Postauthorisation Safety Study (PASS) Information

Acronym/title	FIRST-2.5: Finerenone Research of Early Safety and Effectiveness, Part 2.5
Protocol version and date	v 2.0, 03 JUL 2024
IMPACT study number	22663
Study type/study phase	Postapproval ☒ 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) ATC code: C03DA05
Medicinal product	Kerendia
Product reference	EU/1/21/1616

Comparator/reference therapy	Patients with chronic kidney disease and type 2 diabetes not using finerenone
Study initiator and funder	Bayer AG, 51368 Leverkusen
Research question and objectives	This study addresses the research question of whether finerenone is effective and safe when used in real-world populations of adult patients with chronic kidney disease (CKD) and type 2 diabetes (T2D) in the United States compared with that in patients with CKD and T2D not using finerenone. The primary objective in this study is the following: • To assess the effectiveness of finerenone by estimating the risk of a composite cardiovascular outcome (i.e., first occurrence of fatal or nonfatal acute myocardial infarction or hospitalisation for heart failure) in patients with CKD and T2D initiating finerenone compared with that in patients with CKD and T2D not using finerenone

	The secondary objectives in this study are the following: • To estimate the risk of the individual components of a composite cardiovascular outcome (i.e., first occurrence of fatal or nonfatal acute myocardial infarction; first occurrence of hospitalisation for heart failure) in patients with CKD and T2D initiating finerenone compared with that in patients with CKD and T2D not using finerenone (in the same primary study cohort as the primary analysis). • To estimate the risk of new-onset heart failure (i.e., no previous history of heart failure) in patients with CKD and T2D initiating finerenone compared with that in patients with CKD and T2D not using finerenone (in a subset of the primary study cohort from which patients with a history of heart failure are excluded). • To estimate the risk of a decline in urine albumin-creatine ratio (UACR) (i.e., first occurrence of specific UACR decline thresholds) in patients with CKD and T2D initiating finerenone compared with that in patients with CKD and T2D not using finerenone (in a subset of the primary study cohort of patients with baseline UACR values). • To assess the safety of finerenone by estimating the risk of hyperkalaemia in patients with CKD and T2D initiating finerenone compared with that in patients with CKD and T2D not using finerenone • To estimate the risk of the above mentioned outcomes in clinically relevant subgroups of patients with CKD and T2D initiating finerenone compared with that in patients with CKD and T2D not using finerenone • To assess the effectiveness of initiating finerenone and titrating dosage according to the approved label by estimating the risk of outcomes of interest in patients with CKD and T2D initiating finerenone and uptitrating to 20 mg (when recommended) compared with that in patients with CKD and T2D not using finerenone The exploratory objectives in this study are the following: • To estimate the risk of all-cause mortality in patients with CKD and T2D initiating finerenone compared with that in patients with CKD and T2D not using finerenone • To describe the change in UACR over time at 4 months and 12 months in patients with CKD and

	T2D initiating finerenone and in patients with CKD and T2D not using finerenone
Country of study	United States
Author	PPD RTI Health Solutions

Marketing authorisation holder

Marketing authorisation 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.

1. Table of contents

2. List of abbreviations

ACEi	Angiotensin-converting Enzyme Inhibitors
ACEi/ARB	Angiotensin-converting Enzyme Inhibitors/Angiotensin Receptor Blockers
AMI	Acute Myocardial Infarction
ARB	Angiotensin Receptor Blockers
ATT	Average Treatment Effect in the Treated
CI	Confidence Interval
CKD	Chronic Kidney Disease
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus Disease 2019
DALY	Disability-adjusted Life-year
DPP-4i	Dipeptidyl Peptidase-4 Inhibitor
eGFR	Estimated Glomerular Filtration Rate
EHR	Electronic Health Record
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ESKD	End-stage Kidney Disease
EU	European Union
FDA	Food and Drug Administration
FOUNTAIN	Finerenone Multidatabase Network Data Generation
GLP-1 RA	Glucagon-like Peptide-1 Receptor Agonists
GPP	Guidelines for Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practices
HbA1c	Glycated Haemoglobin A1c
HR	Hazard Ratio
ICD-10-CM	*International Classification of Diseases, Tenth Revision, Clinical Modification*
IPC	Inverse Probability of Censoring
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
MRA	Mineralocorticoid Receptor Antagonists
N/A	Not Applicable
NNH	Number Needed to Harm
nsMRA	Non-steroidal Mineralocorticoid Receptor Antagonists
OQ	Office of Quality

OS	Observational Study
PAS	Postauthorisation Study
PASS	Postauthorisation Safety Study
QC	Quality Control
QPPV	Qualified Person responsible for Pharmacovigilance
RR	Relative Risk
RTI	RTI International
RTI-HS	RTI Health Solutions
SAP	Statistical Analysis Plan
SGLT2i	Sodium-glucose Cotransporter 2 Inhibitors
sIPT	Stabilised Inverse Probability of Treatment
SOP	Standard Operating Procedure
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
T1D	Type 1 Diabetes
T2D	Type 2 Diabetes
UACR	Urine Albumin-Creatine Ratio
US	United States

3. Responsible parties

3.1. Main responsible parties

Role: PPD
Name: PPD
Company: Bayer AG

Role: PPD
Name: PPD
Company: Bayer AG

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Role: PPD
Name: PPD
Company: Bayer AG

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

3.2. Further responsible parties

Role: PPD

Name: PPD

Company: RTI Health Solutions

Information on the Executive Advisory and Publication Committee Members are kept as stand-alone documents (Annex 1).

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	FIRST-2.5: Finerenone Research of Early Safety and Effectiveness, Part 2.5
Protocol version and date	2.0, 03 JUL 2024
IMPACT study number	22663
Study type/Study phase	Postapproval ☒ PASS Joint PASS: ☐ YES ☒ NO
Author	PPD, FISPE, RTI Health Solutions
Rationale and background	Finerenone is an oral, selective, non-steroidal mineralocorticoid receptor antagonist for the treatment of chronic kidney disease (CKD) in patients with type 2 diabetes (T2D) in the United States (US) and other countries. This study will evaluate the effectiveness and safety of finerenone in real-world use in the US.
Research question and objectives	This study will address the research question of whether finerenone is effective and safe when used in real-world populations of adult patients in the US with CKD and T2D compared with that in patients with CKD and T2D not using finerenone. The primary objective is to assess the effectiveness of finerenone by estimating the risk of a composite cardiovascular outcome (i.e., first occurrence of fatal or nonfatal acute myocardial infarction or hospitalisation for heart failure) in patients with CKD and T2D initiating finerenone compared with that in patients with CKD and T2D not using finerenone.

	The secondary objectives in this study are the following: • To estimate the risk of the individual components of a composite cardiovascular outcome (i.e., first occurrence of fatal or nonfatal acute myocardial infarction; first occurrence of hospitalisation for heart failure) in patients with CKD and T2D initiating finerenone compared with that in patients with CKD and T2D not using finerenone (in the same primary study cohort as the primary analysis). • To estimate the risk of new-onset heart failure (i.e., no previous history of heart failure) in patients with CKD and T2D initiating finerenone compared with that in patients with CKD and T2D not using finerenone (in a subset of the primary study cohort from which patients with a history of heart failure are excluded). • To estimate the risk of a decline in urine albumin-creatine ratio (UACR) (i.e., first occurrence of specific UACR decline thresholds) in patients with CKD and T2D initiating finerenone compared with that in patients with CKD and T2D not using finerenone (in a subset of the primary study cohort of patients with baseline UACR values) • To assess the safety of finerenone by estimating the risk of hyperkalaemia in patients with CKD and T2D initiating finerenone compared with that in patients with CKD and T2D not using finerenone • To estimate the risk of the above mentioned outcomes in clinically relevant subgroups of patients with CKD and T2D initiating finerenone compared with that in patients with CKD and T2D not using finerenone • To assess the effectiveness of initiating finerenone and titrating dosage according to the approved label by estimating the risk of outcomes of interest in patients with CKD and T2D initiating finerenone and uptitrating to 20 mg (when recommended) compared with that in patients with CKD and T2D not using finerenone The exploratory objectives in this study are the following: • To estimate the risk of all-cause mortality in patients with CKD and T2D initiating finerenone compared with that in patients with CKD and T2D not using finerenone • To describe the change in UACR over time at 4 months and 12 months in patients with CKD and

	T2D initiating finerenone and in patients with CKD and T2D not using finerenone
Study design	This is a new user cohort study based in existing healthcare data of patients with CKD and T2D initiating finerenone and patients with CKD and T2D not using finerenone.
Population	The study cohort will be composed of adults (aged ≥ 18 years) with CKD and T2D who are eligible for finerenone prescription during the time period since finerenone became available in the US (beginning 09 July 2021). The study cohort will identify patients who initiate finerenone (Time 0 = finerenone initiation date) and a comparator group of individuals with CKD and T2D not using finerenone (Time 0 = all dates with a recorded diagnosis of CKD meeting the inclusion criteria). For inclusion, patients will be required to have sufficient enrolment in the data source, have no previous use of finerenone, be aged 18 years or older, and fulfil algorithms for the diagnoses of T2D and CKD. Patients will be excluded if they have evidence of type 1 diabetes, end-stage kidney disease or kidney cancer, or contraindications to or conditions warning against treatment with finerenone (i.e., adrenal insufficiency, estimated glomerular filtration rate < 25 mL/min/1.73 m^2, recent hyperkalaemia diagnosis or serum potassium > 5.0 mEq/L, use of a strong CYP3A4 inhibitor, pregnancy, or hepatic impairment). Patients will be followed from Time 0 until occurrence of a study outcome or until the end of the study period, disenrollment from the data source, or deviation from their treatment strategy.
Variables	Finerenone exposure will be evaluated using medication prescribing and dispensing records. Outcomes will be identified using recorded diagnoses or laboratory data. Patient characteristics will be evaluated with diagnosis, procedure, laboratory test result, and medication records.
Data sources	This study will be conducted using existing healthcare data from the US. Considered data sources include the HealthVerity® Chronic Kidney Disease Masterset, which includes closed administrative healthcare claims, electronic medical records, and laboratory testing results. Additional data sources may be considered to increase the sample size or representativeness of the study sample. If multiple data sources are used, meta-analytic methods may be considered, as appropriate, to generate summary estimates across data sources.

