Observational Study/Post Authorization Safety Study (PASS) Information

Acronym/Title	FINE-REAL: A non-interventional study providing insights into the use of finerenone in a routine clinical setting
Protocol version and date	V 3.0 28 OCT 2022
IMPACT study number	21785
Study type / Study phase	Observational, post-approval ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS46493
NCT number	NCT05348733
Active substance	Finerenone (BAY-94-8862) Non-steroidal mineralocorticoid receptor (MR) antagonist ATC code: C03DA05
Medicinal product	Kerendia® Firialta®
Product reference	EU/1/21/1616
Procedure number	EMEA/H/C/005200/0000
US NDA number	NDA 215341 (tablet; oral)
Study Initiator and Funder	Bayer, AG

Downloaded by PPD on 07 Nov 2022

Research question and objectives	The aim of this study is to provide insights on characteristics and treatment patterns of participants with CKD and T2D treated with finerenone in routine clinical practice. The primary objective in this study is to describe clinical characteristics of and treatment patterns in participants with CKD and T2D treated with finerenone in routine clinical practice. The secondary objectives of this study are to evaluate the following in a real-world setting: • Overall reported safety of finerenone in treated participants • Hyperkalemia Further objectives in this study are to assess the following in a real-world setting: • Healthcare resource use • Diabetic retinopathy The explorative objectives of this study are: • to identify baseline risk factors associated with adverse events • Collect voluntary blood and urine samples to establish a biobank for future analysis e.g. of changes in levels of selected circulating biochemical and urinary proteins or nucleic acid, from baseline (prior to first use of study drug) and at follow-up visits (only applicable to participants in the US)* * Further details can be found in the corresponding stand-alone document (lab manual).
Country(-ies) /regions of study	USA, Canada, Mexico, Brazil, Colombia, France, Germany, Spain, Italy, Belgium, Denmark, China Mainland, Singapore, Taiwan, The Netherlands, Switzerland, Luxembourg, Saudi Arabia, Chile, Slovenia, Thailand, South Korea
Author	PPD

Marketing authorization holder

Marketing authorization holder(s)	Bayer AG

Downloaded by PPD on 07 Nov 2022

MAH contact person	PPD

The study will be conducted in compliance with the protocol
and any applicable regulatory requirements.

Throughout this document, symbols indicating proprietary names (®, TM) may not be displayed. Hence, the appearance of product names without these symbols does not imply that these names are not protected.

Downloaded by PPD on 07 Nov 2022

1. Table of contents

Downloaded by PPD on 07 Nov 2022

Downloaded by PPD on 07 Nov 2022

2. List of abbreviations

ACEi	Angiotensin Converting Enzyme Inhibitor
AE	Adverse Event
AR	Adverse Reaction
ARB	Angiotensin II Receptor Blocker
ARNI	Angiotensin Receptor-Neprilysin Inhibitor
CFR	Code of Federal Regulations
CRF	Case Report Form
CRO	Contract Research Organization
CV	Cardiovascular
CKD	Chronic Kidney Disease
CVD	Cardiovascular Disease
DMP	Data Management Plan
DOAC	Direct Oral Anticoagulant
DPP-4i	Dipeptidyl Peptidase 4 Inhibitors
EC	European Commission
EDC	Electronic Data Capture
EMA	European Medicines Agency
ENCePP	European Network of Centers in Pharmacoepidemiology and Pharmacovigilance
ESKD	End Stage Kidney Disease
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP1-RA	Glucagon-like Peptide-1 Receptor Agonist
GPP	Good Publication Practice
GVP	Good Pharmacovigilance Practice
ICH	International Conference of Harmonization
HCRU	Healthcare Resource Utilization
HEOR	Health Economics and Outcomes Research
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LMWH	Low Molecular Weight Heparin
MACE	Major Adverse Cardiac Event
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MFDS	Korean Ministry of Food and Drug Safety
MRA	Mineralocorticoid receptor antagonists
MRP	Medical Review Plan
N/A	Not Applicable
NSAID	Non-Steroidal Anti-Inflammatory Drug

Downloaded by PPD on 07 Nov 2022

OS	Observational Study
PAC	Post approval commitment
PAS	Post-Authorization Study
PASS	Post-Authorization Safety Study
PSUR	Periodic Safety Update Report
PV	Pharmacovigilance
Q1	First quartile
Q3	Third quartile
QPPV	Qualified Person Responsible For Pharmacovigilance
QRP	Quality Review Plan
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-Cov2	Severe Acute Respiratory Syndrome Coronavirus Type 2
SGLT2i	Sodium-Glucose Cotransporter-2 Inhibitor
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
SU	Sulfonylurea
T2D	Type 2 Diabetes
VKA	Vitamin K Antagonist

Downloaded by PPD on 07 Nov 2022

3. Responsible parties

3.1 Study initiator and funder

Role:	OS conduct responsible
Name:	PPD
E-mail:	PPD
Role:	Qualified Person responsible for Pharmacovigilance (QPPV)
Name:	PPD
Role:	MAH contact person (Regulatory Affairs)
Name:	PPD
Role:	OS Safety Lead
Name:	PPD
Role:	OS Medical Expert
Name:	PPD
Role:	OS Statistician
Name:	PPD
Role:	OS Data Manager
Name:	PPD
Role:	OS Study Epidemiologist
Name:	PPD
Role:	OS Health Economics and Outcomes Research (HEOR) responsible
Name:	PPD
Role:	OS Regulatory Affairs responsible
Name:	PPD

Contact details of the responsible parties at Bayer AG are available upon request. Signatures of the responsible parties are collected in Annex 5: Signature pages.

Downloaded by PPD on 07 Nov 2022

3.2 Collaborators/Committees

Contact details on the coordinating and/or principal investigators, co-investigators and other site personnel for each country and site participating in the study are listed in a stand-alone document (see Annex 1: List of stand-alone documents) which is available upon request.

Information on the Steering Committee Members and the respective Charters are kept as stand-alone documents (see Annex 1: List of stand-alone documents) which are available upon request.

Administrative changes of responsible persons and/or the composition of the committees will be documented by updating the respective lists, but do not require formal protocol amendments.

4. Abstract

Acronym/Title	FINE-REAL: A non-interventional study providing insights into the use of finerenone in a routine clinical setting
Protocol version and date	V 3.0 28 OCT 2022
IMPACT study number	21785
Study type / Study phase	Observational, post-approval ☒ PASS Joint PASS: ☐ YES ☒ NO
Author	PPD
Rationale and background	Chronic kidney disease (CKD) is a rapidly growing public health burden with high global prevalence. CKD is associated with high healthcare costs, poor quality of life, adverse health outcomes including hospitalization, cognitive decline, cardiovascular disease (CVD), end-stage kidney disease (ESKD), and mortality. Type 2 diabetes (T2D) is the leading cause of ESKD in most parts of the world. For almost three decades now, the treatment strategy for reducing the rate of kidney disease progression has included optimization of blood pressure control, lipid control and glycemic controls. For several years, treatment guidelines have been recommending that patients with T2D and CKD (and albuminuria > 300 mg/day) are to be treated with angiotensin-converting enzyme inhibitors (ACEi) or angiotensin-receptor blockers (ARBs). However, despite the use of ACEi, ARBs and sodium-glucose cotransporter-2 (SGLT2) inhibitors, ESKD rate remain considerably high. The substance class of Mineralocorticoid receptor antagonists (MRAs) such as spironolactone have demonstrated reno-protective effects, through reduction of albuminuria and blood

Downloaded by PPD on 07 Nov 2022

	pressure in kidney disease. However, Spironolactone and Eplerenone MRAs are still not widely used. An important reason for that is likely to be hyperkalemia, an adverse event commonly associated with MRA use. Bayer has developed finerenone, a novel, non-steroidal, selective mineralocorticoid- receptor antagonist. The finerenone development program includes the recently reported FIDELIO and FIGARO-DKD trials. Results of the Phase III, randomized, double-blind, placebo-controlled, multicenter FIDELIO-DKD study showed that finerenone significantly reduced incidence of the primary composite outcome of kidney failure, a sustained decrease of at least 40 % in the eGFR from baseline, or death from kidney-related causes, compared to placebo (HR, 0.82; 95 % confidence interval [CI], 0.73 to 0.93; P=0.001) . Furthermore, finerenone significantly reduced risk of a key secondary outcome event (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure), compared with placebo (HR, 0.86; 95 % CI, 0.75 to 0.99; P=0.03). Within the randomized, double-blind, multicenter phase III FIGARO-DKD trial, finerenone treatment in participants with T2D and stage 2 to 4 CKD with moderately elevated albuminuria or stage 1 or 2 CKD with severely elevated albuminuria led to a significant reduction in the incidence of cardiovascular events, defined as a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure, as compared with placebo (HR, 0.87; 95 % CI, 0.76 to 0.98; P=0.03). In both studies, the overall frequency of adverse events was similar between the finerenone and placebo treatment. However, hyperkalemia-related adverse events were twice as frequent with finerenone as with placebo. Based on the results of these studies, first marketing authorization for finerenone was granted by the US Food and Drug Administration (FDA) in July 2021 for the treatment of adults with chronic kidney disease (CKD) associated with type 2 diabetes mellitus. The study will be initiated after the local approval at participating countries. All safety and efficacy data available at the time of study initiation were gathered from controlled clinical trials and real-world experience from clinical routine is missing.

Downloaded by PPD on 07 Nov 2022

Research question and objectives	The aim of this study is to provide insights on characteristics and treatment patterns of participant with CKD and T2D treated with finerenone in routine clinical practice. The primary objective in this study is to describe clinical characteristics of and treatment patterns in participants with CKD and T2D treated with finerenone in routine clinical practice. The secondary objectives in this study are to evaluate the following in a real-world setting: • Overall reported safety of finerenone in treated participants • Hyperkalemia Further objective in this study is to assess the following in a real-world setting: • Healthcare resource use • Diabetic retinopathy The explorative objectives of this study are: • to identify baseline risk factors associated with adverse events • to collect voluntary blood and urine samples to establish a biobank for future analysis e.g. of changes in levels of selected circulating biochemical and urinary proteins or nucleic acid, from baseline (prior to first use of study drug) and at follow-up visits (only applicable to participants in the US)* * Further details can be found in the corresponding stand-alone document (lab manual).
Study design	This international study is a prospective, non-interventional multicenter, single arm study of participant with a diagnosis of CKD associated with T2D who are newly prescribed finerenone under routine treatment conditions. It is planned to enroll ~5,500 participants with a diagnosis of CKD and T2D for whom the decision was taken by the treating physician to initiate treatment with finerenone. Participants will be observed for a maximum period of 12 months after start of finerenone if treatment is still ongoing, or until 30 days after permanent discontinuation of finerenone, or until death, or withdrawal of consent, or loss-to-follow-up, whichever occurs first.

