Post Authorization Safety Study (PASS)

Acronym/Title	FINEGUST/FINErenone druG Utilization Study and assessment of Temporal changes following availability of different treatment options in patients with chronic kidney disease and type 2 diabetes
Protocol version and date	V1.0, 30 MAY 2022
IMPACT study number	21956
Study type / Study phase	☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	Study not yet registered
NCT number	Study not yet registered
Active substance	Finerenone
Medicinal product	Kerendia (ATC: C03DA05)
Product reference	BAY 94-8862
Procedure number	Not applicable
Study Initiator and Funder	Bayer, AG
Research question and objectives	The overall aim of this study is to describe patient profiles and treatment patterns in medication initiator cohorts of patients with CKD and T2D. The primary objective is to describe baseline patient characteristics, comorbidities, and comedications in adult patients with chronic kidney disease and type 2 diabetes mellitus who initiate a sodium-glucose cotransporter 2 inhibitor (SGLT2i), a glucagon-like peptide-1 receptor agonist (GLP-1-RA), steroidal mineral corticoid receptor antagonists (sMRA), finerenone, or other non-steroidal mineral corticosteroid receptor antagonist (nsMRA) (only in Japan) in each of 2 time periods corresponding to finerenone pre-launch and post-launch dates. The secondary objective(s) are • To describe changes over time in treatments in the initiator cohorts including treatment discontinuation,

	treatment switches, add-on treatments, and titration (finerenone only) in each of 2 time periods corresponding to finerenone pre-launch and post-launch dates. • To describe temporal changes in the baseline characteristics of the medication-specific cohorts before and after finerenone launch
Countries of study	US, Denmark, Japan, The Netherlands, Spain, UK
Author	PPD PPD PPD

Marketing authorization holder

Marketing authorization holder(s)	Bayer AG
MAH contact person	PPD

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

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

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2. List of abbreviations

ACEi	Angiotensin-Converting Enzyme Inhibitors
ACR	Urinary Albumin-to-Creatinine Ratio
AED	Accident & Emergency Department
AER	Urinary Albumin Excretion Rate
ARB	Angiotensin Receptor Blockers
ATC	Anatomical Therapeutic Chemical (Classification System)
BMI	Body Mass Index
CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease-Epidemiology Collaboration
CPR	Central Pharmaceutical Reference
CPRD	Clinical Practice Research Datalink (UK)
DPP-4i	Dipeptidyl Peptidase-4 Inhibitors
EC	European Commission
ED	Emergency Department
eGFR	Estimated Glomerular Filtration Rate
EHR	Electronic Health Record
EMA	European Medicines Agency
EMIS	Egton Medical Information Systems
ENCePP	European Network of Centres in Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GLP-1-RA	Glucagon-like Peptide-1 Receptor Agonists
GOLD	General Practitioner Online Database of CPRD
GP	General Practitioner
GPP	Good Publication Practice
GVP	Good Pharmacovigilance Practice
HbA1c	Haemoglobin A1c (Glycated Haemoglobin)
HCPCS	Healthcare Common Procedure Coding System

HES	Hospital Episode Statistics
ICD	*International Classification of Diseases*
ICD-10	*International Classification of Diseases, 10th Revision*
ICD-10-CM	*International Classification of Diseases, 10th Revision, Clinical Modification*
ICD-10-ES	*International Classification of Diseases, 10th Revision, Spanish Version*
ICD-9	*International Classification of Diseases, 9th Revision*
ICD-9-CM	*International Classification of Diseases, 9th Revision, Clinical Modification*
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISAC	Independent Scientific Advisory Committee of the CPRD
J-CKD-DB	Japan Chronic Kidney Disease Database
J-CKD-DB-Ex	Japan Chronic Kidney Disease Database Extension
LAB_F	Register of Laboratory Results for Research
MAH	Marketing Authorisation Holder
MBDS	Minimum Basic Data Set at Hospital Discharge
MRA	Mineral Corticoid Receptor Antagonists
sMRA	Steroidal Mineral Corticoid Receptor Antagonists
NDC	National Drug Code PAS
ONS	Office for National Statistics
OPTUM CDM	Optum Clinformatics DataMart
OQA	Office of Quality Assurance
PASS	Post-Authorization Safety Study
PHARMO	PHARMO Institute for Drug Outcomes Research
RTI	RTI International
RTI-HS	RTI Health Solutions
SAP	Statistical Analysis Plan
SGLT2i	Sodium-glucose Cotransporter 2 Inhibitors
SIA	Ambulatory Information System
SIP	Population Information System
SNOMED CT	Systematized Nomenclature of Medicine–Clinical Terms

STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
T1D	Type 1 Diabetes Mellitus
T2D	Type 2 Diabetes Mellitus
UK	United Kingdom
US	United States
VHS	Valencia Health System
VID	Valencia Health System Integrated Database

3. Responsible parties

3.1. Study initiator and funder

Role:	OS Conduct Responsible
Name:	PPD
E-mail:	PPD
Role:	OS Content Owner
Name:	PPD
E-mail:	PPD
Role:	OS Medical Expert
Name:	PPD
Role:	OS Statistician
Name:	PPD
Role:	OS Epidemiologist
Name:	PPD
Role:	OS Safety Lead
Name:	PPD
Role:	Qualified Person responsible for Pharmacovigilance (QPPV)
Name:	PPD
Role:	OS Health Economics and Outcomes Research (HEOR) responsible
Name:	PPD
Role:	OS Data Analyst
Name:	PPD
Role:	US Data Generation and Observational Studies
Name:	PPD

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

3.2. Contractors, Collaborators, Committees

Contact details on the principal investigators and research partners participating in the study are listed in a stand-alone document (see Table 6, Annex 1), which is available upon request.

Information on the Executive Advisory and Publication Committee Members and the respective Charters are kept as stand-alone documents (see Table 6, Annex 1), which are available upon request.

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

4. Abstract

Acronym/Title	FINEGUST/**FINE**renone dru**G** **U**tilization **S**tudy and assessment of **T**emporal changes following availability of different treatment options in patients with chronic kidney disease and type 2 diabetes
Protocol version and date	V. 1.0 11 MAY 2022
IMPACT study number	21956
Study type / Study phase	Observational ☒ PASS> <Joint PASS: ☐ YES ☒ NO
Author	PPD PPD PPD
Rationale and background	Patients with chronic kidney disease (CKD) are at high risk of kidney failure, cardiovascular disease, and death. Patients with type 2 diabetes mellitus (T2D) have a high prevalence and incidence of CKD. Prevention, early detection, and treatment of CKD may result in improved patient outcomes, especially among patients with diabetes. Approved therapies to prevent and treat CKD among patients with T2D include angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), and sodium-glucose cotransporter 2 inhibitors (SGLT2i). Glucagon-like peptide-1 receptor agonists (GLP-1 RA) and steroidal mineralocorticoid receptor antagonists (sMRA) are also used for the treatment and prevention of CKD in patients with T2D but are not yet approved for this indication. Finerenone is an oral, selective, non-steroidal mineralocorticoid receptor antagonist (nsMRA) developed by Bayer for the treatment of CKD in patients with T2D. Finerenone has been approved by the United States (US) Food and Drug Administration, the European Medicines Agency (EMA) and the Japanese Pharmaceutical and Medical Devices Agency (PMDA). The clinical landscape for the treatment of patients with CKD and T2D is rapidly evolving with the introduction of new treatments, and it is of interest to study how treatment patterns may evolve with the approval of new drugs with this indication.

Research question and objectives	The overall aim of this study is to describe patient profiles and treatment patterns in medication initiator cohorts of patients with CKD and T2D. The primary objective of this study is • To describe baseline patient characteristics, comorbidities, and comedications in adult patients with CKD and T2D who initiate an SGLT2i, a GLP-1 RA, a sMRA, finerenone, or other nsMRA (only in Japan) in each of 2 time periods corresponding to the finerenone pre- and post-launch dates. The secondary objective(s) of this study are • To describe treatment changes over time in the new-user cohorts, including treatment discontinuation, treatment switches, and add-on treatments in each of 2 time periods corresponding to finerenone pre-launch and post-launch dates; for finerenone treatment titration (e.g., percentages of finerenone patients uptitrating the dose from 10 mg to 20 mg within 6 months) will also be described. • To describe temporal changes in the baseline characteristics of medication-specific cohorts before and after the launch of finerenone.
Study design	A multi-database, multinational, observational (non-interventional) cohort study is planned to describe drug utilisation and temporal changes of different treatment options in adults with CKD and T2D using secondary data from data sources in the EU, Japan, the United Kingdom (UK), and the US. This protocol will serve as the common protocol for all data sources and research partners involved in the study, with adaptations based on data source–specific specifications. The study will identify separate medication-specific cohorts in 2 separate time periods that correspond to the pre-approval and post-approval dates of finerenone; dates of the time periods will vary in each of the study countries. In the pre-finerenone period (study period I), 4 new-user cohorts will be identified, based on the first use of any drug in these classes: SGLT2i, GLP-1 RA, sMRA, or nsMRA. Five new-user cohorts will be created in study period II (SGLT2i, GLP-1 RA, sMRA, finerenone, and other nsMRA). The other nsMRA cohort will only be identified in Japan where esaxerenone is available.
Population	The study population will include a total of 6 data sources, 1 from each of the following countries: Denmark, the Netherlands, Spain, Japan, UK, and the US. For each database, the source population will include patients who fulfil an electronic algorithm for CKD and T2D.

