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 1.0; 09 February 2022
IMPACT study number	21785
Study type / Study phase	Observational, post-approval ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	<Study not yet registered>
NCT number	<Study not yet registered>
Active substance	Finerenone (BAY-94-8862) Non-steroidal mineralocorticoid receptor (MR) antagonist ATC code: C03DA05
Medicinal product	Kerendia©
Product reference	Not yet available – will be added once available.
Procedure number	EMEA/H/C/005200/0000
US NDA number	NDA 215341 (tablet; oral)
Study Initiator and Funder	Bayer, AG

Research question and objectives	The aim of this study is to provide insights on characteristics and treatment patterns of patients with CKD and T2D treated with finerenone in routine clinical practice. The primary objective in this study is to describe treatment patterns in patients 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 patients • Hyperkalemia Further objective in this study is to assess the following in a real-world setting: • Healthcare resource use • Diabetic retinopathy The explorative objective of this study applies only to patients in the US and 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.
Country(-ies) /regions of study	USA, Canada, Mexico, Brazil, Colombia, France, Germany, Spain, Italy, Belgium, Denmark, United Kingdom, China Mainland, Singapore, Taiwan, The Netherlands, Switzerland, Sweden
Author	PPD

Marketing authorization holder

Marketing authorization holder(s)	Bayer AG
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.

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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
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
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
MRA	Mineralocorticoid receptor antagonists
MRP	Medical Review Plan
N/A	Not Applicable
NSAID	Non-Steroidal Anti-Inflammatory Drug
OS	Observational Study
PAS	Post-Authorization Study
PASS	Post-Authorization Safety Study

PSUR	Periodic Safety Update Report
PV	Pharmacovigilance
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
VKA	Vitamin K Antagonist

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.

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) which is available upon request.

Information on the Steering Committee Members and the respective Charters are kept as stand-alone documents (see Annex 1) 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 1.0; 09 February 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 T2D patients with CKD (and albuminuria > 300 mg/day) are to be treated with angiotensin-converting enzyme inhibitors (ACEIs) 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

	pressure in kidney disease. However, Spironolactone and Eplerenone MRAs are still not widely used. An important reason for that is likely to be hyperkaliemia, an adverse event commonly associated with MRAs 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 randomized, double-blind, placebo-controlled, multicenter phase III 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 patients 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.

Research question and objectives	The aim of this study is to provide insights on characteristics and treatment patterns of patients with CKD and T2D treated with finerenone in routine clinical practice. The primary objective in this study is to describe treatment patterns in patients 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 patients • Hyperkalemia Further objective in this study is to assess the following in a real-world setting • Healthcare resource use • Diabetic retinopathy The explorative objective of this study applies only to patients in the US and 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.
Study design	This international study is a prospective, non-interventional multicenter, single arm study of patients with a diagnosis of CKD associated with T2D who are newly prescribed finerenone under routine treatment conditions. It is planned to enroll 4000 patients with a diagnosis of CKD and T2D for whom the decision was taken by the treating physician to initiate treatment with finerenone.
Population	Female and/or male adult patients with a diagnosis of CKD and T2D will be enrolled after the decision for treatment with finerenone has been made by the treating physician. Patients 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.

Variables	The variable for primary endpoint are:
	• Clinical characteristics of underlying disease (CKD, T2D):
	  ○ History and diagnosis of CKD
	  ○ History and diagnosis of T2D
	  ○ Hypertension
	  ○ History of ischemic cardiovascular events
	  ○ 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
	• Type, and duration of concomitant secondary therapies
	
	The variables for secondary endpoints are:
	• Occurrence of AEs/SAEs overall and by MedDRA PTs
	• Occurrence of hyperkalemia
	  ○ Occurrence of hyperkalemia leading to study drug discontinuation
	  ○ Occurrence of hyperkalemia leading to dialysis
	  ○ Occurrence of hyperkalemia leading to hospitalization
	
	The variables for further endpoint are:
	• Reasons, frequency and duration of inpatient, outpatient and emergency visits
	• Occurrence of newly diagnosed diabetic retinopathy or progression of existing disease at study entry

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

Study size	In total, 4000 patients 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 patient numbers are sufficient and if required for local reasons. Whenever reasonable, data will be stratified by subgroups (e.g. age, gender, baseline characteristics). Interim analysis will consist of demographic and baseline data of patients 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) 15-May-2022 Last Patient First Visit (LPFV) 15-Oct-2024 Last Patient Last Visit (LPLV) 15-Nov-2025 Clean Database (CDB) 15-Feb-2026 Study Report 15-Aug-2026

5. Amendments

None

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) that is available upon request.