Downloaded by PPD on 07 Nov 2022

Population	Female and/or male adult participants with a diagnosis of CKD and T2D will be enrolled after the decision for treatment with finerenone has been made by the treating physician. Participants who have been prescribed finerenone in accordance with existing label and whose finerenone treatment has been started up to 8 weeks before or after the ICF is signed will be eligible for enrollment. Contraindications according to the local market authorization should be carefully considered.
Variables	The variable for primary endpoint are: • Clinical characteristics of underlying disease (CKD, T2D): o History and diagnosis of CKD o History and diagnosis of T2D o Hypertension o History of ischemic cardiovascular events o Chronic heart failure o Atrial fibrillation o Diabetic retinopathy • Reasons for introducing finerenone • Reasons for discontinuation of finerenone • Planned and actual duration of treatment with finerenone • Dose and frequency of finerenone treatment • Type, and duration of concomitant secondary therapies The variables for secondary endpoints are: • Occurrence of AEs/SAEs • Occurrence of hyperkalemia o Occurrence of hyperkalemia leading to permanent study drug discontinuation o Occurrence of hyperkalemia leading to dialysis o Occurrence of hyperkalemia leading to hospitalization The variables for further endpoint are:

Downloaded by PPD on 07 Nov 2022

	• Reasons, frequency and duration of in-patient [1], out-patient and emergency department visits • Occurrence of newly diagnosed diabetic retinopathy or progression of existing disease at treatment initiation
Data sources	The investigator or a delegate collects historic data (demographic and clinical characteristics) from medical records, or else by interviewing the participant. Likewise, the investigator or a delegate collects treatment related data during visits that take place in routine practice.
Study size	In total, ~5,500 participants are planned to be enrolled. The study is not aimed to confirm or reject pre-defined hypotheses. Therefore, the sample size was determined due to feasibility reasons.
Data analysis	Statistical analyses will be of explorative and descriptive nature. The study is not intended to test pre-defined statistical hypotheses. All variables will be analyzed descriptively with appropriate statistical methods: categorical variables by frequency tables (absolute and relative frequencies) and continuous variables by summary statistics (i.e. mean, standard deviation, minimum, median, quartiles and maximum). All analyses will be performed for the total study population (overall population) and separately for each participating country if participant numbers are sufficient and if required for local reasons. Whenever reasonable, data will be stratified by subgroups (e.g. age, sex, baseline characteristics). Interim analysis will consist of demographic and baseline data of participants enrolled as well as available safety data. Further details will be given in the statistical analysis plan (SAP). All statistical details including calculated variables and proposed format and content of tables will be detailed in the Statistical Analysis Plan (SAP).
Milestones	First Patient First Visit (FPFV) 13-Jun-2022 (actual) Last Patient First Visit (LPFV) 01-Sep-2026 Last Patient Last Visit (LPLV) 01-Sep-2027 Clean Database (CDB) 01-Jan-2028

[1] In-patient visits are defined as ≥1 overnight stay

Downloaded by PPD on 07 Nov 2022

	Study Report 01-Jun-2028

5. Amendments

Amendment Number	Reason for Amendment	New version number	Effective Date
Amendment 1	Change of responsibilities, Update of inclusion/exclusion criteria to assure on-label use, Quality review process has been updated to accommodate for the latest requirements, Update on variables collected as well as clarification added regarding AE/SAE collection	v 2.0	15 AUG 2022
Amendment 2	Update of coutry list (South Korea added due to request by South Korean health authority to conduct a local study; Change from Argentina to Chile for administrative reasons), Increase in study population because of addition of the South Korean sample, Adaption of Milestones, Adaption of inclusion criteria to mitigate the risk of underreporting of AE during the time between start of finerenone and ICF, Technical adaption regarding AE definitions required due to incorporation of South Korea, Addition of exloratory objective to identify baseline risk factors associated with adverse events	V 3.0	28 OCT 2022

6. Milestones

Table 1 presents planned milestones for the project. These milestones are based on a timely review and approval of the project. Administrative changes to milestones due to delays in study preparation and enrolment do not require amendments to the protocol. Revised study timelines and milestones which do not constitute a need for a formal protocol amendment are kept as stand-alone document (Annex 1: List of stand-alone documents) that is available upon request.

Table 1: Milestones

Milestone	Planned or actual date
Start of data collection (FPFV) - actual	13-Jun-2022
Interim analyses*	
Interim analysis> FPFV+1 year	13-Jun-2023
Interim analysis> FPFV+2 years	13-Jun-2024

Downloaded by PPD on 07 Nov 2022

Interim analysis> FPFV+3 year	13-Jun-2025
Last Patient First Visit (LPFV)	01-Sep-2026
Last Patient Last Visit (LPLV)	01-Sep-2027
End of data collection	01-Sep-2027
Clean Database (CDB)**	01-Jan-2028
Final report of study results	01-Jun-2028

* In line with the requirements of the MFDS, (bi-) annual reports for the South Korean cohort will be submitted to MFDS with the following submission timelines: Jan-2023, Jul-2023, Jan-2024, Jul-2024, Jul-2025, Jul-2026, Jul-2027, Aug 2028.

** Please note that CDB for the global cohort (excluding South Korea) is planned to be reached earlier (15-Mar-2026). Follwowing this date, a study report will be written displaying clean and final data for the global cohort (excluding South Korea). For participants recruited by South Korean sites, unclean data will be provided in a table, listings, and figure (TLF) document, which will be added to the report as stand-alone document.

7. Rationale and background

Chronic kidney disease (CKD) is a rapidly growing public health burden with high global prevalence [1]. CKD is associated with high healthcare costs, poor quality of life, adverse health outcomes including hospitalization, cognitive decline, cardiovascular disease (CVD), end-stage kidney disease (ESKD) (requiring kidney replacement therapy (also known as renal replacement therapy- RRT)) and mortality [2].
Type 2 diabetes (T2D) is the leading cause of ESKD in most parts of the world, and worldwide cases of RRT are increasing substantially and are projected to more than double by the year 2030 [3].

For almost three decades now, the treatment strategy for reducing the rate of kidney disease progression has included optimization of blood pressure control, lipid control and glycemic controls [4]. For several years, treatment guidelines have been recommending that T2D patients with CKD (and albuminuria > 300 mg/day) are to be treated with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin-receptor blockers (ARBs) [5] [6]. However, despite the use of ACEi, ARBs and sodium-glucose cotransporter-2 (SGLT2) inhibitors, ESKD rate remain considerably high [7].

Recently, the results for SGLT2 inhibitors have emerged in this treatment space for patients with T2D with albuminuria and an estimated glomerular filtration rate (eGFR) > 30 mL/min/1.73 m^2. SGLT2 inhibitors were shown to reduce cardiovascular (CV) events, with increasing evidence that they may reduce rate of kidney disease progression [7] [8] [9]. Despite increasing evidence, SGLT2 inhibitors have not yet become standard treatment in these patients.
A different class of molecules known as the Mineralocorticoid receptor antagonists (MRAs) such as spironolactone have demonstrated reno-protective effects, through reduction of albuminuria and blood pressure in kidney disease. However, Spironolactone and Eplerenone MRAs are still not

Downloaded by PPD on 07 Nov 2022

widely used. An important reason for that is likely to be hyperkalemia, an adverse event commonly associated with MRAs use [4].
Bayer has developed finerenone, a novel, non-steroidal, selective mineralocorticoid- receptor antagonist.

The finerenone development program includes the recently reported FIDELIO and FIGARO-DKD trials [5] [10].

Within the randomized, double-blind, placebo-controlled, multicenter phase III FIDELIO-DKD study, 5,734 participants with CKD and T2D were randomized 1:1 to receive finerenone or placebo. For analysis, 5,674 participants were available, n= 2,833 participants in the finerenone and n=2,841 in the placebo arm. The results showed that finerenone significantly reduced incidence of the primary composite outcome of kidney failure, a sustained decrease of at least 40 % in the eGFR from baseline, or death from kidney-related causes, compared to placebo (HR, 0.82; 95 % confidence interval [CI], 0.73 to 0.93; P=0.001) . Furthermore, finerenone significantly reduced risk of a key secondary outcome event (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure), compared with placebo (HR, 0.86; 95 % CI, 0.75 to 0.99; P=0.03).
In general, adverse events incidence during the treatment period was similar in the finerenone and placebo groups. Hyperkalemia-related adverse events were twice as frequent with finerenone as with placebo (18.3 % and 9.0 %, respectively), and the frequency of hyperkalemia leading to discontinuation of the trial regimen was also higher with finerenone (2.3 % and 0.9 %, respectively). No fatal hyperkalemia adverse events were reported [5].

Within the randomized, double-blind, multicenter phase III trial FIGARO-DKD trial, 7,437 participants with CKD and T2D were randomized 1:1 to receive finerenone or placebo. Of those, 7,352 participants were available for analysis (n= 3,686 participants in the finerenone and n= 3,666 participants in the placebo arm). Among participants with T2D and stage 2 to 4 CKD with moderately elevated albuminuria or stage 1 or 2 CKD with severely elevated albuminuria, finerenone therapy led to a significant reduction in the incidence of cardiovascular events, defined as a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure, as compared with placebo (HR, 0.87; 95 % CI, 0.76 to 0.98; P=0.03). The overall frequency of adverse events did not differ substantially between groups. Cases of hyperkalemia occurred more frequently with finerenone than with placebo (10.8 % vs. 5.3 %), and more finerenone-treated participants were hospitalized or discontinued the study due to hyperkalemia than placebo-treated participants (0.6 % and 1.2 % vs. 0.1 % and 0.4 %, respectively). However, none of these adverse events resulted in death [10].

Based on these study results, first marketing authorization for finerenone was granted by the US Food and Drug Administration (FDA) in July 2021 for the treatment of adults with CKD associated with T2D. The study will be initiated after the local approval at participating countries. Since all available safety and efficacy data were gathered from controlled clinical trials, real-world experience from clinical routine is missing. The FINE-REAL study aims at collecting real-world data and providing insights into the use of finerenone in routine clinical setting.

Downloaded by PPD on 07 Nov 2022

8. Research questions and objectives

The aim of this study is to provide insights on characteristics and treatment patterns of participants with CKD and T2D treated with finerenone in routine clinical practice.

8.1 Primary objective

The primary objective in this study is to describe clinical characteristics of and treatment patterns in participants with CKD and T2D treated with finerenone in routine clinical practice.

8.2 Secondary objective

The secondary objectives in this study are to evaluate the following in a real-world setting:

- Overall reported safety of finerenone in treated participants
- Hyperkalemia

8.3 Further objectives

Further objective in this study is to assess the following in a real-world setting:

- Healthcare resource use
- Diabetic retinopathy

Exploratory objectives of this study are:

- to identify baseline risk factors associated with adverse events
- to collect voluntary blood and urine samples to establish a biobank for future analysis e.g. of changes in levels of selected circulating biochemical and urinary proteins or nucleic acid, from baseline (prior to first use of study drug) and at follow-up visits. This might be correlated to clinical and demographic details to determine association with disease progression and/or outcomes. Since the exact analyses have not yet been defined, no corresponding endpoints or variables are defined in Sections 9.1.3 and 9.3.3, respectively. A separate stand-alone document describes more details (Central Laboratory Services Manual) (Annex 1: List of stand-alone documents). This exploratory objective applies to participants in the US only.

9. Research methods

9.1 Study design

This international study is a prospective, non-interventional multicenter, single arm study of participants with a diagnosis of CKD associated with T2D who are newly prescribed finerenone under routine treatment conditions. It is planned to enroll ~5,500 participants with a diagnosis of CKD and T2D for whom the decision was taken by the treating physician to initiate treatment with finerenone.
The study will be conducted in the following countries: USA, Canada, Mexico, Brazil, Colombia, France, Germany, Spain, Italy, Belgium, Denmark, China Mainland, Singapore, Taiwan, The

Downloaded by PPD on 07 Nov 2022

Netherlands, Switzerland, Luxembourg, Saudi Arabia, Chile, Slovenia, Thailand, South Korea.For the global cohort, participants will be recruited within a period of approximately 30 months. Recruitment for the South Korean Cohort will last 38 months.
Participants will be followed up for maximum period of 12 months after start of finerenone if treatment is still ongoing, or until 30 days after permanent discontinuation of finerenone, or until death, or withdrawal of consent, or loss-to-follow-up, whichever occurs first.
The end of observation visit will occur up to 12 months after start of finerenone treatment in case that finerenone therapy is ongoing, or about 30 days after end of finerenone treatment if treatment with finerenone is less than 12 months.
In case of a temporary finerenone treatment pause of ≤ 6 months, participants should stay in the study and followed up as planned. Finerenone treatment pauses of > 6 months are considered as permanent treatment discontinuation and end of observation should be documented in such cases (please also refer to section 9.2.5).