Study size	Sample size estimates suggest that there would be a greater than 80% probability of the 95% confidence interval of the relative risks to exclude 1 at total sample sizes of approximately 30,000 individuals (2,727 finerenone users, and the rest comparators) for the higher estimate of composite cardiovascular outcome incidence and 60,000 individuals (5,455 finerenone users) for the lower estimate of composite cardiovascular outcome incidence. For secondary effectiveness and safety outcomes with lower expected incidence, larger sample sizes would be required to achieve the same level of precision.
Data analysis	The characteristics of treated and untreated groups will be described. Incidence rates of outcomes by treatment group will be estimated, and the cumulative incidence over time will be plotted. Outcome occurrence in the treatment groups will be compared with the stabilised inverse probability of treatment-weighted hazard ratios and 95% confidence intervals. Time-specific risk ratios and risk differences will be estimated to describe potentially changing risk over time. Subgroup analyses will be performed, and sensitivity analyses and negative control outcomes will evaluate the impact of potential biases. A secondary objective evaluating a different treatment strategy of finerenone initiation and label-directed uptitration will also be evaluated.
Milestones	The data collection (i.e., start of data extraction for the secondary use of data) is expected to start 01 October 2024 and end 30 June 2025, with the final report of study results expected by 31 December 2025.

5. Amendments

Table 1: Amendments and updates

Amendment number	Reason for amendment	New version number	Effective date
AM01	• Inclusion of change in UACR endpoint (time to 30% decline) as a secondary outcome, with potential consideration of other threshold values • Clarification that the secondary analyses of individual components of the primary composite outcome will be performed in the same analysis set as the primary composite outcome • Clarification that secondary subgroup analyses and secondary treatment strategy analyses may be performed for outcomes other than the primary compositive cardiovascular outcome • Removal of new-onset atrial fibrillation as an exploratory outcome • Inclusion of change in UACR over time at 4 months and 12 months as exploratory outcomes • Change of data source to HealthVerity® Chronic Kidney Disease Masterset and associated changes to the Representativeness, Study Size, Data Management, Quality Control, and Protection of Human Subjects sections	v 2.0	03 JUL 2024

AM = amendment; UACR = urine albumin-creatine ratio.

6. Milestones

Table 2 presents planned milestones for the project. These milestones are based on 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 that do not constitute a need for a formal protocol amendment are tracked in a stand-alone document (Annex 1).

Table 2. Milestones

Milestone	Planned date
PRC approval	14-MAR-2024
Public registration of study protocol	30-JUL-2024
Start of data collection[a]	01-OCT-2024
Start of data analysis	01-OCT-2024
End of data collection/analysis	30-JUN-2025
Final report of study results	31-DEC-2025

PRC = protocol review committee.
[a] For secondary use of data, the start of data collection is the date from which data extraction starts.

7. Rationale and background

Chronic kidney disease (CKD) is defined as abnormalities of kidney structure or function that are present for more than 3 months and have serious health implications. Patients with CKD have an increased risk of kidney failure, cardiovascular disease, and death. Thus, the treatment goal in CKD is not only to prevent dialysis or transplant but also to reduce the cardiovascular disease burden; this is especially relevant among patients with diabetes [1,2]. Patients with type 2 diabetes (T2D) have a high prevalence and incidence of CKD [3]. The prevalence of CKD among patients with diabetes is 38% in the United States (US) [4].

Disease management strategies for patients with CKD and T2D include treatment of risk factors for CKD (e.g., high blood pressure) with drugs or lifestyle modification [5], with the goal to prevent further loss of kidney function or progression to end-stage kidney failure. Multiple available therapies are indicated for (or commonly used for, though not formally indicated) the prevention and treatment of CKD among patients with T2D in the US, including renin-angiotensin system inhibitor drugs (e.g., angiotensin-converting enzyme inhibitors [ACEi], angiotensin receptor blockers [ARB]), sodium-glucose cotransporter 2 inhibitors (SGLT2i), and finerenone.

Finerenone is an oral, selective non-steroidal mineralocorticoid receptor antagonist (nsMRA) developed by Bayer for the treatment of CKD in patients with T2D. Because of its mechanism of action, finerenone is expected to have a lower risk of inducing hyperkalaemia than spironolactone—a steroidal nonselective mineralocorticoid receptor antagonist (MRA)—which has been shown in clinical studies [6]. In the phase 3, event-driven, placebo-controlled FIDELIO trial [7], results showed that, among patients with stage 3 or 4 CKD with severely elevated albuminuria and T2D, finerenone, when added to standard of care, reduced the incidence of CKD progression [8] and a composite cardiovascular outcome that included time to cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalisation for heart failure [9]. In the FIGARO trial [10], patients receiving finerenone had less severe kidney impairment, either stage 2 to 4 CKD and moderately elevated albuminuria, or stage 1 or 2 CKD and severely increased albuminuria, but the cardiovascular benefit seen in the FIDELIO trial extended to those patients with less kidney impairment but who were still at high cardiovascular risk [11]. In the prespecified pooled analysis of the FIDELIO and

FIGARO trials (FIDELITY) [12], the positive effects were demonstrated for both CKD and cardiovascular outcomes across a broad spectrum of CKD [12].

Finerenone received approval from the US Food and Drug Administration (FDA) on 09 July 2021 and is indicated for adult patients with CKD associated with T2D to reduce the risk of sustained estimated glomerular filtration rate (eGFR) decline, kidney failure, cardiovascular death, nonfatal myocardial infarction, and hospitalisation for heart failure [13].

Because patients receiving finerenone in clinical practice may differ from patients who are included in controlled clinical trials, it is important to evaluate the real-world effectiveness and safety of finerenone early after marketing approval as part of routine clinical practice. For example, pivotal trials of finerenone required participants to be on maximally tolerated doses of an ACEi or ARB, and participants needed to meet strict definitions of CKD, including persistent very high albuminuria and eGFR less than 60 [14,15]; however, the US label for finerenone [13] and treatment guidelines [16] allow for broader use of finerenone in less severe kidney disease and without comedication use.

The FIRST-2.5 study is part of the larger research programme conducted within the Finerenone Multidatabase Network Data Generation (FOUNTAIN) research programme. The FIRST-2.5 study is the third study of the FIRST programme, a series of studies conducted in cohorts of patients with CKD and T2D in clinical practice. The goal of the currently ongoing FIRST-1 study is to describe renal and cardiovascular outcomes and healthcare resource utilisation among patients who initiate ACEi/ARB, SGLT2i, glucagon-like peptide-1 receptor agonists (GLP-1 Ras), or steroidal MRA. FIRST-2.0 will describe patients who initiate finerenone in the initial time period after FDA approval in the US and will describe temporal changes in eGFR and urine albumin-creatinine ratio (UACR) and the incidence of short-term clinical outcomes. The current study, FIRST-2.5, will evaluate the effectiveness and safety of finerenone in real-world use by estimating the association of finerenone use with cardiovascular events and other secondary and exploratory endpoints in patients with CKD and T2D in the US.

8. Research questions and objectives

This study addresses the research question of whether finerenone is effective and safe when used in real-world populations of adult patients in the US with CKD and T2D compared with that in patients with CKD and T2D not using finerenone. The primary treatment strategy evaluated by this study will be initiating treatment with finerenone according to the approved label in the US and not discontinuing treatment, except in the case of hyperkalaemia or end-stage kidney failure (Section 9.3.2.1).

8.1. Primary objective

The primary objective in this study is the following:

- To assess the effectiveness of finerenone by estimating the risk of a composite cardiovascular outcome (i.e., first occurrence of fatal or nonfatal acute myocardial infarction or hospitalisation for heart failure) in patients with CKD and T2D initiating finerenone compared with that in patients with CKD and T2D not using finerenone.

8.2. Secondary objectives

The secondary objectives in this study are the following:

- To estimate the risk of the individual components of a composite cardiovascular outcome (i.e., first occurrence of fatal or nonfatal acute myocardial infarction; first

occurrence of hospitalisation for heart failure) in patients with CKD and T2D initiating finerenone compared with that in patients with CKD and T2D not using finerenone (in the same primary study cohort as the primary analysis).

- To estimate the risk of new-onset heart failure in patients with CKD and T2D initiating finerenone compared with that in patients with CKD and T2D not using finerenone (in a subset of the primary study cohort from which patients with a history of heart failure are excluded).
- To estimate the risk of a decline in UACR (i.e., first occurrence of specific UACR decline thresholds) in patients with CKD and T2D initiating finerenone compared with that in patients with CKD and T2D not using finerenone (in a subset of the cohort of patients with baseline UACR values).
- To assess the safety of finerenone by estimating the risk of hyperkalaemia in patients with CKD and T2D initiating finerenone compared with that in patients with CKD and T2D not using finerenone.
- To estimate the risk of the above mentioned outcomes in clinically relevant subgroups of patients with CKD and T2D initiating finerenone compared with that in patients with CKD and T2D not using finerenone.
- To assess the effectiveness of initiating finerenone and titrating dosage according to the approved label by estimating the risk of outcomes of interest in patients with CKD and T2D initiating finerenone and uptitrating to 20 mg (when recommended) compared with that in patients with CKD and T2D not using finerenone.

8.3. Exploratory objectives

The exploratory objectives in this study are the following:

- To estimate the risk of all-cause mortality in patients with CKD and T2D initiating finerenone compared with that in patients with CKD and T2D not using finerenone.
- To describe the change in UACR over time at 4 months and 12 months in patients with CKD and T2D initiating finerenone and in patients with CKD and T2D not using finerenone (in a subset of the cohort of patients with baseline UACR values).