	For each participating data source, **study period I** will begin on 01 January 2012 (01 January 2014 for Japan) and will end on 30 June 2021 . **Study period II** will begin after the launch date of finerenone in each data source and will include all available post-finerenone follow-up time until the end of the overall study period, 30 September 2024. For each medication-specific new-user cohort in each study period, new users will be patients with a prescription or dispensing for a drug in the study medication class during the study period and no prescription or dispensing for any medication in that class during the previous 12 months. For each study period and for each study medication, the index prescription or dispensing will be the first eligible prescription or dispensing that fulfils the definition of new use during the study period. The index date will be defined as the date on which each identified new user receives the index prescription for the study medication. Individual patients may be eligible for multiple new-user cohorts. Other inclusion criterion: • Active registration or continuous enrolment for at least 12 months in 1 of the selected data sources before the index date • Aged 18 years or older as of the index date Exclusion criteria assessed on or before the index date: • Type 1 diabetes identified by appropriate algorithms in each participating data source • Kidney cancer • Kidney failure Follow-up will start the day after the index date and will continue up to the first occurrence of 1 of the following censoring criteria: • End of the study period • Disenrolment from the database or emigration from the database catchment area • Development of kidney failure during follow-up • Development of kidney cancerDeath
Variables	Exposure to the study medications will be identified from prescriptions in the electronic health record (EHR) or administrative data for prescription or dispensing of medications, depending on the data source. Current medication use will cover the day after the index date to the end of supply for consecutive prescriptions and dispensings plus a grace period of 30 days. Sensitivity analyses extending the period to 60 and/or 90 days

	will be conducted. Dose will be the dosage at the index date. Treatment discontinuation will be defined by the date corresponding to the end of current use. Algorithms using diagnosis and medication codes will be used to identify T2D. Depending on the data source, algorithms using combinations of diagnosis and medication codes and laboratory results (as available) will be used to identify CKD. At the index date, patients will be characterised using all the data available in the previous 365 days. For medications, the previous 180 days will be used; and for some variables for which codes may not be updated periodically (e.g., kidney transplant), all of the available lookback period will be used. The following variables will be used (where available) to characterise the patients: • Sociodemographic characteristics (e.g., age, sex) • Duration and severity of T2D • Complexity of treatment for T2D and CKD • Other treatments for CKD • Congestive heart failure • Severe liver disease • Other comorbidities measured by the Charlson Comorbidity Index or the Chronic Disease Score or as single entities • Duration and severity of CKD • Hyperkalaemia • Cardiovascular risk factors, including lifestyle risk factors as available in each data source • Other medications General practitioner and specialist visits; hospital and emergency department visits
Data sources	The study will be conducted using data from data sources in 6 countries: Denmark (the Danish National Health Registers), Japan (the Japan Chronic Kidney Disease Database), the Netherlands (PHARMO), Spain (the Valencia Health System Integrated Database), UK (CPRD), and the US (Optum). A common statistical analysis plan (SAP) will be adapted to specifications in each data source. The study coordinating centre, which will compile aggregated results from each data source into study reports, will oversee the study.
Study size	Not applicable