9.1.1 Primary endpoint(s)

The primary endpoint is to describe clinical characteristics of and treatment pattern in participants with CKD and T2D treated with finerenone, based on:

- Clinical characteristics of participants with CKD and T2D
- Reasons for introducing finerenone
- Reasons for discontinuation of finerenone
- Planned and actual duration of treatment with finerenone
- Dosing[2] of finerenone
- Use of secondary therapies in participants with CKD and T2D.

9.1.2 Secondary endpoint(s)

The secondary endpoints are:

- Reported AE/SAEs
- Reported hyperkalemia
  - Reported hyperkalemia leading to permanent study drug discontinuation
  - Reported hyperkalemia leading to dialysis
  - Reported hyperkalemia leading to hospitalization

9.1.3 Further Endpoints

Further endpoints are:

- Reported visits with healthcare providers (reasons, frequency and duration)

[2] Dosing means daily dose and frequency of administration.

Downloaded by PPD on 07 Nov 2022

- In-patient[3], out-patient and emergency department visits.

- Reported diabetic retinopathy and its progression if existing at time of treatment initiation

9.2 Setting

9.2.1 Eligibility

Female and/or male adult participants with a diagnosis of CKD and T2D will be enrolled after the decision for treatment with finerenone has been made by the treating physician.

Participants who have been prescribed finerenone in accordance with existing label will be eligible for enrollment. Contraindications according to the local market authorization should be carefully considered.

Evidence of assessment of all eligibility criteria by the physician or a delegate, as well as enrollment of a participant in the study should be documented in the participant medical records.

9.2.1.1 Inclusion criteria

- Adult female or male participant (≥18 years old)
- Diagnosis of CKD associated with T2D based on assessment by physician
- Treatment according to local marketing authorization, finerenone 20 or 10 mg. Treatment should have been started up to 8 weeks before or after the ICF is signed.
- Signed informed consent

9.2.1.2 Exclusion criteria

- Participation in an investigational trial at any time during the course of this study
- Contra-indications according to the local label

9.2.2 Withdrawal

In this observational study, withdrawal from the study is independent of the underlying therapy and will not affect the participant´s medical care. A participant may withdraw from the study at any time without giving a reason. If a participant wants to terminate the study participation, no further data will be collected. In case a participant would like to withdraw the consent given earlier, s/he should inform his/her doctor and the site should document the withdrawal in the (electronic) Case Report Form (CRF) as well as in the participant medical records.

9.2.3 Replacement

Participants who drop out (e.g. withdrawal, lost to follow-up) will not be replaced.

9.2.4 Representativeness

The representativeness of the study population, with regard to the range of characteristics that are reflective of the broader target population, is addressed by the fact that the study will include typical participants, which constitute more heterogeneous populations than those participating in randomized clinical trials (e.g., wide range of age, ethnicity, and comorbidities). In addition, the

[3] In-patient visits are defined as ≥1 overnight stay

Downloaded by PPD on 07 Nov 2022

inclusion of a representative sample of study sites (i.e. health care providers, hospitals, etc.) in terms of geography, practice size, and academic or private practice type is aimed for as a measure to enhance the generalizability of study results.

The participants documented in the study should be selected based only on eligibility according to a minimal set of selection criteria (sections 9.2.1.1 and 9.2.1.2). No further selection should be applied, thus increasing the generalizability of the study results. Physicians or delegates will be asked to sample consecutive participants whenever possible. This consecutive sampling approach is intended to reduce selection bias by the treating physicians or delegates as to whom to enroll in the study, especially with regard to factors that may be associated to the outcome or prognosis of those participants (e.g. demographic characteristics, multiple comorbidities, as well as concomitant medications), thus maintaining the observational character and enhancing the external validity of the study.

The sample of study sites should, ideally, reflect the distribution of treatment settings in each participating country in the background of the specific local health system. Nevertheless, the final sample of study sites will strongly depend on the willingness of investigators to participate in the study.

9.2.5 Visits

The investigator or a delegate documents abaseline visit, follow-up visits and the end of observation/final visit for each participant in the Case Report Form (CRF). Baseline and follow-up visits occur during routine practice, the study protocol does not define exact referral dates for those visits.

Participants will be followed up for a maximum period of 12 months after start of finerenone if treatment is still ongoing, or until 30 days after permanent discontinuation of finerenone, or until death, or withdrawal of consent, or loss-to-follow-up, whichever occurs first.

Please note that during temporary finerenone treatment pauses of ≤ 6 months, the participant should stay in the study. In the context of this study, treatment pauses > 6 months are considered as permanent treatment discontinuation leading to end of observation. For such cases, the date of the first visit after a treatment pause of > 6 months should be considered as date for end of observation.

Premature end of therapy does not automatically imply end of documentation: the participant should be followed up at least 30 days after receiving the last finerenone therapy.

Baseline visit

Once a participant is found eligible for inclusion, the investigator or designated staff will inform the participant about the study. Where applicable, this will include discussing the participant information sheet (PIS) and informed consent form (ICF) and asking the participant to read and – when agreeing to participate – sign the informed consent.

The investigator documents a baseline visit, follow-up visits and the end of observation/final visit for each patient in the electronic case report form (eCRF).
The baseline visit is defined as the first visit by the patient to the study physician after the treatment decision for finerenone in CKD with T2D was made. Reasons for starting finerenone treatment must be based on treatment start day to ensure all outcome-relevant data is captured.

Downloaded by PPD on 07 Nov 2022

Baseline visit can be on the same day of treatment decision if a physical examination is done on the same day, but sites need to consider that treatment decision must happen independently of and before the study enrolment.

Baseline information (considered as data collected no more than 1 month prior to the 1st dose of finerenone) recorded with the status at baseline visit before the first drug administration.

Follow-up visit(s)

Follow-up visits occur during routine practice, the study protocol does not define exact referral dates for those visits. However, the treating physicians are expected to follow-up their according to local label.

During that timeframe, each visit, near this time points performed per routine clinical practice, should be documented.

End of Observation/Final Visit

The end of observation visit should be documented 12 months after start of finerenone treatment in case that finerenone therapy is ongoing, or about 30 days after end of finerenone treatment if treatment with finerenone is less than 12 months, or after death, or withdrawal of informed consent, or loss-to-follow-up, whichever occurs first.

At this final observation point, the participant´s condition and a treatment assessment will be documented, including:

- Date of final data collection
- Date of last dose of finerenone
- Therapy status at end of observation

Primary reason for discontinuation of the observational study (if applicable) should be documented, i.e. participant lost to follow-up, consent withdrawn by participant, investigator decision, pregnancy, lack of efficacy, (Serious) Adverse Event/Adverse Drug Reaction, participant died, permanent treatment discontinuation of finerenone (no administration of finerenone > 6 months) resulting in change of therapy (which therapy and reason for switch), center closed and study terminated by Bayer AG.

Lost to follow-up

A participant will be considered as ‘lost to follow-up’ if no information collected within 12 months since the last data collection time point.

Typical information to be collected at the visits are summarized in Table 2.

Downloaded by PPD on 07 Nov 2022

Table 2: Tabulated overview on data collected according to the clinical routine practice during the study

	Baseline visit	**Follow-up visit(s) (Including end of observation)**
Date/type of visit	X	X
Eligibility/Informed Consent	X	
Demography	X	
Vital signs	X	
Disease history	X	
Co-morbidities (medical history, concomitant diseases)	X	
Concomitant medication	X	X
Exposure/treatment	X	X
Laboratory parameters	X	X
Adverse events	(X)	X*
Hyperkalemia		X
End of Observation		X
Healthcare resource utilization (in-patient/out-patient/emergency **department** visits)	X	X
Diabetic retinopathy assessment	X	X
Sampling of blood and urine samples for biobanking (for participant in the US only)**	X	X

* Adverse events (up to 30 days after the final treatment with Finerenone)

** For details, please refer to the corresponding stand-alone document (lab manual)

9.3 Variables

The investigator or a delegate collects study-relevant data for each participant (as described in section 9.4) and documents it in the Case Report Form (CRF). The CRF used for data collection in this study are kept as stand-alone documents (see Annex 1: List of stand-alone documents) and are available upon request.

9.3.1 Variables to determine the primary endpoint(s)

The variable for primary endpoint are:

- Clinical characteristics of underlying disease (CKD, T2D):

Downloaded by PPD on 07 Nov 2022

- History and diagnosis of CKD
- History and diagnosis of T2D
- Hypertension (resistant or non-resistant)
- History of ischemic cardiovascular events such as:
  - Myocardial infarction
  - Acute coronary syndrome
  - Stroke
  - Percutaneous coronary intervention
  - Coronary artery bypass grafting
  - Peripheral artery disease including but not limited to event such as limb ischemia, claudication, limb ulcers or limb amputation
- Chronic heart failure
- Atrial fibrillation
- Diabetic retinopathy

- Reasons for introducing finerenone
- Reasons for discontinuation of finerenone
- Planned and actual duration of treatment with finerenone
- Dose and frequency of finerenone treatment (planned and actual)
- Type, and duration of concomitant therapies:

  The following types of medication are considered to be relevant:

  - Oral and injectable antidiabetic treatments
    - SGLT2i
    - GLP1-RA
    - DPP-4i
    - SU
    - Metformin
  - Lipid lowering treatment
    - Statins
  - Renin-angiotensin-system (RAS) inhibitors (including ARNI)
    - ACEi
    - ARB
    - ARNI
  - MRA[4]
  - Digoxin

[4] Another MRA should not be given together with finerenone, however we are interested to know if a participant was exposed before the initiation of finerenone.

Downloaded by PPD on 07 Nov 2022

- Betablocker
- Diuretics
  - Loop
  - Thiazides
  - Potassium sparing
- Potassium supplements
- Potassium binders
- Herbal therapy
- Traditional Chinese medicine
- Anti-thrombotic treatment
  - Acetylsalicylic acid
  - Anticoagulants
    - Warfarin or VKA
    - DOAC
    - LMWH
- Vaccination against Sars-Cov2
- NSAID (including over the counter NSAID)

9.3.2 Variables to determine the secondary endpoints

The variables for secondary endpoints are:

- Occurrence of AEs/SAEs
- Occurrence of hyperkalemia
  - Occurrence of hyperkalemia leading to permanent study drug discontinuation
  - Occurrence of hyperkalemia leading to dialysis
  - Occurrence of hyperkalemia leading to hospitalization

9.3.3 Variables to determine the further endpoints

- Reasons, frequency and duration of in-patient[5], out-patient and emergency department visits
- Occurrence of newly diagnosed diabetic retinopathy or progression of existing disease at treatment initiation

9.3.4 Participant characteristics/demography

- Year of birth
- Ethnic group
- Race (black/non-black)[6]

[5] In-patient visits are defined as ≥1 overnight stay

[6] please note: assessment of this variable is essential for calculation of eGFR by CKD-EPI formula according to Levey et al. Ann Intern Med. 2009

Downloaded by PPD on 07 Nov 2022

- Sex
- Smoking habits and alcohol consumption
- Vital signs and physical examination
    - Weight
    - Height
    - Blood pressure

9.3.5 Laboratory measurements

Variables collected at baseline:

- Serum creatinine (last available value)
- eGFR value as determined by investigator and formula used for calculation of eGFR
- Liver function (last available value of AST and ALT)
- Hemoglobin (Hb) (last available value)
- Serum[7] potassium (last available value)
- Serum sodium (last available value)
- HbA1c (last available value)
- Fasting blood glucose (last available value)
- At baseline only: UACR: date and result (value) of the most recent testing
- Result of urine test (last available recording)
    - Presence of blood
    - Presence of other sediments
    - Urinary tract infection

Variables collected at post-baseline visits:

- Serum creatinine[8]
- Serum[9] potassium
- Result of urine test:
    - UACR

[7] Plasma values are also accepted.

[8] Note that eGFR will be calculated by the EDC system.

[9] Plasma values are also accepted.