9. Research methods

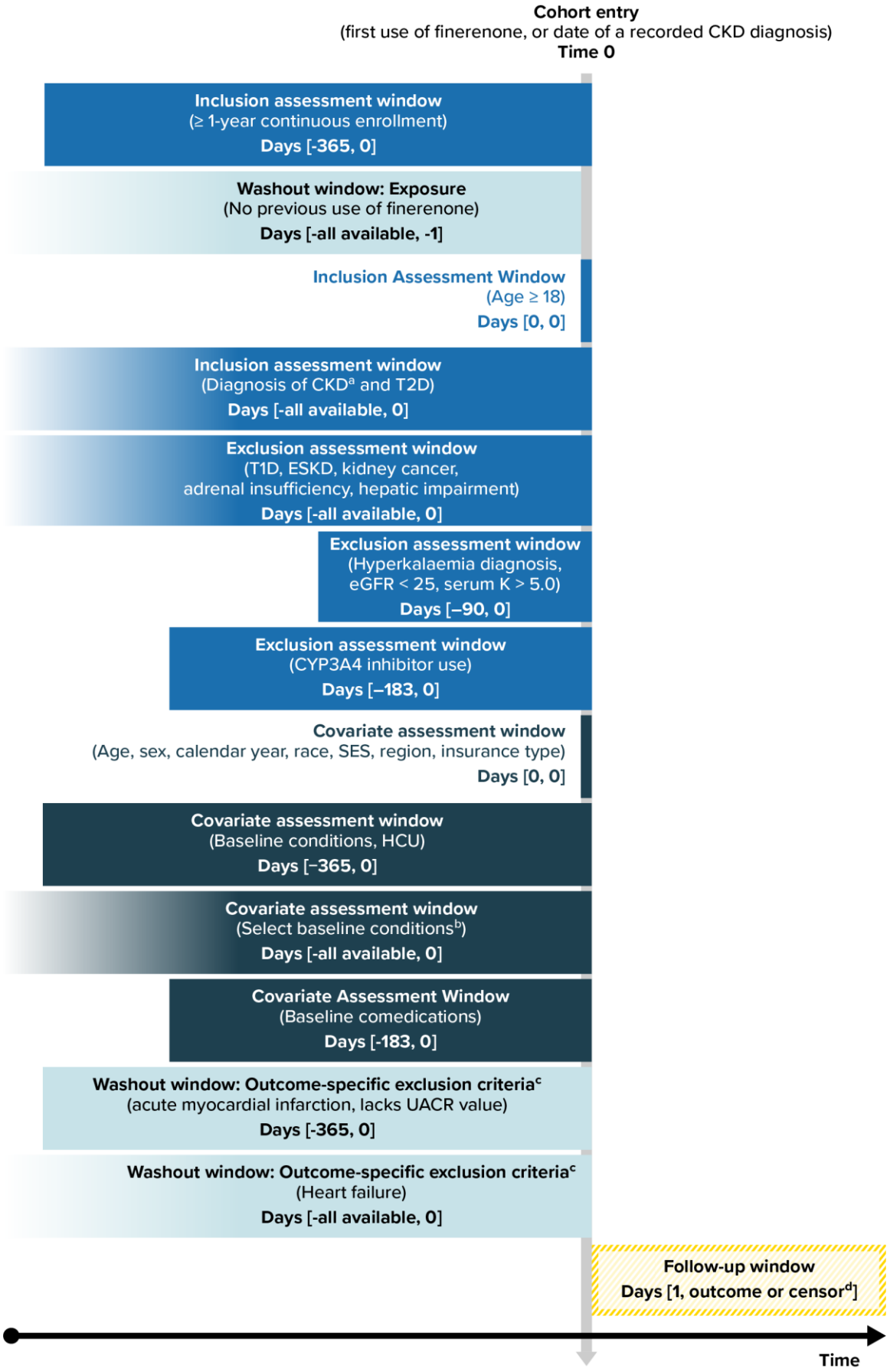
9.1. Study design

This is a new user cohort study utilising existing healthcare data of patients with CKD and T2D initiating finerenone compared with patients with CKD and T2D not using finerenone. The cohort design will allow for observation of all person-time since finerenone initiation and will correctly align the evaluation of eligibility criteria with the beginning of follow-up.

Time 0 will be identified for both the exposed and comparator groups (Section 9.2.1.1), and all variable assessment time windows (e.g., washout, covariate assessment, follow-up) will be anchored on Time 0 (Figure 1).

Before the start of the analyses, a statistical analysis plan (SAP) will be prepared to describe the details of the statistical techniques, define concepts, and operationalise all study variables needed for analysis in the data source(s).

Figure 1: Study design overview



AMI = acute myocardial infarction; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; HCU = healthcare utilisation; K = potassium; SES = socioeconomic status; T1D = type 1 diabetes; T2D = type 2 diabetes.

[a] Identified with recorded diagnosis of CKD or eGFR measurements.

[b] Duration of T2D; amputations of lower limb; duration of CKD; CKD stage.

[c] Outcome-specific washout criteria will be applied to create the relevant analysis sets for each outcome.

[d] End of the study period; disenrollment from the database; deviation from the treatment strategy (finerenone use or non-use).

9.2. Setting

9.2.1. Study population and selection criteria

The source population for the study will consist of adults with CKD and T2D who are eligible for finerenone prescription after the approval of finerenone in the US. The study cohort will identify patients who initiate finerenone and a comparator group of individuals with CKD and T2D not using finerenone. All eligible adult individuals (aged ≥ 18 years) in the data source will be selected for the study cohort without sampling from the source population. There will be no restrictions of the study population based on sex, race, or ethnicity.

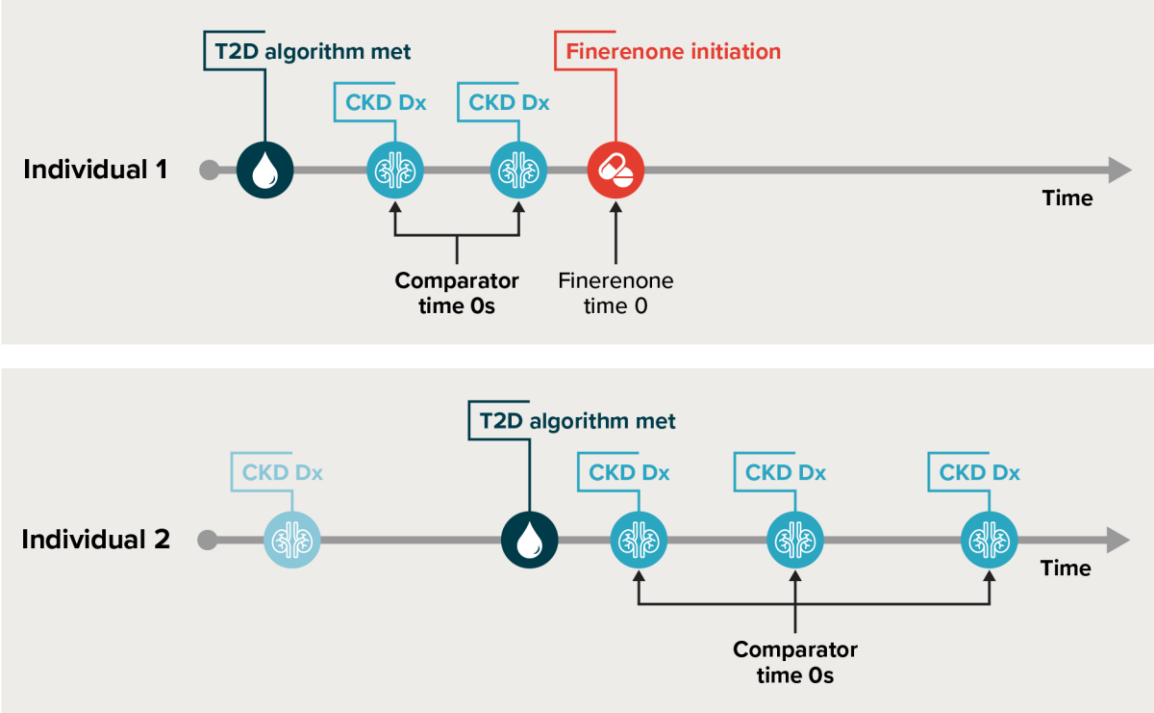
9.2.1.1. Study entry and Time 0

The identification of potential Time 0s for the exposure and comparator groups is illustrated in Figure 2—a schematic of 2 hypothetical individuals with diagnoses of CKD and T2D, 1 of whom initiates finerenone.

The date of an individual's first observed prescription for finerenone during the cohort entry period will be Time 0 for the exposure group (i.e., the date a patient was initially prescribed finerenone). The selection criteria (Section 9.2.1.2) for the exposed group will be evaluated on Time 0. Only the first observed finerenone initiation date per person will be considered.

The comparator group of patients with T2D and CKD untreated with finerenone will consist of all encounters during which an individual was recognised as having CKD and was eligible to be prescribed finerenone but was not. All calendar dates with an encounter with a recorded diagnosis of CKD will be considered as potential Time 0s. The selection criteria (Section 9.2.1.2) will be evaluated at every identified potential Time 0, and all Time 0s meeting the selection criteria will be included in the comparator group. Multiple comparator Time 0s per person may be eligible and selected (Figure 2), including dates for individuals who subsequently initiate finerenone (i.e., information on an individual's future prescription or dispensing for finerenone will not be used to define eligibility). Although this is difficult to confirm before conducting the analysis, the general assumption is that patients with CKD and T2D would visit a physician at least once per year. At each interaction, the physician could potentially recognise the patient as having CKD (i.e., record the diagnosis in the electronic health record [EHR]). When combining the above assumption with an estimated maximum study period of 3 years, we anticipate the number of potential Time 0s per individual in the comparator group to generally be less than 5.

Figure 2: Identification of treated and untreated Time 0s



CKD = chronic kidney disease; D_x = diagnosis; T2D = type 2 diabetes.
Note: The analytic cohort identified from these 2 hypothetical patients would consist of 1 observation in the exposure group and 5 observations in the comparator group. In individual 2, the first CKD diagnosis would not be an eligible untreated Time 0 because the patient had not yet met the T2D criterion.

9.2.1.2. Selection criteria

Individuals must meet all the following inclusion criteria on or before Time 0 to be included in the cohort:

- Active registration or continuous enrolment for at least 365 days in the data source before Time 0 (days [−365, 0])
- No recorded use of finerenone before Time 0 (days [−all available, 0])
- Aged 18 years or older on Time 0
- Diagnosis of T2D at any time on or before Time 0 (days [−all available, 0])
- Evidence of CKD on or before Time 0 (days [−all available, 0]), identified by meeting any of the following criteria:
  - A diagnosis code indicating CKD stage 1, 2, 3, 4, or stage unspecified
  - Two UACR test results ≥ 30 mg/g separated by at least 90 days and no more than 540 days.
  - Two different eGFR test results ≥ 15 mL/min/1.73 m^2 AND < 90 mL/min/1.73 m^2 [17] separated by at least 90 days and no more than 540 days. If a reported eGFR test result is available in the data, it will be used as recorded to determine eligibility (as that was the eGFR value available to the prescribing clinician at the time of Time 0). If an eGFR value is not reported, but there is sufficient information to calculate the eGFR, it will be calculated using the creatinine-based 2021 CKD-EPI equation [18] (Section 9.3.1).