Data analysis	The following analyses will be conducted separately for both **study period I** and **study period II**:
	• Attrition of patients after applying eligibility and exclusion criteria will be described by each study cohort and data source.
	• Descriptive statistics will be presented for the variables in the variable section separately for each new-user cohort in each data source.
	The characteristics of each new-user cohort will be described at the index date as follows:
	• Total number of new users
	• Total length of study follow-up
	• Characteristics of index prescription/dispensing: dose, dose frequency, strength, number of units, amount of drug prescribed, monotherapy, fixed-dose combination
	• Index medication classification will be based on the previous use of the study medications (and ACEi and ARB) 90 days before the index date and on whether the index medication meets a pattern of adding on or switching to relative to the previous medications. (Detailed definitions for medication classification will be specified in the SAP and may vary by data source.)
	• Changes in the study medications during follow-up:
	  • Number who discontinued the index medication
	  • Number who started another study medication
	  • Number who added another study medication to the index therapy
	Changing treatment states over time for the treatments in each period will be displayed using shift tables and Sankey diagrams with the number of days since the initial prescription on the horizontal-axis in increments, such as 90 or 180 days.
	To address the secondary objectives, temporal change analyses in baseline characteristics of the study cohorts in the pre-finerenone and post-finerenone periods will be conducted. Baseline characteristics for the pre-finerenone and post-finerenone cohorts will be displayed in a tabular or graphical manner to describe temporal differences in cohort characteristics at the 2 different periods. These analyses will be descriptive without formal comparisons between the 2 periods.

Milestones	Start of data collection	01 SEP 2022	
	End of data collection	30 SEP 2024	
	Data analysis I completed	31 OCT 2022	
	Data analysis II completed	31 OCT 2024	
	Temporal changes analysis completed	31 OCT 2024	
	Final report of study results	31 DEC 2024	

5. Amendments

None

6. Milestones

Table 1 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, data release, and analysis do not require amendments to the protocol. Revised study timelines and milestones that do not constitute a need for a formal protocol amendment are kept as a stand-alone document (Annex 1, Table 6), which is available upon request. Note that planned dates for start and end of data collection will be adapted based on data availability in the different data sources.

Table 1: Milestones

Milestone	Planned date
Registration in the EU PAS register	01 JUNE 2022
Analysis plan completed	30 JUNE 2022
Start of data collection	01 SEP 2022
End of data collection	30 SEP 2024
Data analysis I completed	31 OCT 2022
Data analysis II completed	31 OCT 2024
Temporal changes analysis completed	31 OCT 2024
Final report of study results	31 DEC 2024

7. Rationale and background

Chronic kidney disease (CKD) is defined as abnormalities of kidney structure or function, present for more than 3 months, with implications for health. Markers of kidney damage include the presence of increased urinary albumin excretion rate (AER) ≥ 30 mg/24 hours; urinary albumin-to-creatinine ratio (ACR) ≥ 30 mg/g [≥ 3 mg/mmol]). Markers of impaired kidney function include a reduced glomerular filtration rate (GFR) (GFR < 60 mL/min/1.73 m^2) (1, 2). 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 (3, 4).

Patients with type 2 diabetes mellitus (T2D) have a high prevalence and incidence of CKD (5). The prevalence of CKD among patients with diabetes is 17% to 24% in Denmark (6, 7); 28% in Spain

(8) and the Netherlands (9); 38% in the United States (US) (10); 42% in the United Kingdom (UK) (11); and 46% in Japan, which is the highest prevalence (12).

Available therapies indicated for the prevention and treatment of CKD among patients with T2D include renin-angiotensin system inhibitor drugs (e.g., angiotensin-converting enzyme inhibitors [ACEi], angiotensin receptor blockers [ARB]), sodium-glucose cotransporter 2 inhibitors (SGLT2i), and finerenone (in the US); additional prevention strategies include treatment of risk factors for CKD (e.g., high blood pressure) with drugs or lifestyle modification (13).

Clinical trials have shown improvement of kidney outcomes in patients with T2D treated with SGLT2i. The CREDENCE trial demonstrated a lower risk of kidney failure and cardiovascular events among adult patients with T2D treated with canagliflozin than among patients receiving a placebo (14). The DAPA-CKD trial showed that patients treated with dapagliflozin compared with a placebo had a lower risk of a composite outcome (sustained decline in eGFR of at least 50%, kidney failure, or death from kidney or cardiovascular events), and the effect was consistent whether or not the participants had T2D (15). Canagliflozin received approval by the US Food and Drug Administration (FDA) in August 2020; for adults with T2D and diabetic nephropathy with albuminuria (16); dapagliflozin received FDA approval in April 2020 for adults with CKD at risk of progression (17). Dapagliflozin also received a positive opinion for market authorisation for the same indication from the European Medicines Agency (EMA) in October 2021 (18).