Downloaded by PPD on 07 Nov 2022

- Presence of blood
- Presence of other sediments
- Urinary tract infection

9.4 Data sources

The investigator or a delegate collects historic data (demographic and clinical characteristics) from medical records, or else by interviewing the participant. Likewise, the investigator or a delegate collects treatment related data during visits that take place in routine practice.

Each participant is identified by a unique central participant identification code, which is only used for study purposes. For the duration of the study and afterwards, only the participant's treating physician or authorized site personnel is able to identify the participant based on his/her identification code.

9.5 Study size

In total, ~5,500 participants are planned to be enrolled. Hereof, 1,500 participants by study sites located in South Korea.

The aim of the study is to describe treatment patterns and to obtain useful estimates with adequate precision for safety outcome endpoints. The study is not aimed to confirm or reject pre-defined hypotheses. Therefore, the sample size was determined due to feasibility reasons.

Treatment patterns will be analyzed by using descriptive statistics, such as frequencies for categorical variables and sample statistics for continuous variables, as described in section 9.7.3 Confidence intervals are not applicable.

For the secondary endpoints incidence proportions, cumulative incidences and incidence rates will be estimated and corresponding two-sided 95% confidence intervals will be provided, as described in sections 9.7.1 and 9.7.4.

With a sample size of 5,500 participants, for potential incidence proportions of 1%, 5%, 10% and 50%, respectively, the following precisions can be expected:

# of participants	Incidence proportion (%)	95% CI of incidence proportion	Width (%) of 95% CI
5,500	1%	(0.8%, 1.3%)	0.5%
	5%	(4.4%, 5.6%)	1.2%
	10%	(9.2%, 10.8%)	1.6%
	50%	(48.7%, 51.3%)	2.6%

The 50% incidence proportion maximizes the precision width, therefore, maximum width with 5,500 participants will not be greater than 2.6%.

In accordance with regulatory requirement by the applicable South Korean authority (Korean Ministry of Food and Drug Safety, MFDS) as described in 'Section 3 of Article 6 on Notification No. 2020 -

Downloaded by PPD on 07 Nov 2022

122, Re-examination Standard of New drug (Amended 14-Dec-2020)', Kerendia® (finerenone) fits into the category of total required target patient number of 1,500 participants in South Korea for re-examination for 6 years according to the regulatory rules relating to new drug formulations. The probability to observe at least 1 event with a true underlying incidence risk of at least 0.3% is equal to 99% in a population of 1,500 participants.

9.6 Data management

A Contract Research Organization (CRO) will be selected and assigned for EDC system development. The CRF will be part of the EDC system which allows documentation of all variables and covariates by all participating sites in a standardized way. Detailed information on data management, including procedures for data collection, retrieval and preparation are given in the Data Management Plan (DMP). DMP and information on the EDC system are available upon request (see Annex 1: List of stand-alone documents).

For information on quality control, refer to section 9.8.

9.7 Data analysis

9.7.1 Statistical considerations

Statistical analyses will be of explorative and descriptive nature. The study is not intended to test pre-defined statistical hypotheses.

All variables will be analyzed descriptively with appropriate statistical methods: categorical variables by frequency tables (absolute and relative frequencies) and continuous variables by descriptive statistics (i.e. mean, standard deviation, minimum, median, quartiles and maximum). Continuous variables will be described by absolute value and as change from baseline per analysis time point, if applicable.

All analyses will be performed for the total study population (overall population) and separately for each participating country if participant numbers are sufficient and/ or if required for local reasons. Whenever reasonable, data will be stratified by subgroups (e.g. age, sex, baseline characteristics).

Additionally, safety analyses for special population (e.g. participants with hepatic impairment) will be performed.

Sample size and disposition information by analysis time point will be displayed in a frequency table.

All therapies documented in the following forms will be coded using the latest version of the World Health Organization Drug Global available at time of database lock.

- Prior and concomitant medication

Any diagnoses/diseases/event terms documented in the following forms will be coded using the latest Medical Dictionary for Regulatory Activities (MedDRA) version:

- Co-morbidities (medical history, concomitant diseases)
- Adverse events
- Procedure

Downloaded by PPD on 07 Nov 2022

As an explorative analysis, a Chi-square test or Fisher´s Exact test will be carried out to identify any association with the overall safety. Variables used in the analysis would include demographic factors, concomitant medications, comorbidities, etc. Also, logistic regression will be used to quantify the effect of the factors on the overall safety (i.e. the occurrence of any adverse event). A list of potential baseline factors can be found in section 9.3. Each factor will be fitted univariately to show its association with overall safety. Further details will be described in the Statistical Analysis Plan (SAP).

All statistical details including calculated variables and proposed format and content of tables will be detailed in the Statistical Analysis Plan (SAP). The SAP will be finalized before data cut for first annual report analysis. The SAP is available upon request (see Annex 1: List of stand-alone documents).

Interim analysis will consist of demographic and baseline data of participant enrolled as well as available safety data. Further details will be given in the statistical analysis plan (SAP).

The final analysis will be performed after end of the study which is the date the analytical dataset is completely available.

9.7.2 Analysis of population characteristics

Demographic and other baseline characteristics, including clinical characteristics of the underlying disease (CKD, T2D), will be described by frequency tables or summary statistics. Other baseline characteristics will include UACR, eGFR, diabetes duration, serum potassium, systolic blood pressure, diastolic blood pressure, HbA1c and CKD stage. Some continuous variables will be categorized and presented in frequency tables in addition to summary statistics. Categories will be defined in the SAP.

The subjects medical history conditions will be displayed by a frequency table.

Subjects with prior and concomitant medication will be presented by frequency tables or summary statistics.

The standard of care for chronic kidney disease (including Beta Blocker, ACEi or ARB, MRA, Any RAS Inhibitor) will be tabulated by participant frequencies.

The mean and median length of follow-up together with the participant-years will be presented for the primary endpoint.

9.7.3 Analysis of primary endpoint(s)

Analysis of the clinical characteristics will be performed as described in section 9.7.2. Descriptive statistics will be used to analyze the following variables assessing the treatment patterns relating to finerenone:

- Reasons for introducing/discontinuing finerenone
- Planned and actual duration of treatment with finerenone
- Dose and frequency of finerenone treatment (planned and actual)
- Actions taken after finerenone introduction (e.g. continue treatment, addition of second therapy, interrupt treatment, discontinue treatment)

Downloaded by PPD on 07 Nov 2022

- Actions taken after finerenone interruption (e.g. restart finerenone alone, introduce concomitant therapy, discontinue finerenone)
- Treatment pathways for concomitant medications after introduction of finerenone,
- Type, dose and duration of prior and concomitant therapies

Frequencies will be provided in summary tables along with graphical summaries such as histograms.

Continuous variables will be summarized in tables with the appropriate measures (mean, median, SD, Q1, Q3).

More details will be provided in the SAP.

9.7.4 Analysis of secondary endpoints

The analysis of the secondary endpoints will be of a descriptive nature. The use of endpoint refers to the secondary endpoints described in section 9.1.2.

In addition to the analyses mentioned in Section 9.7.1, the following metrics will be provided:

- Number and proportion of subjects with endpoint
- Number of occurrences of the endpoint
- Incidence rates of the endpoint per 100 participant-years

In addition, AEs will be classified by MedDRA PT using the latest version of MedDRA. A summary of AEs will be presented by primary System Organ Class (SOC) and Preferred Term (PT). Aggregate frequencies at the SOC level will be presented.

For hyperkalemia frequency tables will be provided and cumulative incidences will be provided in the form of Aalen-Johansen estimates and curves, given adequate data is available.
More details will be provided in the SAP.

9.7.5 Analysis of further endpoints

Reasons, frequency and duration of in-patient, out-patient and emergency room visits will be summarized by descriptive statistics. For diabetic retinopathy, frequency tables describing the severity will be presented for each eye data permitting.

More details will be provided in the SAP.

9.7.6 Analysis of safety data

Besides the analyses of the safety endpoints detailed in sections 9.7.1 and 9.7.4, AEs/SAEs will be summarized based on the total study population (overall population).

The occurrence, duration, treatment, causal relationship to finerenone as assessed by the physician and outcome of AEs and SAEs will be listed.

As required by MFDS, additional analysis for AEs and SAEs will be performed regarding severity for the participants included by sites located in South Korea.

More details will be provided in the SAP.

Downloaded by PPD on 07 Nov 2022

9.8 Quality control

9.8.1 Data quality

Before study start at the sites, all investigators and other involved site personnel will be sufficiently trained on the background and objectives of the study and ethical as well as regulatory obligations. Investigators and site personnel will have the chance to discuss and develop a common understanding of the OS protocol and the CRF. They will be trained on the importance to ensure that all relevant study data entered in the EDC should be retrievable from the participant's medical records.

A CRO will be selected and assigned for EDC system development, quality control, verification of the data collection, data analysis and data transfer to Bayer.

All observations will be recorded in a standardized CRF. After data entry, missing or implausible data will be queried, and the data will be validated. A check for multiple documented participants will be done.

Detailed information on checks for completeness, accuracy, plausibility and validity are given in the Data Management Plan (DMP).

Medical Review of the data will be performed according to the Medical Review Plan (MRP). The purpose of the Medical Review is to verify the data from a medical perspective for plausibility, consistency, and completeness and to identify potential issues that could affect the robustness of the collected study data or the progress of the study. Detailed information on the Medical review will be described in the MRP.

National and international data protection laws as well as regulations on observational studies will be followed. Electronic records used for capturing participant documentation (eCRF) will be validated according to FDA Code of Federal Regulations (CFR) Title 21, Part 11 [11]. 21 CFR 11 regulations describe the criteria to consider electronic records including e-signatures to be reliable and generally equivalent to paper records and handwritten signatures. They mandate access controls to ensure that only authorized individuals can use the system, additionally a computer-generated audit trail has to be in place to record the date and time of any actions to create, modify, or delete electronic records.

DMP, MRP and validation documentation are kept as stand-alone documents (Annex 1: List of stand-alone documents).

9.8.2 Site Monitoring

Site monitoring will follow a risk-based approach and consists of several measures and tasks to be carried out throughout the site's course of the study e.g. regular off-site and on-site monitoring visits well as ad-hoc and for-cause monitoring visits which can happen at any point in time.

Data reviews will be conducted during regular on-site monitoring visits. The purpose is to review the documented data for completeness and plausibility, adherence to the OS protocol and verification with source documents.

Detailed measures for site monitoring will be described in the Site Operations Plan (SiOpsP). The SiOpsP is available upon request (see Annex 1: List of stand-alone documents).

Downloaded by PPD on 07 Nov 2022

9.8.3 Storage of records and archiving

Bayer will ensure that all relevant documents of this study will be stored after the end or discontinuation of the study for at least 25 years or according to local regulations. Any data as well as programs from statistical programming performed to generate results will be stored within the programming system for at least 25 years.

Participating study sites are required to archive and retain study documents for the period stipulated by local regulations, considering possible audits and inspections from Bayer AG and/or local authorities.

9.9 Limitations of the research methods

Because of the non-interventional study design and limitations inherent to observational studies, findings generated from this study are subject to biases, such as selection bias, limitations to availability of historical medical data, and differences in treatment or reporting owing to local guidelines.

Although the study aims to include participants from a variety of geographic regions, there may be local limitations that reduce the representativeness of participants recruited, such as participant's access to recruiting physicians (including differences in participant profile in specialized, recruiting sites vs local general practice), finerenone availability and reimbursement, and decisions relating to local standard of care.

First intake of finerenone preceding the ICF signature could influence reported safety and treatment patterns. The exposure of participants to finerenone before ICF signature will create a bias in such a way that only those who tolerated the drug well enough to reach the ICF signature process would be accounted for. This might lead to an overestimation of participants' compliance with treatment and underestimation of AEs.