Individuals will be excluded if they meet any of the following exclusion criteria on or before Time 0:

- Type 1 diabetes (T1D) at any time on or before Time 0 (days [all available, 0]), as finerenone is not indicated for use in T1D
- Evidence of end-stage kidney disease (ESKD) at any time on or before Time 0 (days [all available, 0]) —as finerenone is not recommended to be initiated in individuals with ESKD or severely reduced eGFR—identified as any of the following criteria:
  - Two different eGFR test results < 15 mL/min/1.73 m^2 [17] separated by at least 90 days and no more than 540 days
  - Dependence on dialysis (at least 3 sessions over at least 90 days)
  - A diagnosis code indicating kidney failure or CKD stage 5 (*International Classification of Diseases, 10th Revision, Clinical Modification* [ICD-10-CM] code N18.5)
  - A diagnosis code indicating having a kidney transplant (ICD-10-CM code Z94.0)
- Diagnosis of kidney cancer at any time on or before Time 0 (days [−all available, 0]), as decreased renal function resulting from kidney cancer may differ in treatment response from diabetic CKD.
- A diagnosis of adrenal insufficiency (i.e., congenital adrenogenital disorders of enzyme deficiency, primary or secondary adrenocortical insufficiency, Addison's disease, pituitary neoplasm, or other pituitary disorder [19]) at any time on or before Time 0 (days [−all available, 0]), as finerenone is contraindicated in individuals with adrenal insufficiency [13]
- Evidence of hepatic impairment, including hepatic failure, fibrosis, cirrhosis, or chronic hepatitis, at any time on or before Time 0 (days [−all available, 0]), as treatment with finerenone is to be avoided in individuals with severe liver impairment [13]
- An eGFR measurement < 25 mL/min/1.73 m^2 on or in the 90 days before Time 0 (days [−90, 0]), as finerenone is not recommended to be initiated in individuals with eGFR < 25 mL/min/1.73 m^2 [13]
- Evidence of recent increased serum potassium or hyperkalaemia, as finerenone is not recommended for initiation in individuals with elevated serum potassium [13], identified as either of the following:
  - A serum potassium test result > 5.0 mEq/L on or in the 90 days before Time 0 (days [−90, 0])
  - A diagnosis code indicating hyperkalaemia on or in the 90 days before Time 0 (days [−90, 0])
- Use of a strong CYP3A4 inhibitor on or in the 183 days before Time 0 (days [−183, 0]), as finerenone is a CYP3A4 substrate and is contraindicated in users of strong CYP3A4 inhibitors [13]. Examples include the following [20,21]:
  - Cobicistat
  - Itraconazole

  - Ketoconazole
  - Posaconazole
  - Ritonavir
  - Telithromycin
  - Troleandomycin
  - Voriconazole
- Evidence of pregnancy measured on or in the 40 weeks before Time 0, as clinical practice guidelines discourage the use of finerenone during pregnancy [16]

9.2.1.3. Follow-up

Individuals will be followed-up from the day after Time 0 (i.e., day 1) until the first occurrence of 1 of the following:

- The date of an occurrence of the study outcome under evaluation (each outcome will be evaluated separately, and individuals may have different follow-up times for each outcome)
- Censoring at any of the following events:
  - End of the study period (i.e., end of available study data)
  - Loss to follow-up in the data source
  - Deviation from the treatment strategy defined on Time 0 for the primary analysis
    - Finerenone-exposed individuals discontinuing use of finerenone for reasons other than hyperkalaemia (pausing or discontinuing treatment for elevated serum potassium is consistent with treatment dose adjustment strategies [13]) or ESKD (discontinuing treatment for ESKD is consistent with treatment recommendations) [22]
    - Nonusers initiating finerenone

9.2.2. Study timeframe

The cohort entry period (the time period during which all Time 0s will be identified) will begin on 09 July 2021 (the date of FDA approval in the US) and will end at the latest available data in the data source at the time of analysis. Data from before 09 July 2021 will be used—and potentially back to 01 October 2015, as available—to define selection criteria, washout periods, and covariates.

9.2.3. Representativeness

The selection criteria for this study are designed to identify all individuals eligible for finerenone treatment according to the approved label [13] and medical society treatment recommendations [16]. Thus, the selection criteria for this real-world study differ from the more restrictive criteria used in pivotal randomised controlled trials [14,15]. In line with the approved label for finerenone in the US, this study includes a broader population than was included in the pivotal trials. Consequently, the results of this study will be representative of the on-label population in the US. This study will include all eligible individuals identified in the data source(s).

The initial data source used for this study will be the HealthVerity® Chronic Kidney Disease Masterset, which contains information on over 10 million unique patients, including those with commercial, Medicare Advantage, and Medicaid insurance plans.

9.3. Variables

9.3.1. Measures of kidney function

Determining the level of kidney function (i.e., eGFR and CKD stage) is required at numerous points in this analysis to determine study eligibility and define baseline CKD stage. Kidney function may be determined either with eGFR measurements, recorded CKD diagnoses, or UACR measurements.

When required to be calculated from recorded serum creatinine values, eGFR will be calculated using the creatinine-based 2021 CKD-EPI equation (without including cystatin-C) [18,23-27]:

$$eGFR = 142 \times \min\left(\frac{Scr}{\kappa}, 1\right)^{a_1} \times \max\left(\frac{Scr}{\kappa}, 1\right)^{a_2} \times c^{Age} \times d$$

Where:

- a_1 = −0.241 for female individuals and −0.302 for male individuals
- a_2 = −1.200
- c = 0.9938
- d = 1.012 for female individuals and 1 for male individuals
- κ = is 0.7 for female individuals and 0.9 for male individuals
- min indicates the minimum of $\frac{Scr}{\kappa}$ and 1, and max indicates the maximum of $\frac{Scr}{\kappa}$ and 1.
- The coefficient a_1 is used for levels of creatinine less than or equal to 0.9 mg/dL for male individuals and 0.7 mg/dL for female individuals.
- The coefficient a_2 is used for levels of creatinine greater than 0.9 mg per decilitre for male individuals and 0.7 mg per decilitre for female individuals.

CKD stage at Time 0 (Section 9.3.3.3) will be defined based on either the most recent eGFR level or recorded diagnosis of CKD stage on or before Time 0. CKD stage based on eGFR categories (mL/min/1.73 m^2) or diagnosis coding will be defined as follows:

- Stage 1: eGFR ≥ 90, normal or high
- Stage 2: eGFR 60-89, mildly decreased
- Stage 3: eGFR 30-59, mildly to severely decreased
- Stage 4: eGFR 15-29, severely decreased
- Stage 5: eGFR < 15 or treatment with chronic dialysis or kidney transplant, ESKD
- Stage unspecified (for individuals with only stage-unspecified CKD diagnosis codes)

Albuminuria will be measured using the most recent UACR [28] value on or during the 365 days before Time 0, and selection criteria will include both eGFR and UACR-based entry definitions of kidney function (Section 9.2.1.2). For those individuals with UACR values

available, the extent of albuminuria will be categorised as follows (UACR mg/g is approximately equivalent to albumin excretion rate mg/d):

- A1: < 30, normal to mildly increased
- A2: 30-300, moderately increased
- A3: > 300, severely increased
- Unknown, for individuals without baseline UACR values

The UACR categories will be identified if available, as they provide additional information regarding cardiovascular disease risk and kidney prognosis [5], but they will be defined as a separate variable from CKD stage; for CKD staging, only eGFR values or diagnosis codes will be used.

The most recent UACR value on or during the 365 days before Time 0 will be used as the baseline UACR value for the UACR-specific analysis set. Additional UACR laboratory values occurring during follow-up will be identified to define UACR-based outcomes.

Additionally, diagnoses of proteinuria and nephrotic syndrome will be identified. ICD-10-CM diagnosis codes for proteinuria do not indicate stage, and there may be considerable overlap between diagnosis-based measures and the UACR measurements for those with available laboratory values; however, diagnosis-based measures may be used in combination with laboratory test–based measures.

9.3.2. Exposure definition

Finerenone exposure will be identified from provider prescription records in EHRs or pharmacy dispensing records from pharmacy claims, as available. The first observed record for a finerenone prescription or dispensing during the study period will be considered the date of finerenone initiation. If any previous finerenone use is observed at any point before the finerenone prescription (using all available lookback data per person), the prescription will not be considered an incident prescription (i.e., each individual will contribute only 1 potential finerenone Time 0 to the study). Treatment discontinuation will be estimated from prescribing and pharmacy dispensing records from EHRs and/or claims data.

Combinations of prescribing and dispensing records may be used to define treatment periods, and discontinuation dates may be estimated from the available information in the database. Various grace periods and different sets of assumptions may be considered to define exposure periods based on the availability of different types of prescription data (i.e., EHR-based written prescription records and claims-based pharmacy dispensing) and will be described in the SAP.

9.3.2.1. Finerenone initiation treatment strategy

The treatment strategy evaluated by this study will be initiation and continuing use of finerenone. Deviation from the treatment strategy will be defined as discontinuation of finerenone for reasons other than elevated potassium or ESKD, which is consistent with the label and treatment recommendations.

Finerenone initiation will be defined as the first observed finerenone prescription during the study period. For the primary analysis, finerenone initiators will be permitted to up-titrate or down-titrate dosages while remaining adherent to the treatment strategy. Guidelines allow for pauses in finerenone treatment after the occurrence of elevated serum potassium [13]; thus, gaps in use or discontinuation of finerenone after an elevated serum potassium laboratory measurement or diagnosis of hyperkalaemia will not be considered deviation from the

treatment strategy. Additionally, the European Union (EU) label explicitly calls for discontinuation of finerenone in ESKD [22]; thus, discontinuation for ESKD will not be considered deviation from the treatment strategy.

9.3.2.2. Comparator, non-use treatment strategy

The treatment strategy for the comparator group will be not initiating finerenone. For the comparator group, previous use of finerenone at any point before Time 0 will be evaluated using all available data to ensure that the individuals are free of any previous use of finerenone. The non-use treatment strategy will require individuals to be free of finerenone use; individuals will be considered to have deviated from the treatment strategy if they initiate finerenone use during follow-up.

9.3.2.3. Finerenone initiation and titration treatment strategy

As a secondary analysis, an additional treatment strategy will be evaluated in which patients are required to initiate finerenone and up-titrate to the target daily dosage of 20 mg, per the approved US label [13]. Patients using this treatment strategy will be identified at finerenone initiation (either at 10 mg or 20 mg). Among those who initiate finerenone at 10 mg per day, failure to up-titrate to 20 mg per day by 10 weeks after initiation (more than twice the recommended 4-week period) will be considered deviation from the treatment strategy (unless serum potassium levels are greater than 4.8 mEq/L, as the US label instructs maintaining the 10-mg daily dosage). Those who initiate finerenone at 20 mg per day will be considered adherent to the treatment strategy. Subsequent down-titration back to 10 mg will be allowed, consistent with allowed dose adjustments [13].

9.3.3. Outcomes definition

Outcomes will be identified during follow-up in outcome-specific analysis sets (except where noted) using diagnosis and procedure coding.

9.3.3.1. Primary composite cardiovascular outcome

The primary composite cardiovascular outcome will evaluate the first occurrence of any of the following events during follow-up:

- An inpatient hospital diagnosis of fatal or nonfatal acute myocardial infarction [29]
- An inpatient hospitalisation with a primary diagnosis of heart failure [30]

Individuals with prior cardiovascular events are eligible for finerenone treatment; thus, those with an occurrence of these events before Time 0 may be included in the overall study cohort (before application of outcome-specific exclusion criteria). However, to ensure identification of cardiovascular outcomes that newly occur after Time 0, analysis of this composite cardiovascular outcome will be performed in an analysis set that also excludes individuals with an acute myocardial infarction diagnosis in the 365 days before Time 0. Those with a history of heart failure will be included in the analysis, and history of heart failure will be included as an adjustment variable.

