1,1.5, 2, 3, 4, 6, 8, 12, 24,	Yes

Population: Healthy volunteers	Replicates? Yes		Placebo: Yes				36, and 48 hours.	
Design: Crossover			Positive control: Yes					
<u>Treatments:</u> <ul style="list-style-type: none">• Treatment arm A: 20 mg finerenone (20 mg finerenone [1 tablet], placebo matching finerenone [3 tablets], and placebo matching moxifloxacin [1 tablet])• Treatment arm B: 80 mg finerenone (80 mg finerenone [4 × 20 mg tablets] and placebo matching moxifloxacin [1 tablet])• Treatment arm C: placebo (finerenone placebo [4 tablets] and moxifloxacin placebo [1 tablet])• Treatment arm D: 400 mg moxifloxacin (400 mg moxifloxacin [1 tablet] and finerenone placebo [4 tablets])								
3.1 Secondary Studies								
Not applicable.								
3.3 Data pooling								
Data pooling?							No	
Did sponsor propose an assessment for heterogeneity?							N/A	
Is the data pooling appropriate?							N/A	
4. Analysis plan								
4.1 Study Objective related to QT								
What QTc effect size is the analysis trying to exclude?		10 ms (E14)						
4.2 Dose Justification								
See Section 3.1.1								

The point estimate for AUC in patients with CKD and T2D is about 50% higher compared to healthy subjects, reflecting the effect of renal impairment on AUC. There is no effect on Cmax.	
4.3 QT correction method	
Is an HR increase or decrease greater than 10 bpm?	No
Primary method for QT correction	QTcF
4.4 Assay Sensitivity	
Assay sensitivity methods proposed by sponsor	<input checked="" type="checkbox"/> Moxifloxacin <input type="checkbox"/> Exposure-margin <input type="checkbox"/> QT bias assessment <input type="checkbox"/> Not applicable (objective is large mean effects) <input type="checkbox"/> Other
4.5 By Time Analysis	
4.5.1 Investigational drug	
Primary analysis	Yes
Did the sponsor use IUT or descriptive statistics?	IUT
For IUT: Does the sponsor use MMRM to analyze longitudinal values that considers the correlation across time-points or use ANCOVA by time-point without considering correlation?	ANCOVA
For IUT: Is the MMRM model specified correctly with regards to covariance structure, covariates, etc.?	N/A
<i>The change from baseline of QTcF after treatment with finerenone will be analyzed by an analysis of covariance (ANCOVA) for each time point, including the factors sequence, subject (sequence), period and treatment and the baseline value as covariate. Carryover will not be included in the model, since the washout time is considered to be sufficient to assume no (unequal) carryover. Based on these</i>	

analyses, point estimates (LS-Means) and confirmatory upper one-sided 95% confidence intervals of the difference “active-placebo” will be calculated for each time point for 20 mg and 80 mg finerenone.

The comparison of 20 mg and 80 mg finerenone vs. placebo will be performed as a non-inferiority test. The purpose of this test is to show that finerenone does not prolong the QTc time by more than $\Delta=10$ msec, as recommended in the ICH guideline E14 [1] on the clinical evaluation of QT/QTc interval prolongation. The upper limit of the one-sided 95% confidence interval of the mean difference in treatment effect must be below this threshold for each time point. A hierarchical testing procedure will be applied. First, 20 mg finerenone versus placebo will be tested. The non-inferiority test of 80 mg finerenone versus placebo will only be performed if non-inferiority of 20 mg finerenone versus placebo could be established.

Reviewer’s Comment: The sponsor’s ANCOVA model did not incorporate correlations across QTcFs at different timepoints. FDA reviewer used linear mixed model to analyze the data which incorporates correlations across QTcFs at different timepoints.

4.5.2 Positive control

Primary analysis	Yes
Did the sponsor adjust for multiplicity?	No

The change from baseline of HR, QT, QTcB, QTcF and QTcI after treatment with moxifloxacin will be analyzed by an ANCOVA for each time point, including the factors sequence, subject (sequence), period and treatment and the baseline value as covariate. These ANCOVAs will be restricted to the time points from 1 hour to 6 hours after administration according to Darpo [2]. Carryover will not be included in the model, since the washout time is considered to be sufficient to assume no (unequal) carryover. Based on these analyses, point estimates (LS-Means) and exploratory lower one-sided 95% confidence intervals of the difference “moxifloxacin-placebo” will be calculated for each time point.

Assay sensitivity based on the moxifloxacin response will be established, if the lower limit of the one-sided 95% confidence interval for QTcF exceeds 5 msec for at least one time point.

4.6 Concentration-QTc analysis

4.6.1 Investigational drug

5.Primary analysis	No
What is the dependent variable in the sponsor’s model?	Unknown
White paper model?	Unknown
Which concentration covariate(s) are included in the model?	Unknown

Did the sponsor propose an assessment of delayed effects?	Unknown
Did the sponsor propose an assessment of linearity?	Unknown
Did the sponsor propose model selection criteria?	Unknown
What methods did the sponsor use for predicting the QT effect?	<input type="checkbox"/> Model-based confidence intervals <input type="checkbox"/> Bootstrap-derived confidence intervals
4.6.2 Positive control	
Primary analysis	No
Same model as investigational drug	N/A
4.7 Categorical analysis	
QTc?	Yes
Δ QTc?	Yes
PR?	Unknown
QRS?	Unknown
HR?	Unknown
T-wave morphology?	Unknown

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/s/

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