9.10 Other aspects

NA

10. Protection of human subjects

10.1 Ethical conduct of the study

This study is an observational study where finerenone is prescribed in the customary manner in accordance with the terms of the marketing authorization. There is no assignment of a participant to a particular therapeutic strategy. The treatment decision falls within current practice and the prescription of the medicines is clearly separated from the decision to include the participant in the study. No additional diagnostic or monitoring process is required for participation or during the study. Epidemiological methods will be used for the analysis of the collected data.

10.2 Regulatory authority approvals/authorizations

The study will be carried out within an approved indication in accordance with guidelines and regulations of EMA, FDA and applicable local laws and regulations (e.g. Regulation (EU) No 520/2012 [12]). Recommendations given by other organizations will be followed as well (e.g. EFPIA [13], ENCePP [14]).

Downloaded by PPD on 07 Nov 2022

In addition, the guidelines on good pharmacovigilance practices (GVP module VI [15]).

10.3 Independent ethics committee (IEC) or institutional review board (IRB)

In all countries where reference to an IEC/IRB is required, documented approval from appropriate IECs/IRBs will be obtained for all participating centers prior to study start. When necessary, an extension, amendment or renewal of the IEC/IRB approval must be obtained and also forwarded to the study initiator and funder . The IEC/IRB must supply to the study initiator and funder, upon request, a list of the IEC/IRB members involved in the vote and a statement to confirm that the IEC/IRB is organized and operates according to applicable laws and regulations.

10.4 Participant information and consent

Before documentation of any data, informed consent is obtained by the participant.

Informed consent forms will be provided for persons who are capable to give their consent. For adult participant not capable to give their consent, the legal representative should give the consent.

If a participant or the legally acceptable representative is unable to read, an impartial witness (independent of Bayer and the investigator) will be present during the entire informed consent discussion. The informed consent form and any other information to be provided to participants, is read and explained to the participant or the participant´s legally acceptable representative. The participant or the participant´s legally acceptable representative have to orally consent to the participant´s participation in the study and, if capable of doing so, have to personally sign and date the informed consent form. Thereafter the witness will personally sign and date the consent form.

In countries where required by law or regulation, the investigator must have the IECs/IRB written approval/favorable opinion of the informed consent form and any other information to be provided to participants prior to the beginning of the observation.

10.5 Participant insurance

In this observational study, data on routine treatment of participants in daily practice are documented and analyzed with the help of epidemiological methods. Treatment including diagnosis and monitoring of therapy follows exclusively routine daily practice. Current medical daily practice is observed, and for the participant no risks beyond regular therapy exist – there is no additional hazard arising from study participation. As no study related risks exist, there is no need to protect the participant additionally by taking out a participant insurance. The general regulations of medical law and the professional indemnity insurance of the investigators and, respectively, the institutions involved provide sufficient protection for both participant and investigator.

No study medication will be provided to participants. Thus, product insurance is covered by the existing product liability.

10.6 Confidentiality

Bayer as well as all investigators ensure adherence to applicable data privacy protection regulation. Data are transferred in encoded form only. The entire documentation made available to Bayer does not contain any data which, on its own account or in conjunction with other freely available data, can be used to re-identify natural persons. The investigators are obligated to ensure that no documents contain such data.

Downloaded by PPD on 07 Nov 2022

All records identifying the subject will be kept confidential and will not be made publicly available. Participant names will not be supplied to Bayer AG. If the participant name appears on any document, it must be obliterated before a copy of the document is supplied to Bayer AG. Study findings stored on a computer will be stored in accordance with local data protection laws.

The investigator will maintain a list to enable participants´ records to be identified in case of queries. In case of a report of a serious adverse event (SAE), the responsible pharmacovigilance person may ask for additional clarification. In that case, the company is not allowed to directly contact the participant. All additional information will be provided by the investigator.

11. Management and reporting of adverse events/adverse reactions

11.1 Definitions

Adverse event (AE): Any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship (association) with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the product, whether or not related to the product.

Adverse Reaction (AR): an adverse reaction is a noxious and unintended response to a medicinal product. This includes adverse reactions which arise from:

- use of a medicinal product within the terms of the marketing authorization
- use outside the terms of the marketing authorization, including off-label use, overdose, misuse
- abuse and medication errors
- occupational exposure

An adverse reaction, in contrast to an adverse event, is characterized by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

Serious adverse event/serious adverse reaction: an adverse event (AE) or adverse reaction (AR) is serious if it:

- results in death,
- is life-threatening
- requires in-patient hospitalization or prolongation of existing hospitalization.

  A hospitalization or prolongation of hospitalization will not be regarded as a serious adverse event (SAE) if at least one of the following exceptions is met:

  - the admission results in a hospital stay of less than 12 hours;
  - the admission is pre-planned (i.e. elective or scheduled surgery arranged prior to the start of the study);
  - the admission is not associated with an AE (e.g. social hospitalization for purpose of respite care).

Downloaded by PPD on 07 Nov 2022

However, it should be noted that invasive treatment during any hospitalization may fulfill the criterion of 'medically important' and as such may be reportable as an SAE dependent on the clinical judgment. In addition, where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedence;

- results in persistent or significant disability or incapacity
- is a congenital anomaly, birth defect or fetal mental impairment
- is medically significant:
    - Medical and scientific judgment should be exercised in deciding whether an AE/AR may be considered serious (due to an important medical event) because it jeopardizes the health of the participant or may require intervention to prevent another serious condition (death, a life-threatening condition, hospitalization or persistent or significant disability).
    - Examples of such events are :
        - invasive treatment during any hospitalization, in an emergency room or at home for allergic bronchospasm
        - blood dyscrasia or convulsions that do not require hospitalization
        - development of any drug dependency or abuse
        - lack of drug effect if the finerenone was used for the treatment of acute life-threatening diseases (apply medical judgment) or reports of any transmission of an infectious agent via a finerenone

11.1.1 Additional definitions only applicable for South Korea

As required by the MFDS, the following definitions are to be reflected by study sites in South Korea

Criteria for causal relationship assessment of AEs:

1. Certain

   The time elapsed between the administration of the drug and the occurrence of the event is plausible and the event can't be explained by other drugs, chemicals or concurrent disease. The patient showed clinically plausible response following withdrawal of the drug, and the event is definitive pharmacologically or phenomenologically following rechallenge with the same drug, if necessary.

2. Probable/likely

   The time elapsed between the administration of the drug and the occurrence of the event is reasonable and the event is unlikely to be attributed to other drugs, chemicals or concurrent disease. The patient showed clinically reasonable response following withdrawal of the drug (no information about rechallenge).

3. Possible

   The time elapsed between the administration of the drug and the occurrence of the event is reasonable but, the event could also be explained by other drugs, chemicals or concurrent disease. And information on drug withdrawal may be lacking or unclear.

Downloaded by PPD on 07 Nov 2022

4. Unlikely

   The event is temporary that makes a relationship improbable with the administration of the drug and other drugs, chemicals or concurrent disease provide plausible explanations.

5. Conditional/unclassified

   More data for proper assessment needed or additional data under examination.

6. Unassessible/unclassifiable

   Cannot be judged because information is insufficient or contradictory and data cannot be supplemented or verified.

7. No

For the combined analysis of the South Korean and global cohorts, the causality assessment definitions applicable to South Korea will be mapped to the causality assessment definitions used in other countries. Further details will be defined in the SAP.

Severity of AEs shall be judged based on the following:

- Mild

  There is a subjective or objective symptom, but it doesn't affect daily life.

  Continuous treatment is doable without changing the dose of target drug.

- Moderate

  There is a symptom that lets a patient feel inconvenience in daily life, which needs the reduction of dose or the treatment due to the AE

- Severe

  There is a symptom that obstructs daily life, which requires suspending the dose of target drug due to strong AE

11.2 Collection

Starting with the first application of finerenone, all non-serious AEs must be documented on the AE Report Form or in the CRF/EDC system and forwarded to the MAH: a) within 7 calendar days of awareness in EU-countries; b) within 30 calendar days of awareness in non-EU countries. All serious AEs (SAE) must be documented and forwarded to the MAH immediately (within one business day of awareness). For each AE, the investigator or a delegate must assess and document the seriousness, duration, relationship to product, action taken and outcome of the event.

If a pregnancy in female participants occurs during the study, although it is not a serious adverse event itself, it should be documented and forwarded to the MAH within the same time limits as a serious adverse event. The result of a pregnancy will be followed-up according to applicable Bayer SOPs. Any data on abnormal findings concerning either the mother or the baby will be collected as adverse events.

The documentation of any AE/SAE ends with the completion of the observation period of the participant. However, any AE/SAE - regardless of the relationship and the seriousness - occurring

Downloaded by PPD on 07 Nov 2022

up to 30 days after the last dose of finerenone within the study period has to be documented and forwarded to the MAH within the given timelines, even if this period goes beyond the end of observation.

As long as the participant has not received any finerenone within the frame of the study AEs /SAEs do not need to be documented as such in this observational study. However, they are part of the participant´s medical history.

For any serious product-related AE occurring after study end, the standard procedures that are in place for spontaneous reporting have to be followed.

11.3 Management and reporting

Non-serious AEs

The outcome of all reported AEs will be followed up and documented. Where required, investigators might be contacted directly by the responsible study staff to provide further information.

Non-serious ARs

All non-serious ARs occurring under treatment with finerenone that qualify for expedited reporting will be submitted to the relevant authorities according to EU PV legislation (Regulation (EU) No 1235/2010 [16] and Directive 2010/84/EU [17], Module VI [15]) and according to national regulations by the MAH; however, all investigators must obey local legal requirements.

For non-serious ARs occurring under non-Bayer products the investigator has to account for and comply with the reporting system of the product's Marketing Authorization Holder within the frame of local laws and regulations as well as other locally applicable laws and regulations.

Serious AEs

Any SAE or pregnancy entered into the CRF/EDC system will be forwarded immediately by the EDC system (or alternatively the CRO manually within one business day of awareness) to the pharmacovigilance country head (PVCH) being responsible for SAE processing. The outcome of all reported SAEs (resolution, death etc.) will be followed up and documented. Where required, investigators might be contacted directly by the pharmacovigilance country head (PVCH) in charge to provide further information.

Submission to the relevant authorities according to national regulations will be done by the MAH for SAEs related finerenone treatment; however, all investigators must obey local legal requirements.

For any serious drug-related AE occurring after study end, the standard procedures that are in place for spontaneous reporting have to be followed.

For SAEs that occurred while administering non-Bayer products the investigator has to account for and comply with the reporting system of the product's Marketing Authorization Holder within the frame of local laws and regulations as well as other locally applicable laws and regulations.

Where locally required, submission of SAEs related to non-Bayer products to the relevant authorities according to national regulations will be done by the MAH.

Downloaded by PPD on 07 Nov 2022

11.4 Evaluation

Whenever new important safety information is received, e.g. case reports from an investigator, the reports are processed and entered into the global pharmacovigilance safety database. These reports will be reviewed on a regular basis (for information on collection, management and reporting of case reports, refer to 11.2 and 11.3). If a potential safety signal is suspected, an investigation of the suspected potential signal will be performed according to internal standard operating procedures, for further evaluation within the context of benefit risk.

12. Plans for disseminating and communicating study results

This study will be registered at “www.clinicaltrials.gov" and in in the EU PAS register at “http://www.encepp.eu/encepp_studies/indexRegister.shtml”. Results will be disclosed in a publicly available database within the standard timelines.

The results of this observational study are intended to be published in a peer-reviewed journal and as abstracts/presentations at medical congresses under the oversight of the MAH. BAYER is committed to adhering to the prevailing standards for “Good Publication Practice”. Current guidelines and recommendation will be followed (e.g. GPP3 Guidelines [18], STROBE [19]), as well as the criteria for authorship established by the International Committee of Medical Journal Editors (ICMJE). No individual investigator may publish on the results of this study, or their own participants, without prior approval from the MAH.