9.3.3.2. Secondary outcomes

Secondary outcomes will include individual components of the primary composite cardiovascular outcome as well as additional safety and effectiveness outcomes of secondary interest.

9.3.3.2.1. Acute myocardial infarction

Finerenone is indicated in the US for the prevention of cardiovascular death and nonfatal acute myocardial infarction (AMI), among other events [13]. The AMI outcome will identify the first occurrence of an inpatient hospital diagnosis of fatal or nonfatal AMI [29] during follow-up. To ensure that AMI events identified during follow-up represent new events rather than continuing care for previous events occurring before Time 0, the analysis of this outcome will be performed in the same analysis set as the primary composite outcome, which also excludes individuals with an AMI diagnosis in the 365 days before Time 0.

9.3.3.2.2. Hospitalisation for heart failure

Finerenone is indicated in the US to prevent hospitalisations for heart failure, among other events [13]. Hospitalisation for the heart failure outcome will identify the first occurrence of an inpatient hospitalisation with a primary diagnosis of heart failure [30] during follow-up. This analysis will include individuals with a history of heart failure before Time 0, and history of heart failure will be included as an adjustment variable. No outcome-specific exclusion criteria will be applied, but this outcome will be evaluated in the same analysis set as the primary composite outcome.

9.3.3.2.3. New-onset heart failure

The US indication for finerenone includes the prevention of hospitalisation for heart failure, and the secondary hospitalisation for heart failure outcome (Section 9.3.3.2.2) will include individuals with a history of heart failure before Time 0. A secondary outcome will further evaluate new diagnoses of heart failure among individuals without a history of heart failure. The secondary new-onset heart failure outcome will evaluate the first occurrence of an inpatient hospital or emergency department diagnosis of heart failure [30] during follow-up. To ensure identification of new-onset heart failure, analysis of this outcome will be performed in an analysis set that also excludes individuals with a diagnosis of heart failure at any point before Time 0.

9.3.3.2.4. Change in UACR

In clinical trials, finerenone has been demonstrated to have beneficial effects on UACR [31,32], and UACR declines of 30% have been associated with favourable long-term kidney outcomes [32-34]. Guidelines for CKD management in patients with T2D recommend targeting 30% reductions in UACR to prevent CKD progression [35]. In this study, the secondary analysis will evaluate the time to a 30% decrease from baseline UACR values during follow-up; additional thresholds (e.g., 50% decline, 70% decline) may also be considered. This analysis will be performed in an analysis set of those with available baseline UACR laboratory values, and recorded UACR laboratory values during follow-up will be used to define the outcomes of interest.

9.3.3.2.5. Hyperkalaemia

Hyperkalaemia is listed in the warning and precautions section of the US and EU labels as a potential concern associated with finerenone use [13,22]. The secondary safety outcome of hyperkalaemia will evaluate the first occurrence of a hospitalisation or emergency department visit with a diagnosis code for hyperkalaemia [36] during follow-up.

As part of the study's selection criteria, individuals with a recent diagnosis of hyperkalaemia or elevated serum potassium will be excluded (Section 9.2.1.2), as finerenone initiation is not recommended in those with elevated serum potassium [16]. Thus, no additional outcome-specific exclusion criteria will be applied to the analysis of hyperkalaemia. Estimates of

hyperkalaemia incidence in secondary healthcare databases may vary widely depending on the operational definition used or the reference range for the serum potassium level at that laboratory [37,38].

9.3.3.3. Exploratory outcomes

9.3.3.3.1. All-cause mortality

The exploratory all-cause mortality outcome will evaluate the time to death, as recorded in the database.

9.3.3.3.2. Change in UACR values over time

The exploratory analysis of UACR values over time will be performed in the analysis set of those with available baseline UACR values. Recorded UACR values during follow-up will be identified to describe changes in UACR over time, specifically at 4 months and 12 months of follow-up.

9.3.4. Covariate definitions

Covariates include risk factors for renal progression [39,40], cardiovascular outcomes [41,42], or hyperkalaemia [43-45]. Variables potentially associated with the use or non-use of finerenone and the outcomes of interest—e.g., concomitant medications, comorbidities—will be identified for all cohort members before or on Time 0 using diagnosis, procedure, or medication information available in the data source. A detailed description of definitions and code lists for all covariates that will be used in the data source will be specified in the SAP. Covariates will be defined using ICD-10-CM diagnosis codes, laboratory records, procedure coding, or medication coding, as appropriate for each variable.

The following demographic characteristics will be evaluated as of Time 0:

- Age
- Sex
- Calendar year of Time 0
- Race and/or ethnicity (as available in the data)
- Socioeconomic status (as available in the data)
- US geographic region
- Insurance plan type

The following clinical characteristics of patients will be defined using the 365 days before and including Time 0, except where specified otherwise:

- Markers of T2D severity (as available in the data source) and components of the Diabetes Severity Complications Index [46,47] not listed elsewhere
  - Duration of T2D (in all available lookback, as available in the data source)
  - Insulin use
  - Haemoglobin A1c (glycated haemoglobin) (HbA1c) (most recent recorded laboratory value in the 183 days before and closest to Time 0, if available)
  - Hyperosmolar hyperglycaemic state
  - Ketoacidosis

  - Lower limb amputations (all available lookback, as available in the data source)
  - Neuropathy
  - Retinopathy
- Markers of kidney dysfunction severity
  - Duration of CKD (all available lookback, as available in the data source)
  - CKD stage, defined based on eGFR, or stage-specific diagnosis codes (using all available lookback) (Section 9.3.1)
  - Albuminuria stage defined based on UACR values (Section 9.3.1)
  - Proteinuria, defined based on diagnosis codes (Section 9.3.1)
  - Nephrotic syndrome, based on diagnosis codes (Section 9.3.1)
  - Glomerulonephritis
  - Renovascular disease
  - Polycystic kidney disease
  - Autoimmune disease
  - Gout/hyperuricaemia
  - Hospitalisation episodes for acute kidney injury

The following comorbidities will be defined using all available lookback before and including Time 0:

- Cardiovascular comorbidities
  - Acute myocardial infarction
  - Atherosclerosis
  - Atrial fibrillation
  - Cerebrovascular disease (stroke or transient ischaemic attack)
  - Congestive heart failure
  - Hypercholesterolaemia
  - Hyperlipidemia
  - Hypertension
  - Peripheral vascular disease
  - Unstable angina
- Other components of the Charlson Comorbidity Index or similar comorbidity score [48,49] (as single entities, not listed elsewhere)
  - Anaemia
  - Chronic obstructive pulmonary disease
  - Congestive heart failure
  - Dementia

  - Human immunodeficiency virus
  - Liver disease
  - Malignancy other than kidney cancer or nonmelanoma skin cancer
  - Paralysis
- Other comorbidities
  - Coronavirus disease 2019 (COVID-19) diagnosis
  - Hyperkalaemia (history of hyperkalaemia, more than 90 days before Time 0)
  - Osteoporosis
  - Pneumonia

The following lifestyle cardiovascular factors will be defined, as available in the data:

- Body mass index or evidence of obesity
- Smoking status
- Alcohol abuse

The following healthcare utilisation measures will be identified in the 365 days before and including Time 0 to characterise patients' healthcare access, healthcare-seeking behaviour, and indicators of disease state at the time of index medication initiation:

- Healthcare utilisation
  - Hospital visits and hospital admissions
  - Emergency department visits
  - Long-term care or skilled nursing facility residence
  - Number of eGFR laboratory tests performed
  - Number of serum potassium laboratory tests performed
- Preventive health services
  - Influenza vaccination
  - Pneumococcal vaccination
  - COVID-19 vaccination
  - Bone mineral density test
  - Screening mammogram
  - Other cancer screening
- Frailty indicators [50]
  - Arthritis
  - Bladder dysfunction
  - Dementia
  - Psychiatric illness
  - Weakness
  - Vertigo

The following comedications will be identified in the 183 days before and including Time 0 to characterise individuals' recent treatments and indicators of disease state at the time of index medication initiation:

- Medications for T2D
  - Alpha glucosidase inhibitors
  - Dipeptidyl peptidase-4 inhibitors (DPP-4i)
  - GLP-1 RA
  - Meglitinides
  - Metformin
  - SGLT2i
  - Sulfonamides
  - Sulfonylureas
  - Thiazolidinediones
  - Insulin
- Cardiovascular medications
  - Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEi/ARBs)
  - Aldosterone receptor blockers
  - Angiotensin receptor-neprilysin inhibitor
  - Anticoagulants
  - Aspirin and other antiplatelets (e.g., clopidogrel, ticlopidine, prasugrel)
  - Beta-blockers
  - Digoxin
  - Direct renin inhibitors
  - MRAs, other than finerenone
  - Nitrates and other vasodilators
  - All calcium channel blockers
  - Lipid-lowering drugs
  - Loop diuretics
  - Other antihypertensives
  - Potassium-sparing diuretics
  - Thiazide-like diuretics
  - Statins
  - Potassium Binders
- Other medications
  - Acetaminophen

- Anti-inflammatory drugs
- Anticonvulsants
- Antibiotics, antifungals, and antituberculars
- Bronchodilators
- Calcineurin inhibitors
- Chemotherapeutic agents
- Non-steroidal anti-inflammatory drugs

9.4. Data sources

This study will be conducted using existing healthcare data from the US. Considered data sources include the HealthVerity® Chronic Kidney Disease Masterset. This data source includes closed administrative health insurance enrolment, medical claims, and pharmacy claims data supplemented with laboratory test results, electronic medical record information, and mortality records. The Masterset contains information on over 10 million unique patients with evidence of CKD in the US with commercial, Medicare Advantage, or Medicaid insurance coverage.

Additional data sources may be considered to increase the sample size or representativeness of the study sample. If multiple data sources are used, meta-analytic methods may be considered, as appropriate, to generate summary estimates across data sources. Should additional data sources be added, the data source will be recorded and described in an update of the protocol, and a data source–specific SAP will be prepared to describe and document any data source–specific adaptations.