The glucagon-like peptide-1 receptor agonists (GLP-1 RA) liraglutide and dulaglutide may also have beneficial effects on kidney outcomes. In a secondary analysis of the LEADER trial (19), among patients with T2D at high risk for cardiovascular disease, a lower risk of a composite kidney outcome was observed with liraglutide compared with placebo. In an exploratory analysis of the REWIND trial (20) that examined the effect of dulaglutide on cardiovascular disease in adults with T2D, the exploratory results suggested a reduction in the progression of kidney disease with about 5 years of exposure to dulaglutide. Neither of these drugs has been approved either by the FDA or the EMA to improve kidney outcomes among patients with T2D. A systematic review and network meta-analysis comparing GLP-1 RA and SGLT2i concluded that both drug classes have cardiovascular and kidney benefits but with notable differences in benefits and harms (21).

The steroidal mineralocorticoid receptor antagonists (sMRA) spironolactone (non-selective) and eplerenone (selective) have limited evidence of potential kidney benefit among patients with CKD and T2D (22, 23). These drugs are not approved for the treatment and prevention of CKD in patients with T2D, but they are used among patients with T2D for other indications such as hypertension and heart failure (22).

Finerenone is a novel, oral, selective non-steroidal mineralocorticoid receptor antagonist 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, which has been shown in clinical studies (24). In the phase 3, event-driven, placebo-controlled FIDELIO trial (25), results showed that, among patients with stage 3 or 4 CKD with severely elevated albuminuria and type 2 diabetes, finerenone, when added to standard of care, reduced the incidence of CKD progression (26) and a composite cardiovascular outcome that included time to cardiovascular death, myocardial infarction, stroke, or hospitalisation for heart failure (27). In the FIGARO trial (28), patients on 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 (29). In the pre-specified pooled analysis of the FIDELIO and FIGARO trials, the positive effects were demonstrated for both CKD and cardiovascular outcomes across a broad spectrum of CKD (30).

Finerenone received approval from the FDA on 09 July 2021 and is indicated in adult patients with CKD associated with T2D to reduce the risk of sustained eGFR decline, kidney failure, cardiovascular death, non-fatal myocardial infarction, and hospitalisation for heart failure (31, 32). Finerenone received approval from the EMA on 16 February 2022 and is indicated for the treatment of CKD (stage 3 and 4 with albuminuria) associated with T2D in adults (33). Finerenone received approval from the Pharmaceutical and Medical Devices Agency (PMDA) in Japan on 22 March 2022 (34). Marketing authorisation applications have been submitted to the Medicines and Healthcare Products Regulatory Agency in the UK, and other countries globally.

As seen from the evidence reviewed, the clinical landscape for the treatment of patients with CKD and T2D is rapidly evolving with the introduction of new treatments, and it is of interest to study how treatment patterns may evolve with the approval of new drugs for this indication.

8. Research questions and objectives

The overall aim of this study is to describe patient profiles and treatment patterns in medication initiator cohorts of patients with CKD and T2D.

8.1. Primary objective

The primary objective of this study is

- To describe baseline patient characteristics, comorbidities, and comedication of adult patients with CKD and T2D who initiate an SGLT2i, a GLP-1 RA, a sMRA, finerenone, or another non-steroidal MRA (only in Japan) in each of 2 time periods corresponding to the finerenone pre-launch and post-launch dates.

8.2. Secondary objectives

The secondary objective(s) of this study are

- To describe treatment changes over time in the new-user cohorts, including treatment discontinuation, treatment switches, and add-on treatments in each of 2 time periods corresponding to finerenone pre-launch and post-launch dates; for finerenone, treatment titration (e.g., the percentages of finerenone patients uptitrating the dose from 10 mg to 20 mg within 6 months) will also be described.
- To describe temporal changes in the baseline characteristics of the medication-specific cohorts before and after finerenone launch.

9. Research methods

9.1. Study design

This is a multi-database, multinational, observational (non-interventional) cohort study to describe drug utilisation and temporal changes of different treatment options in adults with CKD and T2D using secondary data from population-based data sources in Europe, Japan, UK, and the US. Data source selection may be revised during the course of the study, including the addition or removal of data sources. This protocol will serve as the common protocol for all data sources and research partners involved in the study, with adaptations based on data source–specific specifications.