13. References

[1] N. R. Hill, S. T. Fatoba, J. L. Oke, J. A. Hirst, C. A. O'Callaghan, D. S. Lasserson und F. D. R. Hobbs, „Global Prevalence of Chronic Kidney Disease - A Systematic Review and Meta-Analysis,“ *PLoS One*, p. e0158765, 6 July 2016.

[2] G. Eknoyan, N. Lameire und K.-U. Eckardt, „KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease,“ *Kidney International Supplements*, pp. 1-150, January 2013.

[3] T. Liyanage, T. Ninomiya und V. Jha, „Worldwide access to treatment for end-stage kidney disease: a systematic review,“ *Lancet*, pp. 1975-1982, 16 May 2015.

[4] M. Lainscak, F. Pelliccia und G. Rosano, „Safety profile of mineralocorticoid receptor antagonists: Spironolactone and eplerenone,“ *International Journal of Cardiology*, pp. 25-29, 1 December 2015.

[5] G. L. Bakris, R. Agarwal und S. D. Anker, „Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes,“ *The New England Journal of Medicine*, pp. 2219-2229, 3 December 2020.

Downloaded by PPD on 07 Nov 2022

[6] P. Gaede, H. Lund-Andersen und H.-H. Parving, „Effect of a multifactorial intervention on mortality in type 2 diabetes," *The New England Journal of Medicine,* pp. 580-591, 7 February 2008.

[7] A. D. Association, „2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2019," *Diabetes Care,* pp. S13-S28, January 2019.

[8] V. Perkovic, M. J. Jardine und B. Neal, „Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy," *The New England Journal of Medicine,* pp. 2295-2306, 13 June 2019.

[9] P. K. Whelton, R. M. Carey und W. S. Aronow, „2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary," *Hypertension,* pp. 1269-1324, June 2018.

[10] B. Pitt, G. Filippatos und R. Agarwal, „Cardiovascular Events with Finerenone in Kidney Disease and Type 2 Diabetes," *New England Journal of Medicine,* p. Online ahead of print, 28 August 2021.

[11] FDA, "Code of Federal Regulations.," *Title 21, Volume 1. 21CFR11: Electronic records; electronic signatures.,* 01 Apr 2012.

[12] EU, "Commission implementing regulation (EU) No 520/2012 of 19 June 2012 on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 and Directive 2001/83/EC of the European Parliament and of the Council," *Official Journal of the European Union,* 20 Jun 2012.

[13] EFPIA, "Code on the Promotion of Prescription-Only Medicines to and Interactions with Healthcare Professionals," Oct 2007.

[14] EMA, "ENCePP guide on methodological standards in pharmacoepidemiology.," 05 Nov 2010.

[15] EMA, "GPV Module VI - Management and reporting of adverse reactions to medicinal products (Rev 1)," *Guideline on good pharmacovigilance practices (EMA/8731138/2011_Rev1),* 08 Sep 2014.

[16] EU, „amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products...," *Regulation (EU) No 1235/2010 of the European Parliament and of the Council of 15 December 2010,* 15 December 2010.

[17] EU, „amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use," *Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010,* 15 December 2010.

[18] C. Graf, W. P. Battisti, D. Bridges, V. Bruce-Winkler, J. M. Conaty, J. M. Ellison, E. A. Field, J. A. Gurr, M. E. Marx, M. Patel, C. Sanes-Miller and Y. E. Yarker, "International Society for Medical

Downloaded by PPD on 07 Nov 2022

Publication Professionals. Research Methods & Reporting. Good publication practice for communicating company sponsored medical research: the GPP2 guidelines," *BMJ,* 2009.

[19] E. von Elm, D. G. Altman, M. Egger, S. J. Pocock, P. C. Gøtzsche and J. P. Vandenbroucke, "STROBE-Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting of observational studies. J Clin Epidemiol. 2," *J Clin Epidemiol.,* 2008.

[20] ICH, "ICH Harmonized Tripartite Guideline: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (E2D)," Nov 2003.

[21] EMA, "GPV Module VIII - Post-authorisation safety studies (Rev 1)," *Guideline on good pharmacovigilance practices (EMA/813938/2011_Rev1),* 19 Apr 2013.

[22] EMA, „GPV Module VIII Addendum 1 - Member States' requirements for transmission of information on non-interventional post-authorisation safety studies (Rev 1),“ *Guideline on good pharmacovigilance practices (EMA/395730/2012_Rev 1),* 19 Apr 2013.

[23] EU, "Eudralex - Volume 9A of the Rules Governing Medicinal Products in the European Union: the Guidelines on Pharmacovigilance for Medicinal Products for Human Use," 2008.

[24] P. a. R. D. B. Rosenbaum, „The central role of the propensity score in observational studies for causal effects,“ *Biometricka,* Bd. 70, pp. 41-55, 1983.

[25] K. D. I. G. O. (. D. W. Group, „DIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease,“ *Kidney Int.,* Oct 2020.

Downloaded by PPD on 07 Nov 2022

Annex 1: List of stand-alone documents

Document Name

- 21785_<Steering Committee Charter>; v1.0 , 15 Nov 2021
- 21785_<CRF>; <v 4.0, 15 Jun 2022
- 21785_<DVP>; <v1.0 , 30 May 2022
- 21785_<EDC System>; v4.0, 15 Jun 2022
- 21785_<DMP>; v1.0 , 13 May 2022
- 21785_<SiOpsP>
- 21785_<MRP>; v1.0 , 26 Apr 2022
- Central Laboratory Services Manual v1.0 27-Apr-2022

Downloaded by PPD on 07 Nov 2022

Annex 2: ENCePP checklist for post-authorization safety study (PASS) protocols

Study title: FINE-REAL: A non-interventional study providing insights into the use of finerenone in a routine clinical setting

EU PAS Register® number: study not yet registered
Study reference number (if applicable):

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[7]	☒	☐	☐	6
1.1.2 End of data collection[8]	☒	☐	☐	6
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☒	☐	☐	6
1.1.5 Registration in the EU PAS Register®	☐	☒	☐	
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	See below
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8; 8.1; 8.2; 8.3
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2.1; 9.2.4
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Downloaded by PPD on 07 Nov 2022

Section 3: Study design		Yes	No	N/A	Section Number
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.4
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.7.4
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☒	☐	
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11 incl. sub-sections

Comments:

Section 4: Source and study populations		Yes	No	N/A	Section Number
4.1	Is the source population described?	☒	☐	☐	9.2.1
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☐	☐	☒	
	4.2.2 Age and sex	☒	☐	☐	9.2.1.1
	4.2.3 Country of origin	☐	☒	☐	
	4.2.4 Disease/indication	☒	☐	☐	9.2.1.1
	4.2.5 Duration of follow-up	☒	☐	☐	9.2.5
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.1

Comments:

Downloaded by PPD on 07 Nov 2022

Section 5: Exposure definition and measurement	Yes	No	N/A	Section Number
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.1; 9.7.3
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☒	☐	
5.3 Is exposure categorised according to time windows?	☐	☒	☐	
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	9.7.3
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

Section 6: Outcome definition and measurement	Yes	No	N/A	Section Number
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.1.1 to 9.1.3
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.7.3 to 9.7.5
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☒	☐	
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☒	☐	☐	9.1.1; 9.1.3

Comments:

Downloaded by PPD on 07 Nov 2022

Section 7: Bias	Yes	No	N/A	Section Number
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☐	☒	☐	
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.2.4
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☒	☐	9.9

Comments:

Section 8: Effect measure modification	Yes	No	N/A	Section Number
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	9.7.1

Comments:

Section 9: Data sources	Yes	No	N/A	Section Number
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☐	☐	9.3/ 9.3.1
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☐	☐	9.3/ 9.3.2
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☐	☐	☐	9.3/ 9.3.1/ 9.3.4
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.7.1
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.7.1
9.3.3 Covariates and other characteristics?	☐	☐	☒	

Downloaded by PPD on 07 Nov 2022

Section 9: Data sources	Yes	No	N/A	Section Number
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	9.4

Comments:

Section 10: Analysis plan	Yes	No	N/A	Section Number
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7.1 to 9.7.6
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7.1 to 9.7.6
10.4 Are stratified analyses included?	☒	☐	☐	9.7.1
10.5 Does the plan describe methods for analytic control of confounding?	☐	☒	☐	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7 Does the plan describe methods for handling missing data?	☐	☒	☐	
10.8 Are relevant sensitivity analyses described?	☐	☒	☐	

Comments:

Statistical analyses will be detailed in the Statistical Analysis Plan which will be finalized before study database lock.

Section 11: Data management and quality control	Yes	No	N/A	Section Number
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.8.1; 9.8.3
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8.2
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations	Yes	No	N/A	Section Number
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9

Downloaded by PPD on 07 Nov 2022

Section 12: Limitations	Yes	No	N/A	Section Number
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	9.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.5

Comments:

Section 13: Ethical/data protection issues	Yes	No	N/A	Section Number
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.3
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	10.6/ 10.4

Comments:

Section 14: Amendments and deviations	Yes	No	N/A	Section Number
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	Annex 4

Comments:

Section 15: Plans for communication of study results	Yes	No	N/A	Section Number
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Downloaded by PPD on 07 Nov 2022

Annex 3: Additional information

Not applicable

Downloaded by PPD on 07 Nov 2022

Annex 4: Description of updates and amendments

Global amendment 01;15 AUG 2022

Text in bold indicates new text, text that is struck through was deleted

Protocol section	**Description**
Abstract	EU PAS register number, NCT number, Product reference added Medicinal product updated - Firialta® added Study countries updated – ~~United Kingdom, Sweden~~ removed, **Luxembourg, Saudi-Arabia, Argentina, Slovenia, Thailand** added
2	**CKD**, **ESKD**, **PAC**, **T2D** added to list of abbreviations
3.1	- Responsible changes Regulatory Affairs responsible/ MAH contact person: PPD OS Statistician: PPD
4	The primary objective in this study is to describe **clinical characteristics of and** treatment patterns in participants with CKD and T2D treated with finerenone in routine clinical practice. The variables for secondary endpoints are: • Occurrence of AEs/SAEs overall ~~and by MedDRA PTs~~ • Occurrence of hyperkalemia • Occurrence of hyperkalemia leading to **permanent** study drug discontinuation The variables for further endpoint are: • Reasons, frequency and duration of in-patient[1], out-patient and emergency **department** visits • Occurrence of newly diagnosed diabetic retinopathy or progression of existing disease at ~~study entry~~ **treatment initiation** Timelines updated (see below)
5	Summary of amendment 1 added
Table 1 Milestone	FPFV adapted to actual date ~~15 May 2022~~ **13 Jun-2022** LPFV updated ~~15 Oct 2024~~ **15-Nov-2024** Dates of interim analyses postponed by ~ 1month CBD updated ~~15 Feb 2026~~ **15 Mar 2026**
7	~~In China's Mainland, the approval of finerenone 10/20 mg [OAD] in T2D and CKD patients will be granted with a potential request for a post-authorization commitment study. China's Mainland is added to the FINE-REAL study to fulfill this request.~~