9.5. Study size

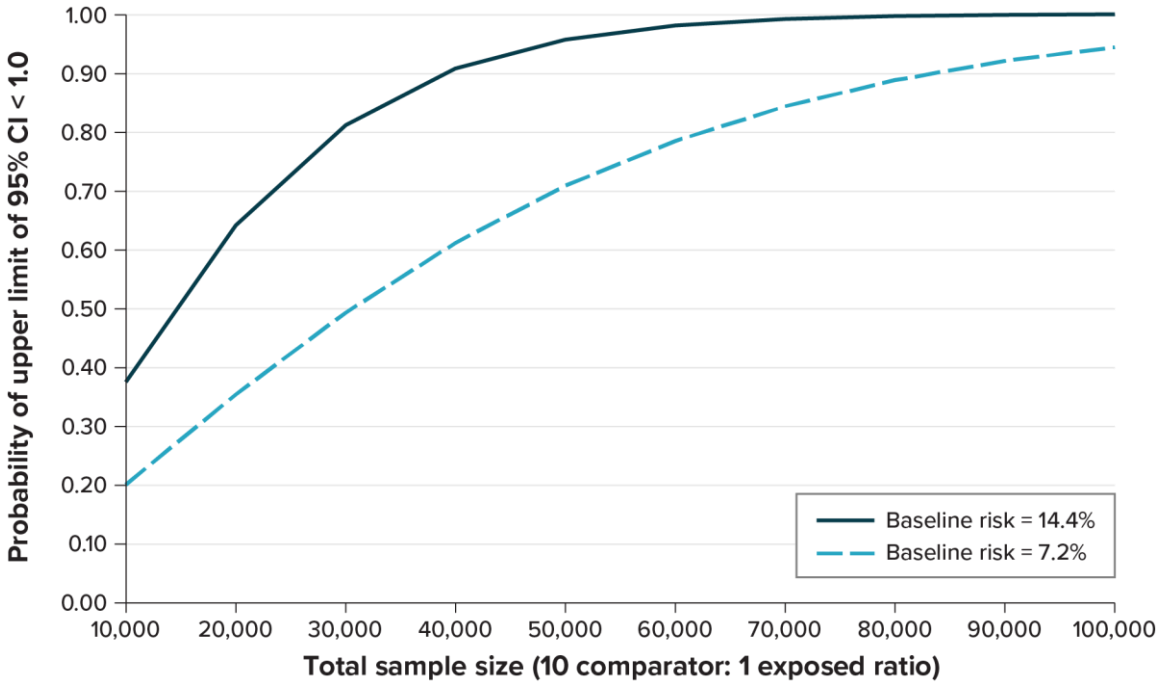
For the primary effectiveness composite cardiovascular outcome, the precision of the relative risk (RR) estimates was estimated with assumptions based on results from a combined analysis of pivotal randomised trials of finerenone [8,11,12]. The composite cardiovascular outcome used in those trials differed slightly from the outcome proposed in this study (the trial outcome included nonfatal stroke and all cardiovascular death). The sample size estimate for the current study assumed a RR of 0.86 (the hazard ratio [HR] for the composite outcome, as noted in the combined analyses [12], acknowledging that HRs for the individual components of the trial composite outcome included in this study's composite outcome were all similar, ranging from 0.78 [hospitalisation from heart failure] to 0.91 [nonfatal myocardial infarction]).

The risk of the composite cardiovascular outcome in the comparator group in the combined trial data was 14.4% [12] over up to 4 years of follow-up (median follow-up of 3.0 years) [12]. Because the trial composite outcome included additional components not included in the current study, standard care has evolved since the trial, and the follow-up time of the current study may be less than the median of 3 years in the trial, assumptions of risk in the comparator group of 14.4% (observed in the trial) and a reduced estimate of 7.2% were considered.

With these assumptions of outcome occurrence, the estimated precision of RR estimates in sample sizes ranging up to 50,000 were estimated with an assumed comparator-to-finerenone user ratio of 10:1. For the effectiveness outcomes, the probability of the upper limit of the 95% confidence interval (CI) being below 1 was estimated, as the intention of those analyses

was to evaluate real-world effectiveness. Sample size calculations were performed with EpiSheet [51].

Figure 3: Precision of estimated risk ratios for the composite cardiovascular outcome at an array of sample sizes



CI = confidence interval.

The RR precision estimates for the primary cardiovascular effectiveness outcome are shown in Figure 3. Under these assumptions, there would be a greater than 80% probability of the 95% CI of the RRs to exclude 1 at total sample sizes of approximately 30,000 included records (2,727 finerenone users, and the rest comparators) for the higher estimate of composite cardiovascular outcome incidence and 60,000 records (5,455 finerenone users) for the lower estimate of composite cardiovascular outcome incidence. For secondary effectiveness and safety outcomes with lower expected incidence, larger sample sizes would be required to achieve the same level of precision.

Based on initial feasibility assessments in the HealthVerity® Chronic Kidney Disease Masterset, we are expecting to include at least 20,000 individuals initiating finerenone. Although no specific feasibility was conducted to assess the number of patients with CKD and T2D fulfilling the criteria for finerenone prescription, based on current prescription patterns of finerenone, we are expecting the number of potential individuals in the comparator group to far exceed those required for this study.

9.6. Data management

Routine procedures will include checking electronic files, maintaining security and data confidentiality, following analysis plans, and performing quality control (QC) checks of all programmes. Data management will be conducted at the research centre(s) according to internal (e.g. HealthVerity) standard operating procedures (SOPs) or guidance documents.

Security processes will be in place to ensure the safety of all systems and data. Every effort will be made to ensure that data are kept secure so that they cannot be accessed by anyone except select study staff.

Appropriate data storage and archiving procedures will be followed. Standard procedures will be in place to restore files in the event of a hardware or software failure.

9.7. Data analysis

9.7.1. Included patients

The number of individuals selected for the study will be reported by treatment group, including the following parameters: attrition of individuals due to study exclusion criteria, the number of eligible individuals included in the study cohort, and the number of individuals excluded for not meeting each inclusion criterion along with the reasons for exclusion. The number of eligible Time 0s and unique individuals will be reported.

Counts and percentages of the reasons for censoring will also be reported.

9.7.2. Descriptive analyses

To better understand finerenone treatment patterns, the distribution of baseline finerenone dosage will be described in the treatment group by eGFR and serum potassium levels.

Distributions of the covariates will be described by treatment group. For binary and categorical variables, the frequency distributions (e.g., counts, proportions) will be displayed. For continuous variables, means, standard deviations, medians, first quartiles, third quartiles, first percentile, and 99th percentile will be calculated as appropriate. The relative balance of characteristics across treatment groups (finerenone users vs. comparators) will be described with absolute standardised differences [52] to observe differences in the distribution of characteristics by treatment group. These descriptive analyses will be performed in the crude overall study cohort.

To account for potential confounding resulting from differences in the baseline characteristics of the treatment groups, propensity score methods will be used. Propensity scores will be estimated for each treated and untreated Time 0 using logistic regression with prespecified baseline characteristics as independent variables and finerenone initiation as the dependent variable [53]. After estimation of the propensity scores, the coefficients of the logistic model will be evaluated to understand the relationships between observed covariates and finerenone initiation. The distribution of propensity scores will be plotted by treatment group and assessed. If imbalance of the propensity score distributions is observed (suggesting potential non-exchangeability of the treatment groups), additional steps to improve exchangeability will be considered (e.g., re-evaluation of propensity score variables to ensure that instrumental variables are not included [54], alteration of eligibility criteria to more fully align the treatment groups [55]).

The propensity scores will be used to estimate stabilised inverse probability of treatment (sIPT) weights. Additional propensity score–based weighting techniques may be considered (e.g., average treatment effect in the treated [ATT] weights), as appropriate, based on the observed distribution of propensity scores [53]. The weights will be applied to all analyses, creating weighted pseudopopulations with balanced covariates across treatment groups. Absolute standardised mean differences will also be assessed in the treatment groups after applying the propensity score weights. If residual imbalances of measured characteristics are observed (i.e., absolute standardised differences far from 0) after weighting (suggesting residual confounding), additional refinement of the propensity score approach will be considered (e.g., inclusion of additional covariates, addition of interaction terms or higher-order terms, trimming or truncation of extreme weights, use of ATT weights instead of sIPT weights [56]).

9.7.3. Primary effectiveness analyses

The primary composite cardiovascular outcome will be evaluated in an analytic subset after the application of outcome-specific exclusion criteria to ensure analysis of new-onset disease (Section 9.3.3.1) using an outcome-specific propensity score model; the assessment of weighted covariate balance (Section 9.7.2) in this analytic subset will be evaluated.

To account for baseline confounding, the propensity score–based weights will be applied to the cohort to balance characteristics across treatment groups, and analyses will be performed in the weighted cohort [57]. Because the 2 treatment groups will be subject to censoring after follow-up begins, selection bias may be introduced if individuals are censored differentially between treatment groups. To account for this potential bias, time period–specific inverse probability of censoring (IPC) weights will be estimated with logistic regression with censoring status as the dependent variable and updated time-varying characteristics as the independent variables. A full description of included variables and operationalisations will be provided in the SAP. The IPC weights will also be applied to the analysis [57]; the product of the baseline sIPT and time period–specific IPC weights will be applied during each time period of follow-up to account for both baseline confounding and selection bias in follow-up.

The incidence rates and 95% CIs of the composite cardiovascular outcome across all of follow-up will be estimated in the weighted cohort. A weighted cumulative incidence plot will be generated by treatment group using the cumulative incidence function estimator to visualise the occurrence of outcome events by follow-up time, accounting for censoring criteria and the competing risk of death [58]. This approach will estimate the “total effect” of finerenone on the outcome events or the cause-specific cumulative incidence [59]. Time since Time 0 (i.e., treatment initiation) will be the time scale.

As a summary of the relative difference in outcome incidence between the treatment groups, a HR and 95% CI will be estimated with weighted Cox proportional hazards ratios. The 95% CI will be estimated with robust sandwich estimators to account for the sIPT and IPC weighting and for the possibility of a single individual contributing multiple observations with different Time 0s.

To evaluate potentially changing differences over time since treatment initiation, time-specific RRs will be estimated from the cumulative incidence curves by dividing the weighted daily risk estimate for the finerenone group by the daily risk estimate for the comparator group. Similarly, time-specific risk differences will be estimated by subtracting the daily risk estimate for the comparator group from the daily risk estimate for the finerenone group. Time-specific estimates will be calculated at 6 months, 12 months, and 18 months. The 95% CIs for the time-specific RRs and risk differences will be estimated with nonparametric bootstrapping [60].

Before the primary analyses of the efficacy outcomes are performed, a negative control outcome analysis will be performed to evaluate the potential for unmeasured confounding (Section 9.7.7.1).

9.7.4. Secondary outcome analyses

9.7.4.1. Individual components of the composite cardiovascular outcome

For the separate secondary analyses of AMI and hospitalisation for heart failure, the same analysis set as that for the primary composite cardiovascular outcome will be used, with the same propensity score model. Each of the 2 outcomes will be evaluated separately; thus, follow-up may differ for the 2 outcomes. For each outcome, the weighted treatment group–

specific incidence rates, cumulative incidence plots, and overall HR will be estimated following the same methods as those for the primary outcome (Section 9.7.3).

9.7.4.2. New-onset heart failure

The analyses of new-onset heart failure will be performed in an analysis set after the application of outcome-specific exclusion criteria (Section 9.3.3.2.3). The treatment group–specific incidence rates, cumulative incidence plots, and overall HR will be estimated following the same methods as those used for the primary outcome (Section 9.7.3).