Table 1: Milestones

Milestone	Planned date
Start of data collection (FPFV)	15-May-2022
Annual safety report	2022-2025
Interim analysis> FPFV+1 year	15-May-2023
Interim analysis> FPFV+2 year	15-May-2024
Interim analysis> FPFV+3 year	15-May-2025
Last Patient First Visit (LPFV)	15-Oct-2024
Last Patient Last Visit (LPLV)	15-Nov-2025
End of data collection	15-Nov-2025
Clean Database (CDB)	15-Feb-2026
Final report of study results	15-Aug-2026

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 m2. 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 widely used. An important reason for that is likely to be hyperkaliemia, 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 patients with CDK and T2D were randomized 1:1 to receive finerenone or placebo. For analysis, 5,674 patients were available, n= 2,833 patients 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 patients with CKD and T2D were randomized 1:1 to receive finerenone or placebo. Of those, 7,352 patients were available for analysis (n= 3,686 patients in the finerenone and n= 3,666 patients in the placebo arm). Among patients 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 patients were hospitalized or discontinued the study due to hyperkalemia than placebo-treated patients (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 CDK 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.
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.

8. Research questions and objectives

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

8.1 Primary objective

The primary objective in this study is to describe treatment patterns in patients 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 patients
- 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 objective (for patients in the US only)

An exploratory objective 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 Chapters 9.1.3 and 9.3.3, respectively. A separate stand-alone document describes more details (Biobanking manual).

9. Research methods

9.1 Study design

This international study is a prospective, non-interventional multicenter, single arm study of patients with a diagnosis of CKD associated with T2D who are newly prescribed finerenone under routine

treatment conditions. It is planned to enroll 4000 patients with a diagnosis of CKD and T2D for whom the decision was taken by the treating physician to initiate treatment with finerenone. Patients will be recruited within a period of approximately 30 months and followed up until 30 days after permanent discontinuation of finerenone, or until death, withdrawal of consent, end of study, or loss-to-follow-up, whichever occurs first. In case of a temporary finerenone treatment pause of ≤ 6 months, patients 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). 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 drugs-finerenone 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 drugs will be distributed by an authorized drug responsible person such as pharmacist or study nurse.

9.1.1 Primary endpoint(s)

The primary endpoint is to describe treatment pattern in patients with CKD and T2D treated with finerenone, based on:

- Clinical characteristics of patients with CKD and T2D
- Reasons for introducing finerenone
- Reasons for discontinuation of finerenone
- Planned and actual duration of treatment with finerenone
- Dosing of finerenone
- Use of secondary therapies (concomitant medication) in patients with CKD and T2D.

9.1.2 Secondary endpoint(s)

The secondary endpoints are:

- Reported AE/SAEs overall and by MedDRA PTs
- Reported hyperkalemia
    - Reported hyperkalemia leading to study drug discontinuation
    - Reported hyperkalemia leading to dialysis
    - Reported hyperkalemia leading to hospitalization

9.1.3 Further Endpoints

Further endpoints are:

- Reported hospital visits (reasons, duration and outcomes)

- Out-patient, emergency, in-patient

- Reported diabetic retinopathy and its' progression if existing at time of ICF signature

9.2 Setting

9.2.1 Eligibility

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

Patients 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 patient in the study should be documented in the patient medical records.

9.2.1.1 Inclusion criteria

- Adult female or male patient (≥18 years old)
- Diagnosis of CKD associated with T2D
- Decision to initiate treatment with finerenone was made as per investigator's routine treatment practice
- Signed informed consent

9.2.1.2 Exclusion criteria

- Participation in an investigational study with interventions outside of routine clinical practice
- Contra-indications according to the local marketing authorization

9.2.2 Withdrawal

In this observational study, withdrawal from the study is independent of the underlying therapy and will not affect the patient's medical care. Each patient may withdraw from the study at any time without giving a reason. If a patient wants to terminate the study participation, no further data will be collected. In case a patient 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 patient medical records.

9.2.3 Replacement

Patients 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 patients, which constitute more heterogeneous populations than those participating in randomized

clinical trials (e.g., wide range of age, ethnicity, and comorbidities). In addition, the 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 patients 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 patients 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 patients (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 an initial visit, follow-up visits and the end of observation/final visit for each patient in the Case Report Form (CRF). Initial and follow-up visits occur during routine practice, the study protocol does not define exact referral dates for those visits.

The observation period for each patient will be at least 12 months or the whole treatment period with finerenone if patient permanently discontinues treatment prematurely. Please note that during temporary finerenone treatment pauses of ≤ 6 months, the patient 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 patient should be followed up at least 30 days after receiving the last finerenone therapy.

Baseline or Initial visit

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

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

Follow-up visit(s)

It is assumed, that according to clinical practice, follow-up visits will happen approximately every 3 months during the 1st year of treatment and every 6 months thereafter.