Downloaded by PPD on 07 Nov 2022

8.1	The primary objective in this study is to describe **clinical characteristics of and** treatment patterns in participants with CKD and T2D treated with finerenone in routine clinical practice.
9.1	**The study will be conducted in the following countries: USA, Canada, Mexico, Brazil, Colombia, France, Germany, Spain, Italy, Belgium, Denmark, China Mainland, Singapore, Taiwan, The Netherlands, Switzerland, Luxembourg, Saudi Arabia, Argentina, Slovenia, Thailand.** Participants will be recruited within a period of approximately 30 months and followed up **for maximum period of 12 months if treatment is still ongoing**, or until 30 days after permanent discontinuation of finerenone, or until death, or withdrawal of consent, ~~end of study maximum of 12 months,~~ or loss-to-follow-up, whichever occurs first.- **The end of observation visit will occur up to 12 months after initial visit in case that Finerenone therapy is ongoing, or about 30 days after end of Finerenone treatment if treatment with Finerenone is less than 12 months**. ~~End of study will occur 12 months after last patient first visit, allowing that each patient can be followed up for a minimum of 12 months.~~ ~~In the event that the Chinese Heath Authority requires this study to be a PAC, then free drugsfinerenone will be provided for Chinese patients as requested per local guidelines for such studies. All study drugs are from commercial supplies and relabeled according to the relevant requirements.All study drug will be distributed by an authorized drug responsible person such as pharmacist or study nurse.~~
9.1.1	The primary endpoint is to describe **clinical characteristics of and** treatment pattern in participants with CKD and T2D treated with finerenone, based on:… • Use of secondary therapies ~~(concomitant medication)~~ in participants with CKD and T2D
9.1.2	The secondary endpoints are: • Occurrence of AEs/SAEs overall ~~and by MedDRA PTs~~ • Reported hyperkalemia o Reported hyperkalemia leading to **permanent** study drug discontinuation o Reported hyperkalemia leading to dialysis o Reported hyperkalemia leading to hospitalization
9.1.3	Further endpoints are: • Reported ~~hospital~~ visits **with healthcare providers** (reasons, **frequency** and duration ~~outcomes~~) • In-~~Out~~-patient, out-patient[3] and emergency department visits. ~~Visit (including, but not limited to, emergency room department visits), emergency, in-patient st~~ay • Reported diabetic retinopathy and its progression if existing at time of ~~ICF signature~~**treatment initiation**
9.2.1.1	• Diagnosis of CKD associated with T2D **based on assessment by physician** • **Treatment initiation with finerenone was made as per local label**

Downloaded by PPD on 07 Nov 2022

	• Decision to initiate treatment with finerenone ~~was made as per investigator's routine treatment practice~~ **must be made before ICF is signed**
9.2.1.2	• Participation in an investigational ~~study with interventions outside of routine clinical practice~~ **trial at any time during the course of this study**
9.2.5	The observation period for each participant will be ~~at least~~**for a maximum of** 12 months or the whole treatment period with finerenone if participant permanently discontinues treatment prematurely. Follow-up visit It is assumed, that according to clinical practice, follow-up visits will happen approximately **one month after first drug intake, and then** every 3 months during the 1st year of treatment ~~and every 6 months thereafter~~ End of Observation/Final Vist The final data collection (end of observation) is after ~~36~~**42** months or at the end of study (whatever is earlier). Lost to follow-up A participant will be considered as 'lost to follow-up' if **no information collected within 12 months since the last data collection time point** ~~the last documentation of any information was 3 months prior to the planned observation period (end of study).~~.

9.2.5
Table 2

	Baseline visit	**Follow-up visit(s) (including end of observation)**	~~**End of observation / Final visit**~~
Date/type of visit	X	X	~~X~~
Eligibility/Informed Consent	X		
Demography	X		
Vital signs	X		
Disease history	X		
Co-morbidities (medical history, concomitant diseases)	X		
Concomitant medication	X	X	~~X~~
Exposure/treatment	X	X	~~X~~
Laboratory parameters	X	X	~~X~~
Adverse events	(X)	X	~~X~~*
Hyperkalemia	~~X~~	X	~~X~~
End of Observation		~~X~~	~~X~~
Healthcare resource utilization (in-patient/out-patient/emergency **department** visits)	X	X	~~X~~
Diabetic retinopathy **assessment**	X	X	~~X~~
Sampling of blood and urine samples for biobanking (for participants in the US only)**	X	X	~~X~~

9.3.1	• Dose anf frequency of finerenone treatment **(planned and actual)**

Downloaded by PPD on 07 Nov 2022

<table>
<tr><td></td><td>

Type, and duration of concomitant ~~secondary~~ therapies

Diuretics

Loop
Thiazides
Potassium sparing

Anti-thrombiotic treatment

~~Aspirin~~Acetylsalicylic acid

</td></tr>
<tr><td>9.3.2</td><td>
The variables for secondary endpoints are:

Occurrence of AEs/SAEs ~~overall and by MedDRA PTs~~
Occurrence of hyperkalemia

Occurrence of hyperkalemia leading to permanent study drug discontinuation

</td></tr>
<tr><td>9.3.3</td><td>

Reasons, frequency and duration of in-patient[5], out-patient and emercency department vists
Occurrence of newly diagnosed diabetic retinopathy or progression of existing disease at ~~study entry~~treatment initiation

</td></tr>
<tr><td>9.3.5</td><td>Variables collected at post-baseline visits: UACR</td></tr>
<tr><td>9.5</td><td>
~~Global study~~
~~Subset China~~
~~400 patients are planned to be enrolled from China. For potential incidence proportions of 1%, 5%, 10% and 50%, respectively, the following precisions can be expected.~~
<table>
<tr><th>~~# of patients~~</th><th>~~Incidence proportion (%)~~</th><th>~~95% CI of incidence proportion~~</th><th>~~Width (%) of 95% CI~~</th></tr>
<tr><td>~~400~~</td><td>~~1%~~
~~5%~~
~~10%~~
~~50%~~</td><td>~~(0.0%, 2.0%)~~
~~(2.9%, 7.1%)~~
~~(7.1%, 12.9%)~~
~~(45.1%, 54.9%)~~</td><td>~~2.0%~~
~~4.3%~~
~~5.9%~~
~~9.8%~~</td></tr>
</table>
~~The 50% incidence proportion maximizes the precision width, therefore, maximum width with 400 patients will not be greater than 9.8%.~~
</td></tr>
<tr><td>9.7.1</td><td>
Any diagnoses/diseases/event terms documented in the following forms will be coded using the latest Medical Dictionary for Regulatory Activities (MedDRA) version:

Co-morbidities (medical history, concomitant diseases)
Adverse events
Procedure

</td></tr>
</table>

Downloaded by PPD on 07 Nov 2022

9.7.3	**Analysis of the clinical characteristics will be performed as described in section 9.7.2.** Dose and frequency of finerenone treatment (**planned and actual**) Treatment pathways for ~~secondary~~ **concomitant** medications after introduction of finerenone, Frequencies will be provided in summary tables along with graphical summaries such as **histograms** ~~sunburst plots~~
9.7.5	Reasons, frequency and duration of in-patient, out-patient and emergency **room** visits will be summarized by descriptive statistics.
9.7.6	The occurrence, duration, treatment, ~~severity,~~ **causal relationship to finerenone as assessed by the physician** and outcome of AEs~~, SAEs,~~ and ~~ARs~~**SAEs** will be listed.
9.8.2	~~**Quality Review**~~ **Site Monitoring** ~~Quality review will follow a sequential, risk-based approach: in a first step the site's training status will be assessed via standardized telephone interviews. In a second step, source data verification will be conducted.~~ **Site monitoring will follow a risk-based approach and consists of several measures and tasks to be carried be out throughout the site's course of the study e.g. regular off-site and on-site monitoring visits well as ad-hoc and for-cause monitoring visits which can happen at any point in time. Data reviews will be conducted during regular on-site monitoring visits.** **Detailed measures for** ~~quality review~~**site monitoring** will be described in the ~~Qualtity Review~~ **Site Operations Plan (**~~QRP~~**SiOpsP).** The ~~QRP~~**SiOpsP** is available upon request (see Annex 1).
9.8.3	**…** will be stored after the end or discontinuation of the study for at least 25 years **or according to local regulations**.
9.9	**First intake of finerenone preceding the ICF signature could influence reported safety and treatment patterns. The exposure of participants to finerenone before ICF signature, especially for longer periods of time, will create a bias in such a way that only those who tolerated the drug well enough to reach the ICF signature process would be accounted for. This might lead to an overestimation of participants' compliance with treatment and underestimation of AEs.**
11.2	Starting with the first application of finerenone ~~after enrollment into the study~~, all non-serious ~~adverse events (AE)~~ AEs must be documented on the AE Report Form or in the CRF/EDC system and forwarded to the MAH**: a)** within 7 calendar days ~~(for OS inside the~~of awareness in EU~~) or if required by local regulations of participating country)/ 30 days (for OS that involve only~~ countries~~. outside the~~ **; b) within 30 calendar days of awareness in non-**EU~~) of awareness.~~ countries. All serious AEs (SAE) must be documented and forwarded **to the MAH** immediately (within one business day of awareness).
Annex 1	**Version number and date added for Steering Committee Charter, CRF, DVP, EDC System,DMP, SiOpsP, MRP, Central Laboratory Services Manual**

Downloaded by PPD on 07 Nov 2022

Signatories	**Updated** PPD
General	~~Patient~~ has been replaced by **participant** throughout the whole protocol Minor grammatical and spelling corrections, update of cross references Footnotes added as appropriate

Global amendment 02; 28 OCT 2022

Text in bold indicates new text, text that is struck through was deleted

Protocol section	Description
List of abbreviations	**MFDS Korean Ministry of Food and Drug Safety** added **Q1 First quartile** and **Q3 Third quartile** added
Abstract	The exploratorative objective**s** of this study ~~applies only to participants in the US and is to~~ **are:** • **to identify baseline risk factors associated with adverse events** • **to** collect voluntary blood and urine samples to establish a biobank for future analysis e.g. of changes in levels of selected circulating biochemical and urinary proteins or nucleic acid, from baseline (prior to first use of study drug) and at follow-up visits **(only applicable to participants in the US)*** *** Further details can be found in the corresponding stand-alone document (lab manual).** Coutry list updated: ~~Argentina~~ removed, **Chile** and **South Korea** added Study design adapted: It is planned to enroll ~~4000~~ **~5,500** participants with a diagnosis of CKD and T2D for whom the decision was taken by the treating physician to initiate treatment with finerenone. **Participants will be observed for a maximum period of 12 months after start of finerenone if treatment is still ongoing, or until 30 days after permanent discontinuation of finerenone, or until death, or withdrawal of consent, or loss-to-follow-up, whichever occurs first.** Population adapted: Participants who have been prescribed finerenone in accordance with existing label **and whose finerenone treatment has been started up to 8 weeks before or after the ICF is signed** will be eligible for enrollment. Study size adapted: In total, ~~4000~~ **~5,500** participants are planned to be enrolled. Milestones adapted: Last Patient First Visit (LPFV) ~~15-Nov-2024~~ **01-Sep-2026** Last Patient Last Visit (LPLV) ~~15-Nov-2025~~ **01-Sep-2027** Clean Database (CDB) ~~15-Mar-2026~~ **01-Jan-2028**

Downloaded by PPD on 07 Nov 2022

6	<table><tr><th>Milestone</th><th>Planned or actual date</th></tr><tr><td>Start of data collection (FPFV) - actual</td><td>13-Jun-2022</td></tr><tr><td>Interim analyses*</td><td></td></tr><tr><td>Interim analysis> FPFV+1 year</td><td>13-Jun-2023</td></tr><tr><td>Interim analysis> FPFV+2 years</td><td>13-Jun-2024</td></tr><tr><td>Interim analysis> FPFV+3 year</td><td>13-Jun-2025</td></tr><tr><td>Last Patient First Visit (LPFV)</td><td>~~15-Nov-2024~~ 01-Sep-2026</td></tr><tr><td>Last Patient Last Visit (LPLV)</td><td>~~15-Nov-2025~~ 01-Sep-2027</td></tr><tr><td>End of data collection</td><td>~~15-Nov-~~2025 01-Sep-2027</td></tr><tr><td>Clean Database (CDB)**</td><td>~~15-Mar-2026~~ 01-Jan-2028</td></tr><tr><td>Final report of study results</td><td>~~01-Jun-2026~~ 01-Jun-2028</td></tr></table> *** In line with the requirements of the MFDS, (bi-) annual reports for the South Korean cohort will be submitted to MFDS with the following submission timelines: Jan-2023, Jul-2023, Jan-2024, Jul-2024, Jul-2025, Jul-2026, Jul-2027, Aug 2028.** **** Please note that CDB for the global cohort (excluding South Korea) is planned to be reached earlier (15-Mar-2026). Follwowing this date, a study report will be written displaying clean and final data for the global cohort (excluding South Korea). For participants recruited by South Korean sites, unclean data will be provided in a table, listings, and figure (TLF) document, which will be added to the report as stand-alone document.**
8.3	Exploratory objective**s of this study are** ~~(for participants in the US only)~~**:** • **to identify baseline risk factors associated with adverse events** • ~~An exploratory obkective of this study is~~ to collect voluntary blood and urine samples to establish a biobank for future analysis e.g. of changes in levels of selected circulating biochemical and urinary proteins or nucleic acid, from baseline (prior to first use of study drug) and at follow-up visits. This might be correlated to clinical and demographic details to determine association with disease progression and/or outcomes. Since the exact analyses have not yet been defined, no corresponding endpoints or variables are defined in Sections 9.1.3 and 9.3.3, respectively. A separate stand-alone document describes more details (Central Laboratory Services Manual) (Annex 1). **This exploratory objective applies to participants in the US only.**
9.1	It is planned to enroll ~~4000~~ **~5,500** participants with a diagnosis of CKD and T2D for whom the decision was taken by the treating physician to initiate treatment with finerenone.