9.7.4.3. Change in UACR

The analysis of change in UACR outcomes will be performed in an analysis set restricted to those with baseline UACR values (Section 9.3.3.2.4). Time to a 30% decline in UACR from baseline will be described in each treatment group with incidence rates and cumulative incidence plots. Time to additional thresholds (e.g., 50%, 70%) may also be evaluated separately. Comparisons of the treatment groups using HRs and 95% CIs may be considered, if feasible; to inform the feasibility of performing comparative analyses, the frequency of UACR testing in each treatment group will be described and evaluated for comparability (to be described in the SAP).

9.7.4.4. Hyperkalaemia

The analysis of hyperkalaemia will be estimated in the overall study population without any outcome-specific exclusion criteria (Section 9.3.3.2.5). Treatment group–specific incidence rates will be estimated following the same methods as those for the primary outcome (Section 9.7.3).

9.7.5. Exploratory outcome analyses

9.7.5.1. All-cause mortality

The analysis of all-cause mortality will be estimated in the overall study cohort without any outcome-specific exclusion criteria. Because there are no competing risks for mortality, weighted treatment group–specific Kaplan-Meier survival plots and overall HR will be estimated without accounting for competing risks.

9.7.5.2. Change in UACR values over time

The analysis of change in UACR values over time will be performed in an analysis set restricted to those with available baseline UACR values (Section 9.3.3.2.4). Recorded UACR values during follow-up will be identified and used to estimate change in UACR values from baseline at 4 months and 12 months after the Time 0 with pattern-mixture models [61]. The factors considered as censoring criteria for the other, time-to-event outcomes will be used to define loss-to-follow-up for these analyses.

Descriptive analyses of UACR over time at 4 months and 12 months will be performed in each treatment group. Comparisons between groups may be considered, if feasible, based on descriptive analyses of UACR testing frequency between treatment groups (Section 9.7.4.3; further details to be provided in the SAP).

9.7.6. Subgroup analyses

To evaluate whether the association of finerenone with outcomes of interest differs by clinically relevant subgroups, HRs and 95% CIs across all of follow-up will be estimated in the following subgroups, if feasible due to observed case counts:

- Age groups
- Sex
- SGLT2i use at Time 0
- ACEi/ARB use at Time 0
- GLP-1 RA use at Time 0
- Insulin use at Time 0
- Potassium-sparing diuretic use at Time 0 (for hyperkalaemia only)
- UACR level at Time 0
- eGFR stage at Time 0
- Previous AMI at Time 0 (for AMI only)

As noted, some subgroup analyses will be performed specifically for only select, relevant outcomes.

9.7.7. Sensitivity analyses

9.7.7.1. Negative control analysis

To evaluate the potential for unmeasured confounding and other residual bias, a negative control outcome analysis will be performed. Negative control outcomes should not be causally related to the exposure, but as much as possible, should have the same set of common causes as the study exposure-outcome association being evaluated [62]. The outcomes being evaluated (cardiovascular and kidney outcomes) may also be influenced by other behavioural factors that are difficult to measure in existing healthcare data, such as diet, exercise, or other lifestyle factors; healthcare-seeking behaviour; or adherence to medications. Thus, potential negative control outcomes to assess the impact of unmeasured confounding by these factors would also require some association with healthy lifestyle.

A negative control outcome will be selected using the following criteria:

- The outcome should not be caused by finerenone use, directly or indirectly; thus, any outcomes with known associations, signals detected in pharmacovigilance systems, or published case reports will not be considered.
- The outcome should be severe (requiring hospitalisation or emergency department admission) to match the severity of the primary outcomes.
- The outcome should be reasonably common, matching the expected incidence of the outcomes of interest in this population.

Initially considered negative control outcomes may include the following:

- Hospitalisation or emergency department visit for asthma
- Laceration of hand or finger

9.7.8. Secondary treatment strategy analysis

A secondary analysis will evaluate outcomes using an alternative treatment strategy, requiring uptitration of the daily finerenone dose to 20 mg according to the approved US label (Section 9.3.2.3). This strategy will use methods similar to those for the primary analyses, but the censoring criteria will also include deviation from the new strategy (i.e., failure to titrate by week 10). These analyses will begin with the same study population as that from the primary analysis; thus, the same propensity scores and baseline variables will be used, but new IPC weights will be calculated due to the difference in censoring criteria.

9.8. Quality control

Standard operating procedures or internal process guidance at the research centre(s) will be used to guide the conduct of the study. These procedures include internal quality audits, rules for secure and confidential data storage, methods to maintain and archive project documents, QC procedures for programming, standards for writing analysis plans, and requirements for senior scientific review.

All programming written by 1 study analyst will be reviewed independently by a different analyst, with oversight by a senior statistician; all QC activities will be performed and documented pursuant to RTI-HS SOPs. All key study documents, such as the SAP and study reports, will undergo QC review, senior scientific review, and editorial review.

For RTI-HS, an independent Office of Quality (OQ) may perform audits and assessments that involve various aspects of the project, including but not limited to education and training documentation, data entry and data transfer procedures and documentation, and institutional review board (IRB) documentation. Such audits will be conducted by the OQ according to established criteria in SOPs and other applicable procedures.

A quality assurance audit of this study may be conducted by the study funder or the study funder’s designees.

9.9. Limitations of the research methods

This study will use existing healthcare data. As with all studies based in existing healthcare data sources, the data are generated for healthcare delivery rather than research; thus, missing data or misclassification of study variables is possible.

Written prescription or dispensing data may not reflect actual exposure or nonexposure to finerenone. A prescription issued or a prescription dispensed reflects the intent to use a drug, not actual patient use. Dosage, duration of use, and treatment changes will be estimated from the data; however, not all patient behaviours may be accurately recorded in the data, resulting in potential misclassification of finerenone use, discontinuation date, or dosage.

CKD will be defined using laboratory values (where available) and diagnosis coding. This approach may introduce heterogeneity in the evaluation of CKD severity across study participants. Additionally, formulas for estimating eGFR may vary across time, geographies, and racial and/or ethnic groups. This study will use a standard single equation, CKD-EPI 2021, to estimate eGFR where possible. However, in the absence of complete laboratory records, diagnosis coding will be used, which may lack the granularity of laboratory-based measures.

Cohort entry is defined by meeting electronic algorithms for both T2D and CKD using data available in the data source during the study period. Thus, the original dates of CKD and T2D onset may not be known for each individual. Additional measures of T2D and CKD disease severity will be included as covariates, but duration of illness cannot be considered.

Moreover, specific ordering of the onset of CKD and T2D will not be required. Individuals with T2D who develop CKD may have different treatment patterns and characteristics than those with CKD who develop T2D, but both groups will be included in the present study.

Outcomes will be identified using all relevant diagnosis information using validated algorithms, where available; however, misclassification is possible.

This study will compare finerenone users with nonusers. While the study selection criteria are designed to ensure that all nonusers are eligible to be prescribed finerenone on all identified Time 0s, systematic differences in characteristics may be present between finerenone initiators and nonusers, resulting in unmeasured confounding (e.g., if finerenone users are generally at more advanced disease stages than nonusers, there may be a confounded estimate demonstrating an elevated outcome rate in treated individuals). This study uses a rich set of covariates, including demographic characteristics, comorbidities, and comedications, as well as proxies for healthcare-seeking behaviour and healthy lifestyle. The balance of measured characteristics will be evaluated, negative control outcomes will be evaluated to determine the potential impact of unmeasured confounding, and a sensitivity analysis will use restrictive inclusion criteria to create more similar treatment groups. However, the possibility of unmeasured confounding remains.

Comparisons of medication users with nonusers may be subject to selection bias if treated individuals must meet additional criteria (e.g., additional survival, healthcare interactions) to be included in the study beyond those of the comparator group criteria. For the comparator group in this study, all dates on which individuals had a recorded CKD diagnosis and were eligible for finerenone treatment will be included in the comparator group. This will include a large array of individuals with CKD at each timepoint their CKD was recognised and evaluated. However, if in practice, there are requirements for finerenone prescription that systematically require additional survival (e.g., a long evaluation period), selection bias may be present. This limitation also applies to analyses of the recommended titration schedule of finerenone. Individuals who do not follow the titration schedule will be censored, potentially introducing selection bias in follow-up. Inverse probability of censoring weights will be used to account for selection bias, but residual bias may remain if some key characteristics are not measured in the data.

To optimise internal validity, this study will assess patients who have been or who could have been prescribed finerenone according to the approved label in the US. Some of these eligibility criteria based on the approved label or treatment recommendations are intended to improve comparability of treated and untreated groups (e.g., exclusion of those with recent hyperkalaemia), thus avoiding comparison of treated individuals with untreated individuals whose clinical state makes them unlikely to be treated and more likely to experience negative outcomes. These criteria are primarily intended to impact the untreated comparison group, but they are also likely to exclude a small number of treated individuals. Consequently, this approach may impact the representativeness of the study results. The study results will be representative of patients prescribed finerenone according to the approved label in the US, but results need to be interpreted with care beyond the labelled indication of finerenone in the US.

A secondary objective of this study will assess the effectiveness of initiating finerenone and titrating dosage according to the approved label by estimating the risk of a composite cardiovascular outcome (i.e., first occurrence of fatal or nonfatal AMI or hospitalisation for heart failure) in patients with CKD and T2D initiating finerenone and uptitrating to 20 mg (when recommended) compared with that in patients with CKD and T2D not using finerenone. Patients in the finerenone group will therefore be censored if they do not seem to follow the titration recommendation from the US label. However, in the control group (no

finerenone use), no such censoring will be possible because these patients do not use finerenone.

9.10. Other aspects

9.10.1. Statistical reporting

No formal statistical hypotheses will be tested in this study. In accordance with the recommendations of the American Statistical Association [63], the International Committee for Medical Journal Editors [64], and expert opinion on the misuse of significance testing [65-68], we will avoid relying on statistical significance to interpret the study results. Instead of a dichotomous interpretation based on *P* values and significance testing, we will rely on a quantitative interpretation that considers the magnitude, precision, and possible bias in the estimates that we derive and report. We believe that this is a more appropriate approach than one that ascribes to chance any result that does not meet conventional criteria for statistical significance.

9.10.2. Missing data

Data may potentially be missing for some key variables. Data missingness may manifest as explicitly missing fields for certain variables (e.g., no recorded value for race, no height or weight records from which to estimate body mass index interpreted as “missing” or “unknown” values for those variables). Alternatively, for variables defined by the presence of a record in the claims/EHR data, the absence of a record would be interpreted as the variable not being present (e.g., the lack of any prescription or dispensing records for a medication would be interpreted as the patient not using the medication).

For explicitly missing variables fields, the level of missingness will be described. If there is minimal missingness, indicators for missingness may be used as variable values. For some variables (e.g., CKD stage), combinations of different data types may be used to define the variable (e.g., laboratory values or diagnoses) so that if a laboratory value is missing, diagnosis records may be used to define the variable. Additional details will be provided in the SAP.