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

End of Observation/Final Visit

The final data collection (end of observation) is after 36 months or at the end of study (whatever is earlier).

At this final observation point, the patient'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. patient lost to follow-up, consent withdrawn by patient, investigator decision, pregnancy, lack of efficacy, (Serious) Adverse Event/Adverse Drug Reaction, patient died, permanent treatment discontinuation of finerenone (non-administration of finerenone > 6 months) resulting in change of therapy (which therapy and reason for switch), center closed, study terminated by Bayer AG.

Lost to follow-up

A patient will be considered as 'lost to follow-up' if the last documentation of any information was 3 months prior to the planned observation period (end of study).

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

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

	Baseline visit	Follow-up visit(s)	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
Healthcare resource utilization (inpatient/outpatient/emergency visits)	X	X	X
Diabetic retinopathy	X	X	X
Sampling of blood and urine samples for biobanking (for patients in the US only)**	X	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 patient (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) 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):

- 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
- Type, and duration of concomitant secondary 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[1]
  - Digoxin

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

- Betablocker
- Diuretics
  - Loop
  - Potassium sparing
- Potassium supplements
- Potassium binders
- Herbal therapy
- Traditional Chinese medicine
- Anti-thrombotic treatment
  - Aspirin
  - 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 overall and by MedDRA PTs
- Occurrence of hyperkalemia
  - Occurrence of hyperkalemia leading to 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 inpatient[2], outpatient and emergency visits
- Occurrence of newly diagnosed diabetic retinopathy or progression of existing disease at study entry

9.3.4 Patient characteristics/demography

- Year of birth
- Ethnic group
- Race (black/non-black)[3]

[2] Inpatient visits are defined as ≥1 overnight stay

[3] 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

- 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[4] 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 (y/n)

Variables collected at post-baseline visits:

- Serum creatinine[5]
- Serum[6] potassium
- Result of urine test:
    - Presence of blood

[4] Plasma values are also accepted.

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

[6] Plasma values are also accepted.

- Presence of other sediments
- Urinary tract infection (Y/N)

9.4 Data sources

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

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

9.5 Study size

Global study

4000 patients are planned to be enrolled.

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 section 9.7.4.

With a sample size of 4,000 patients, for potential incidence proportions of 1%, 5%, 10% and 50%, respectively, the following precisions can be expected:

# of patients	Incidence proportion (%)	95% CI of incidence proportion	Width (%) of 95% CI
4,000	1%	(0.7%, 1.4%)	0.7%
	5%	(4.3%,5.7%)	1.4%
	10%	(9.1%, 10.9%)	1.9%
	50%	(48.5%, 51.5%)	3.1%

The 50% incidence proportion maximizes the precision width, therefore, maximum width with 4,000 patients will not be greater than 3.1%.

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:

# of patients	Incidence proportion (%)	95% CI of incidence proportion	Width (%) of 95% CI
400	1%	(0.0%, 2.0%)	2.0%
	5%	(2.9%, 7.1%)	4.3%
	10%	(7.1%, 12.9%)	5.9%
	50%	(45.1%, 54.9%)	9.8%

The 50% incidence proportion maximizes the precision width, therefore, maximum width with 400 patients will not be greater than 9.8%.

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).

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 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 patient numbers are sufficient and if required for local reasons. Whenever reasonable, data will be stratified by subgroups (e.g. age, sex, baseline characteristics).

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

Interim analysis will consist of demographic and baseline data of patients 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). The SAP will be finalized before study database lock. The SAP is available upon request (see Annex 1).

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, ACE-I or ARB, MRA, Any RAS Inhibitor) will be tabulated by patient frequencies.

Number of patients with minimum follow-up will be displayed by suitable categories. The mean and median length of follow-up together with the patient-years will be presented for the primary endpoint.

9.7.3 Analysis of primary endpoint(s)

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
- Actions taken after finerenone introduction (e.g continue treatment, addition of second therapy, interrupt treatment, discontinue treatment)
- Actions taken after finerenone interruption (e.g restart finerenone alone, introduce concomitant therapy, discontinue finerenone)
- Treatment pathways for secondary 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 sunburst plots.

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

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.

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 patient-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 inpatient, outpatient and emergency 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 section 9.7.4, AEs/SAEs will be summarized based on the total study population (overall population).

The occurrence, duration, treatment, severity and outcome of AEs, SAEs, and ARs will be listed.

More details will be provided in the SAP.

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 patient'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 patients 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 patient 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).

9.8.2 Quality review

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. 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 quality reviews will be described in the Quality Review Plan (QRP). The QRP is available upon request (see Annex 1).

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

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 patient 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 patient 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]).

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 Patient information and consent

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

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

If a patient 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 patients, is read and explained to the patient or the patient's legally acceptable representative. The patient or the patient's legally acceptable representative have to orally consent to the patient'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 patients prior to the beginning of the observation.