Downloaded by PPD on 07 Nov 2022

	The study will be conducted in the following countries:…. **ArgentinaChile**, Slovenia, Thailand**, South Korea**. **For the global cohort, P**~~p~~articipants will be recruited within a period of approximately 30 months. **Recruitment for the South Korean Cohort will last 38 months.** **Participants will be** ~~and~~ followed up for maximum period of 12 months **after start of finerenone** if… The end of observation visit will occur up to 12 months after ~~initial visit~~**start of finerenone treatment** in case that Finerenone finerenone therapy is ongoing,
9.2.1.1	• Treatment ~~initiation with finerenone was made as per local~~ **label****according to local marketing authorization, finerenone 20 or 10 mg. Treatment should have been started up to 8 weeks before or after the ICF is signed.** • ~~Decision to initiate treatment with finerenone must be made before ICF is signed~~
9.2.5	The investigator or a delegate documents a~~n initial~~**baseline** visit, follow-up visits and the end of observation/final visit for each participant in the Case Report Form (CRF). ~~Initial~~ **Baseline** and follow-up visits occur during routine practice,… **Participants will be followed up for a maximum period of 12 months after start of finerenone if treatment is still ongoing, or until 30 days after permanent discontinuation of finerenone, or until death, or withdrawal of consent, or loss-to-follow-up, whichever occurs first.** ~~The observation period for each participant will be for a maximum of 12 months or the whole treatment period with finerenone if participant permanently discontinues treatment prematurely.~~ Baseline ~~or Initial~~ Visit **The investigator documents a baseline visit, follow-up visits and the end of observation/final visit for each patient in the electronic case report form (eCRF).** **The investigator documents a baseline visit, follow-up visits and the end of observation/final visit for each patient in the electronic case report form (eCRF). The baseline visit is defined as the first visit by the patient to the study physician after the treatment decision for finerenone in CKD with T2D was made. Reasons for starting finerenone treatment must be based on treatment start day to ensure all outcome-relevant data is captured. Baseline visit can be on the same day of treatment decision if a physical examination is done on the same day, but sites need to consider that treatment decision must happen independently of and before the study enrolment.** Baseline information (considered as data collected no more than 1 month prior to the 1st dose of finerenone) recorded with the status at ~~initial~~ **baseline** visit before the first drug administration. **Follow-up visits occur during routine practice, the study protocol does not define exact referral dates for those visits. However, the treating physicians are expected to follow-up their according to local label.** ~~It is assumed, that according to clinical practice, follow-up visits will happen approximately one month after first drug intake, and then every 3 months during the 1st year of treatment.~~

Downloaded by PPD on 07 Nov 2022

	The end of observation visit should be documented 12 months after start of finerenone treatment in case that finerenone therapy is ongoing, or about 30 days after end of finerenone treatment if treatment with finerenone is less than 12 months, or after death, or withdrawal of informed consent, or loss-to-follow-up, whichever occurs first.~~The final data collection (end of observation) is after 42 months or at the end of study (whatever is earlier).~~
9.5	In total, ~~4000 ~~**5,500** participants are planned to be enrolled. **Hereof, 1,500 participants by study sites located in South Korea.** For the secondary endpoints incidence proportions, cumulative incidences and incidence rates will be estimated and corresponding two-sided 95% confidence intervals will be provided, as described in section**s 9.7.1** and 9.7.4. With a sample size of ~~4,000~~**5,500** participants, for potential incidence proportions of 1%, 5%, 10% and 50%, respectively, the following precisions can be expected: See table below The 50% incidence proportion maximizes the precision width, therefore, maximum width with ~~4,000~~**5,500** participants will not be greater than ~~3.1~~**2.6**%. **In accordance with regulatory requirement by the applicable South Korean authority (Korean Ministry of Food and Drug Safety, MFDS) as described in 'Section 3 of Article 6 on Notification No. 2020 - 122, Re-examination Standard of New drug (Amended 14-Dec-2020)', Kerendia® (finerenone) fits into the category of total required target patient number of 1,500 participants in South Korea for re-examination for 6 years according to the regulatory rules relating to new drug formulations. The probability to observe at least 1 event with a true underlying incidence risk of at least 0.3% is equal to 99% in a population of 1,500 participants.**
9.7.1	All variables will be analyzed descriptively with appropriate statistical methods: categorical variables by frequency tables (absolute and relative frequencies) and continuous variables by ~~summary~~ **descriptive** statistics (i.e. mean, standard deviation, minimum, median, quartiles and maximum). **Continuous variables will be described by absolute value and as change from baseline per analysis time point, if applicable.**

# of participants	Incidence proportion (%)	95% CI of incidence proportion	Width (%) of 95% CI
~~4000~~**5,500**	1%	~~(0.7%, 1.4%)~~**(0.8%, 1.3%)**	**0.5%**~~0.7%~~
	5%	~~(4.3% - 5.7%)~~**(4.4%, 5.6%)**	**1.2%**~~1.4%~~
	10%	~~(9.1% - 10.9%)~~**(9.2%, 10.8%)**	**1.6%**~~1.9%~~
	50%	~~(48.5% - 51.5%)~~**(48.7%, 51.3%)**	**2.6%**~~3.1%~~

Downloaded by PPD on 07 Nov 2022

	All analyses will be performed for the total study population (overall population) and separately for each participating country if participant numbers are sufficient and/ **or** if required for local reasons. Whenever reasonable, data will be stratified by subgroups (e.g. age, sex, baseline characteristics). **Additionally, safety analyses for special population (e.g. participants with hepatic impairment) will be performed.** **Sample size and disposition information by analysis time point will be displayed in a frequency table.** **As an explorative analysis, a Chi-square test or Fisher´s Exact test will be carried out to identify any association with the overall safety. Also, logistic regression will be used to quantify the effect of the factors on the overall safety (i.e. the occurrence of any adverse event). A list of potential baseline factors can be found in section** 9.3**. Each factor will be fitted univariately to show its association with overall safety. Further details will be described in the Statistical Analysis Plan (SAP).** ~~All statistical details including calculated variables and proposed format and content of tables will be detailed in the Statistical Analysis Plan (SAP). The SAP will be finalized before data cut for first annual report analysis. The SAP is available upon request (see Annex 1~~: List of stand-alone documents~~).~~ ~~Number of participants with minimum follow-up will be displayed by suitable categories.~~
9.7.3	Continuous variables will be summarized in tables with the appropriate measures (mean, median, SD, ~~IQR~~**Q1, Q3**).
9.7.4	**In addition to the analyses mentioned in Section 9.**7.1, ~~T~~**t**he following metrics will be provided:
9.7.6	Besides the analyses of the safety endpoints detailed in section**s 9.7.1 and** 9.7.4,… **As required by MFDS, additional analysis for AEs and SAEs will be performed regarding severity for the participants included by sites located in South Korea.**
9.9	The exposure of participants to finerenone before ICF signature~~, especially for longer periods of time,~~ will create a bias in such a way that only those who tolerated the drug well enough to reach the ICF signature process would be accounted for.
11.1.1 (newly added)	**11.1.1 Additional definitions only applicable for South Korea** **As required by the MFDS, the following definitions are to be reflected by study sites in South Korea** **<u>Criteria for causal relationship assessment of AEs:</u>** **1. <u>Certain</u>** **The time elapsed between the administration of the drug and the occurrence of the event is plausible and the event can't be explained by other drugs, chemicals or concurrent disease. The patient showed clinically plausible response following**

Downloaded by PPD on 07 Nov 2022

withdrawal of the drug, and the event is definitive pharmacologically or phenomenologically following rechallenge with the same drug, if necessary.

2. **Probable/likely**

   The time elapsed between the administration of the drug and the occurrence of the event is reasonable and the event is unlikely to be attributed to other drugs, chemicals or concurrent disease. The patient showed clinically reasonable response following withdrawal of the drug (no information about rechallenge).

3. **Possible**

   The time elapsed between the administration of the drug and the occurrence of the event is reasonable but, the event could also be explained by other drugs, chemicals or concurrent disease. And information on drug withdrawal may be lacking or unclear.

4. **Unlikely**

   The event is temporary that makes a relationship improbable with the administration of the drug and other drugs, chemicals or concurrent disease provide plausible explanations.

5. **Conditional/unclassified**

   More data for proper assessment needed or additional data under examination.

6. **Unassessible/unclassifiable**

   Cannot be judged because information is insufficient or contradictory and data cannot be supplemented or verified.

7. **No**

For the combined analysis of the South Korean and global cohorts, the causality assessment definitions applicable to South Korea will be mapped to the causality assessment definitions used in other countries. Further details will be defined in the SAP.

Severity of AEs shall be judged based on the following:

- **Mild**

  There is a subjective or objective symptom, but it doesn't affect daily life. Continuous treatment is doable without changing the dose of target drug.

- **Moderate**

  There is a symptom that lets a patient feel inconvenience in daily life, which needs the reduction of dose or the treatment due to the AE

- **Severe**

  There is a symptom that obstructs daily life, which requires suspending the dose of target drug due to strong AE

Downloaded by PPD on 07 Nov 2022

Annex 5: Signature pages

Signature Page

This protocol is electronically signed in the study management system

Acronym/Title	FINE-REAL: A non-interventional study providing insights into the use of finerenone in a routine clinical setting
Protocol version and date	V 3.0 28 OCT 2022
IMPACT study number	21785
Study type / Study phase	Observational, post-approval ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS46493
NCT number	NCT05348733
Active substance	Finerenone (BAY-94-8862) Non-steroidal mineralocorticoid receptor (MR) antagonist ATC code: C03DA05
Medicinal product	Kerendia® Firialta®
Product reference	EU/1/21/1616
Procedure number	EMEA/H/C/005200/0000
US NDA number	NDA 215341 (tablet; oral)
Study Initiator and Funder	Bayer, AG

Downloaded by PPD on 07 Nov 2022

The signatories confirm that they agree that the study will be conducted under the conditions described in the protocol.

Signatories

Downloaded by PPD on 07 Nov 2022

Signature Page for VV-114891 v1.0

Reason for signing: Approved	PPD
Reason for signing: Approved	PPD
Reason for signing: Approved	PPD
Reason for signing: Approved	PPD
Reason for signing: Approved	PPD
Reason for signing: Approved	PPD
Reason for signing: Approved	PPD

Signature Page for VV-114891 v1.0

Downloaded by PPD on 07 Nov 2022

Signature Page for VV-114891 v1.0

Reason for signing: Approved	PPD

Reason for signing: Approved	PPD

Signature Page for VV-114891 v1.0

Downloaded by PPD on 07 Nov 2022