10. Protection of human subjects

This is a non-interventional study using secondary data collection and does not pose any risks for participants. All data collected in the study will be de-identified with no breach of confidentiality regarding personal identifiers or health information. The coordinating centre and research site(s) will apply for independent ethics committee or IRB reviews, if required according to local regulations.

Data protection and privacy regulations will be observed in collecting, forwarding, processing, and storing data from study participants. All data source–specific requirements regarding privacy, data masking, and data protection will be followed.

RTI International (RTI) holds a Federal-Wide Assurance from the Department of Health and Human Services Office for Human Research Protections that allows the organisation to review and approve human subjects protocols through its IRB committees. RTI Health Solutions (RTI-HS) currently has 3 IRB committees available to review research protocols. One IRB committee is constituted to review medical research and has 2 members who are MDs. These IRBs have been audited by the US FDA and are fully compliant with applicable regulatory requirements. RTI Health Solutions will obtain approval for the study from the RTI International IRB.

11. Management and reporting of adverse events/adverse reactions

For studies in which the research team uses data from automated healthcare databases only, according to the International Society for Pharmacoepidemiology [69] Guidelines for Good Pharmacoepidemiology Practices (GPP),

Aggregate analysis of database studies can identify an unexpected increase in risk associated with a particular exposure. Such studies may be reportable as study reports, but typically do not require reporting of individual cases. Moreover, access to automated databases does not confer a special obligation to assess and/or report any individual events contained in the databases. Formal studies conducted using these databases should adhere to these guidelines.

For non-interventional study designs that are based on secondary use of data, such as studies based on medical chart reviews or electronic healthcare records, systematic reviews, or meta-analyses, reporting of adverse events/adverse drug reactions is not required. Reports of adverse events/adverse drug reactions should only be summarised in the study report, where applicable [70].

According to the European Medicines Agency (EMA) *Guideline on Good Pharmacovigilance Practices (GVP), Module VI – Management and Reporting of Adverse Reactions to Medicinal Products* [70],

"For non-interventional study designs which are based on secondary use of data, adverse reactions reporting is not required. All adverse events/reactions should be summarised in the final study report."[1]

12. Plans for disseminating and communicating study results

Study results will be published following guidelines, including those for authorship, established by the International Committee of Medical Journal Editors [71]. When reporting results of this study, the appropriate Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist will be followed [72]. The Consolidated Standards of Reporting Trials (CONSORT) statement [73] refers to randomised studies but provides useful guidance applicable to non-randomised studies as well.

[1] European Medicines Agency. Guideline on good pharmacovigilance practices (GVP). Module VI – Management and reporting of adverse reactions to medicinal products. 22 June 2012. http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129135.pdf. Accessed 6 March 2013.

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Annex 1: List of stand-alone documents

Document name	Final version and date (if available)
FOUNTAIN_EAC_member list.docx	v3.0, 17-JAN-2023
FOUNTAIN_EAC_Publication Committee member list.docx	v2.0, 17-JAN-2023

Annex 2: ENCePP checklist for postauthorisation safety study (PASS) protocols

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes," the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional postauthorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: FIRST-2.5: Finerenone Research of Early Safety and Effectiveness, Part 2.5

EU PAS Register® number: 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[2]	☒	☐	☐	0
1.1.2 End of data collection[3]	☒	☐	☐	0
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	0
1.1.6 Final report of study results	☒	☐	☐	0

Comments:

Only 1 analysis is planned; thus, no intermediate progress reports or interim reports are planned.

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:				
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)	☒	☐	☐	8
2.1.2 The objective(s) of the study?	☒	☐	☐	8.1, 8.2
2.1.3 The target population? (i.e., population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	8
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	9.10.1

Comments:

There are no formal hypotheses to be tested in this protocol.

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)	☒	☐	☐	9.7.3

[2] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[3] Date from which the analytical dataset is completely available.

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
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))	☒	☐	☐	9.7.3
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

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	☒	☐	☐	9.2.2
	4.2.2 Age and sex	☒	☐	☐	9.2.1
	4.2.3 Country of origin	☒	☐	☐	9.2.1
	4.2.4 Disease/indication	☒	☐	☐	9.2.1.2
	4.2.5 Duration of follow-up	☒	☐	☐	9.2.1.3
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, 9.2.1.2

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)	☒	☐	☐	9.3.2
5.2	Does the protocol address the validity of the exposure measurement? (e.g., precision, accuracy, use of validation sub-study)	☒	☐	☐	9.3.2, 9.9
5.3	Is exposure categorised according to time windows?	☐	☒	☐	
5.4	Is intensity of exposure addressed? (e.g., dose, duration)	☒	☐	☐	9.3.2.1
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	9.3.2.1
5.6	Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	9.3.2.2

Comments:

5.3. All exposure after Time 0 is evaluated. Rather than categorising exposure by time, cumulative incidence analyses will evaluate changing risks over time (Section 9.7.3)

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?	☒	☐	☐	9.3.3
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.3
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)	☒	☐	☐	9.3.3, 9.9
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g., HRQoL, QALYs, DALYs, healthcare services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

This study focuses on clinical outcomes.

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g., confounding by indication)	☒	☐	☐	9.7.2, 9.7.7.1
7.2 Does the protocol address selection bias? (e.g., healthy user/adherer bias)	☒	☐	☐	9.7.3
7.3 Does the protocol address information bias? (e.g., misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.9, 9.10.2

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, subgroup analyses, anticipated direction of effect)	☒	☐	☐	9.7.5

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)	☒	☐	☐	9.3.2, 9.4

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1.2 Outcomes? (e.g., clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.3.3, 9.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	0, 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)	☒	☐	☐	9.3.2
9.2.2 Outcomes? (e.g., date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3.3
9.2.3 Covariates and other characteristics? (e.g., age, sex, clinical and drug use history, comorbidity, comedications, lifestyle)	☒	☐	☐	0
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g., WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.3.2
9.3.2 Outcomes? (e.g., International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.3.3
9.3.3 Covariates and other characteristics?	☒	☐	☐	0
9.4 Is a linkage method between data sources described? (e.g., based on a unique identifier or other)	☐	☐	☒	

Comments:

Linkage between data sources is not required.

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
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7.2
10.4 Are stratified analyses included?	☒	☐	☐	9.7.5
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.7.2, 9.7.3
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☒	☐	☐	9.3.2
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.10.2
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.7.7

Comments:

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)	☒	☐	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	9.7.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	12

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
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)	☐	☒	☐	

Comments:

Feasibility evaluations are ongoing.

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
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	9.6, 10

Comments:

Not yet submitted for ethical review.

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

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)?	☐	☐	☒	
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Study will not be submitted to regulatory agencies.

Name of the main author of the protocol: PPD

Date: 25/June/2024

Signature: Signature will be collected electronically from OS Content Owner

Annex 3: Additional information

Not applicable.

Annex 4: Description of updates and amendments

AM01; 03 JUL 2024

Protocol section	*Description*
PASS information/Title page	Protocol version and date updated Objectives revised to reflect changes made in the protocol body Author list revised to reflect current RTI-HS study team
2. List of abbreviations	Revised to reflect changes applied during AM01
3.1 Main responsible parties	Revised to reflect current Bayer study team
3.2. Further responsible parties	Revised to reflect current RTI-HS study team
4. Abstract	Protocol version and date, authors, research question and objectives, data sources, and milestones revised to reflect changes applied during AM01
5. Amendments	Table 1: Amendments and updates added and the summary of AM01 added.
6. Milestones	Public registration of study protocol, start of data collection, and Start of data analysis milestones revised to reflect current plan at time of AM01
8.2. Secondary objectives	Added a secondary objective evaluating the risk of declines in UACR Clarified that subgroup analyses and alternative treatment strategy analyses would not be restricted to only the primary, composite cardiovascular outcome
8.3 Exploratory objectives	Removed an exploratory objective evaluating new-onset atrial fibrillation Added a secondary objective describing the change in UACR over time at 4 months and 12 months
9.2.3. Representativeness	Revised to replace the description of the data source with HealthVerity CKD Masterset
9.3.1. Measures of kidney function	Clarified the definition of the baseline UACR value to be used for the newly added UACR secondary and exploratory objectives

AM01; 03 JUL 2024

Protocol section	***Description***
9.3.3.2.1. Acute myocardial infarction	Clarified that the secondary analyses of individual components of the primary composite outcome will be performed in the same analysis set as the primary composite outcome
9.3.3.2.2. Hospitalisation for heart failure	Clarified that the secondary analyses of individual components of the primary composite outcome will be performed in the same analysis set as the primary composite outcome
9.3.3.2.4. Change in UACR	Entire section newly added to describe the definitions of endpoints used in the analysis of the newly added secondary objective
9.3.3.3.2. Change in UACR values over time	Entire section newly added to describe the definitions of endpoints used in the analysis of the newly added exploratory objective
9.4. Data sources	Revised to drop reference to the OM1 Real-World Data Cloud and added reference to the HealthVerity CKD Masterset
9.5. Study size	Dropped references to the OM1 Real-World Data Cloud
9.6. Data management	Revised to reflect the data management practices of RTI-HS staff who will be performing the analysis
9.7.4.3. Change in UACR	Entire section newly added to describe the analysis of the newly added secondary objective
9.7.5.2. Change in UACR values over time	Entire section newly added to describe the analysis of the newly added exploratory objective
9.7.8. Secondary treatment strategy analysis	Clarified that titration to 20 mg should be according to the approved US label Clarified that the time window for titration is 10 weeks, to ensure consistency with Section 9.3.2.3
9.8. Quality control	Revised to reflect the QC practices of RTI-HS staff who will be performing the analysis
10. Protection of human subjects	Revised to reflect the ethical review and approval practices of RTI-HS staff who will be performing the analysis
Annex 4: Description of updates and amendments	Changes in AM01 added
Annex 5: Signature pages	Protocol version and date updated

AM01; 03 JUL 2024

Protocol section	*Description*
	Signatories: PPD changed from PPD to PPD

AM = amendment; CKD = chronic kidney disease; PASS = postauthorisation safety study; QC = quality control; RTI-HS = RTI Health Solutions; UACR = urine albumin-creatine ratio; US = United States.

Annex 5: Signature pages

Signature Page

This protocol is electronically signed in the study management system.

Title	FIRST-2.5: Finerenone Research of Early Safety and Effectiveness, Part 2.5
Protocol version and date	v 2.0, 03 JUL 2024
IMPACT study number	22663
Study type/Study phase	Postapproval ☒ PASS Joint PASS: ☐ YES ☒ NO
Active substance	Finerenone
Study initiator and funder	Bayer AG, 51368 Leverkusen

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Signatories

- PPD
- PPD