The study will identify separate medication-specific cohorts in 2 separate periods that correspond to the pre-approval and post-approval dates of finerenone. In the pre-finerenone study period (study period I), 4 new-user cohorts will be identified, based on the first use of a drug in 1 of these classes: SGLT2i, GLP-1 RA, sMRA, or nsMRA. In the post-finerenone study period (study period II), 5 new-user cohorts will be identified: SGLT2i, GLP-1 RA, sMRA, finerenone, and other non-steroidal MRA. The dates of study periods I and II will vary in each study country based on finerenone approval and launch dates. Approval dates for the first drug approved in each of the study medication cohorts are described in Table 2. The end of the study period for the post-finerenone cohort is tentatively set at 30 September 2024.

Table 2: First approval drug dates within each of the study medication cohorts

	Approval date of first medication in the class			
Medication class	**Europe**	**Japan**	**United Kingdom**	**United States**
SGLT2i	November 2012	March 2014	November 2012	January 2014
GLP-1 RA	November 2006	January 2010	November 2006	April 2005
sMRA[a]	Unknown	July 2007	Unknown	January 1960
Finerenone	February 2022	March 2022	Approval pending	July 2021
Other non-steroidal MRA	Not available	January 2019[b]	Not available	Not available

Notes: The first medication in the SGLT2i class in all countries was dapagliflozin. In the GLP-1 RA class, exenatide was the first approved in Europe, the UK, and the US, and liraglutide was the first approved in Japan.

[a] Spironolactone was the first sMRA approved in the US. In Europe, Japan, and the UK, the dates refer to eplerenone approval.

[b] Esaxerenone was the first other non-steroidal MRA approved in Japan (35) (34).

The medication-specific cohorts will not be mutually exclusive, and an individual patient may be included in multiple cohorts. Patients included in a medication-specific cohort who switch to a different study medication will continue to be followed in the first cohort but will also be included as new users of the second medication in the appropriate cohort if they meet the inclusion criteria. This design increases the efficiency of the study, but importantly, as the different medication-specific cohorts are not intended for comparison, this approach allows the assessment of the different medication-specific cohorts as if they were generated as stand-alone new user cohorts.

In each study period, the cohorts will be described with respect to baseline characteristics. Changes in drug utilisation parameters over time will be described in each cohort. Temporal changes of the baseline characteristics in the cohorts in each study period will be described.

9.2. Setting

9.2.1. Study population

For each data source, the source population will include all patients initiating 1 of the study medication classes with at least 12 months of continuous enrolment during each study period, who fulfil an electronic algorithm to identify patients with CKD and T2D. Four new-user cohorts will be created in study period I (SGLT2i, GLP-1 RA, sMRA, non-steroidal MRA). Five new-user cohorts will be created in study period II (SGLT2i, GLP-1 RA, sMRA, finerenone, and other non-steroidal MRA). Eligibility for each new-user cohort in each study period will be considered independently. The other non-steroidal MRA cohort will only be identified in Japan where esaxerenone is available.

9.2.1.1. New-user definition

For each study period, new users will be patients with an outpatient prescription/dispensing for a drug in 1 of the study medication classes during the study period and no prescription/dispensing for that index medication or any medication in that class during the previous 12 months. Patients may initiate multiple study classes during the study period, and patients may be eligible for multiple medication-specific cohorts. Patients who switch to a different class of study medication will remain in the first new-user cohort and will also enter the second new-user cohort at the time of the switch if they meet all inclusion and exclusion criteria. Patients who switch to a different medication within the same class will remain in the initial cohort.