10.5 Patient insurance

In this observational study, data on routine treatment of patients 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 patient 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 patient additionally by a patient 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 patient and investigator.

No study medication will be provided to patients. 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.

All records identifying the subject will be kept confidential and will not be made publicly available. Patient names will not be supplied to Bayer AG. If the patient 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 patients' 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 patient. 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 patient 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 inpatient 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).

  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 patient 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

11.2 Collection

Starting with the first application of finerenone after enrollment into the study, all non-serious adverse events (AE) must be documented on the AE Report Form or in the CRF/EDC system and forwarded to the MAH within 7 calendar days (for OS inside the EU) or if required by local regulations of participating country)/ 30 days (for OS that involve only countries outside the EU) of awareness. All serious AEs (SAE) must be documented and forwarded 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 patient. However, any AE/SAE - regardless of the relationship and the seriousness - occurring 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 patient 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 patient'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.

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 patients, without prior approval from the MAH.

13. References

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Annex 1: List of stand-alone documents

Document Name

- 21785_<Investigator list>; <v (number)>, <dd-MMM-yyyy>
- 21785_<Country & Site list>; <v (number)>, <dd-MMM-yyyy>
- 21785_<Steering/Adjudication/Publication Committee Members>; <v (number)>, <dd-MMM-yyyy>
- 21785_<Steering/Adjudication/Publication Committee Charter>; <v (number)>, <dd-MMM-yyyy>
- 21785_<CRF>; <v (number)>, <dd-MMM-yyyy>
- 21785_<Detailed list of variables>; <v (number)>, <dd-MMM-yyyy>
- 21785_<EDC System>; <v (number)>, <dd-MMM-yyyy>
- 21785_<EDC System Validation>; <v (number)>, <dd-MMM-yyyy>
- 21785_<DMP>; <v (number)>, <dd-MMM-yyyy>
- 21785_<SAP>; <v (number)>, <dd-MMM-yyyy>
- 21785_<QRP>; <v (number)>, <dd-MMM-yyyy>
- 21785_<MRP>; <v (number)>, <dd-MMM-yyyy>
- 21785_<local protocol amendment> <(county)>; <v (number)_(country ID)>, <dd-MMM-yyyy>

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:

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:

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:

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?	☐	☐	☒	

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

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:

Annex 3: Additional information

Not applicable

Annex 4: Description of updates and amendments

None

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 1.0; 09 February 2022
IMPACT study number	21785
Study type / Study phase	Observational, post-approval ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	<Study not yet registered>
NCT number	<Study not yet registered>
Active substance	Finerenone (BAY-94-8862) Non-steroidal mineralocorticoid receptor (MR) antagonist ATC code: C03DA05
Medicinal product	Kerendia©
Product reference	Not yet available – will be added once available.
Procedure number	EMEA/H/C/005200/0000
US NDA number	NDA 215341 (tablet; oral)
Study Initiator and Funder	Bayer, AG

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

Signatories

- PPD (OS Conduct Responsible)
- PPD (Qualified Person responsible for Pharmacovigilance (QPPV))
- PPD (OS Medical Expert)
- PPD (MAH contact person; OS Regulatory Affairs responsible)
- PPD (OS Safety Lead)
- PPD (OS Statistician)
- PPD (OS Data Manager)
- PPD (OS Epidemiologist)
- PPD (OS Health Economics and Outcomes Research (HEOR) responsible)

Signature Page for VV-90381 v1.0

Reason for signing: Approved	Name: PPD Role: OS Conduct Responsible Date of signature: 14-Feb-2022 09:47:17 GMT+0000
Reason for signing: Approved	Name: PPD Role: HEOR Project Lead Date of signature: 14-Feb-2022 09:59:19 GMT+0000
Reason for signing: Approved	Name: PPD Role: OS Medical Expert Date of signature: 14-Feb-2022 10:02:29 GMT+0000
Reason for signing: Approved	Name: PPD Role: OS Safety Lead Date of signature: 14-Feb-2022 10:17:52 GMT+0000
Reason for signing: Approved	Name: PPD Role: OS Epidemiologist Date of signature: 14-Feb-2022 12:23:03 GMT+0000
Reason for signing: Approved	Name: PPD Role: OS Data Manager Date of signature: 14-Feb-2022 12:49:10 GMT+0000
Reason for signing: Approved	Name: PPD Role: Regulatory Affairs Responsible Date of signature: 14-Feb-2022 18:53:07 GMT+0000

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Reason for signing: Approved	Name: PPD Role: OS Statistician Date of signature: 17-Feb-2022 09:41:24 GMT+0000

Reason for signing: Approved	Name: PPD Role: QPPV Date of signature: 18-Feb-2022 08:55:44 GMT+0000

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