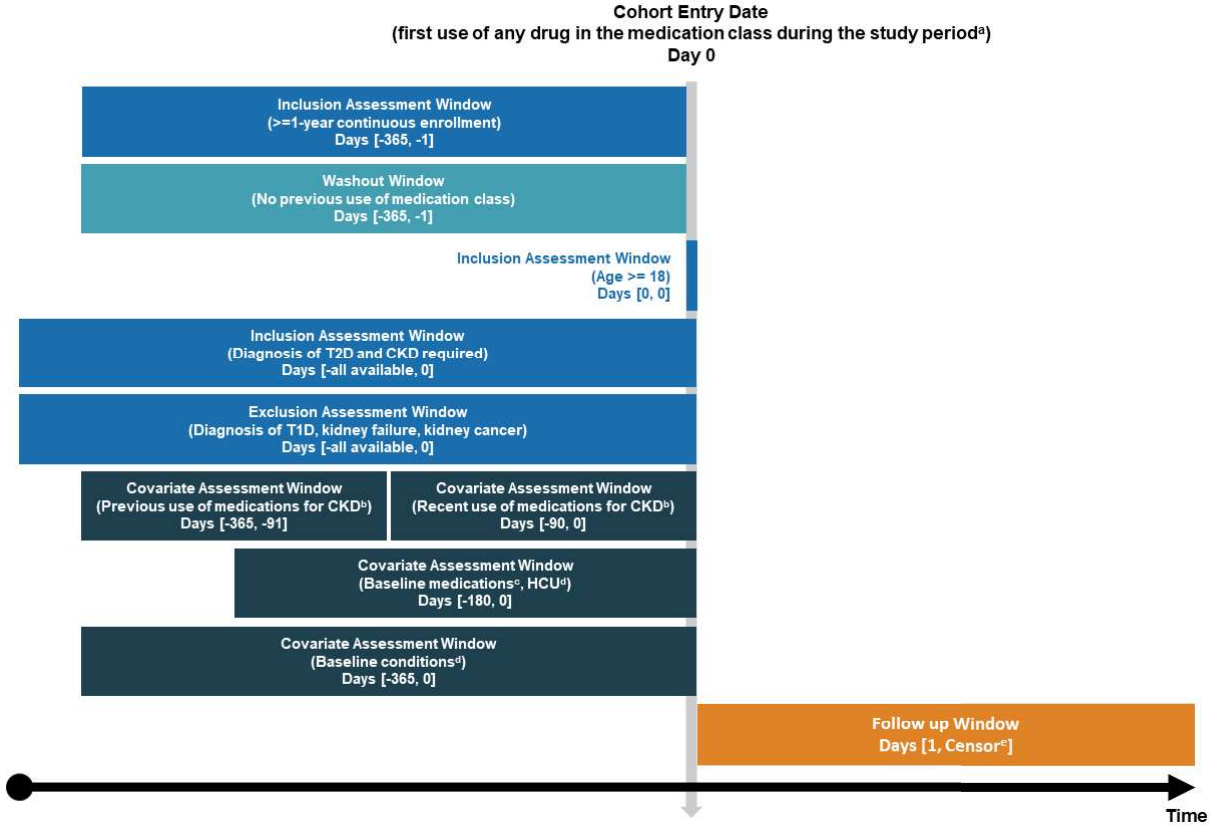
9.2.1.2. Index prescription definition

For each study period and for each study medication, the index prescription and dispensing will be the first eligible prescription that fulfils the definition of new use during the study period.

9.2.2. Study time frame

Figure 1 depicts the study design features regarding cohort eligibility, cohort entry, baseline assessment periods, and follow-up described in previous sections and following the methods described by Schneeweiss et al. (36).

Figure 1: Variable assessment windows relative to the study index date for medication-specific cohorts



ACEi = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blockers; CKD = chronic kidney disease; GLP-1 RA = glucagon-like peptide-1 receptor agonist; GP = general practitioner; HCU = health care utilisation; MRA = mineralocorticoid receptor antagonists; sMRA = steroidal mineralocorticoid receptor antagonists; SGLT2i = sodium-glucose cotransporter 2 inhibitor; T1D = type 1 diabetes; T2D = type 2 diabetes.

[a] Study period I: 01 January 2012 until 30 June 2021; study period II: after finerenone launch in each data source through 30 September 2024.

[b] SGLT2i, GLP-1 RA, sMRA, finerenone, other non-steroidal MRA, ACEi, ARB.

[c] Cardiovascular medications antihypertensives, beta blockers, direct renin inhibitors, angiotensin receptor-neprilysin inhibitor, lipid-lowering medications, anticoagulants, aspirin and other antiplatelets [e.g., clopidogrel, ticlopidine, prasugrel], digoxin, nitrates), anti-inflammatory drugs, antibiotics, other (acetaminophen, anticonvulsants, antifungals, antituberculars, chemotherapeutic agents.

[d] HCU measures: GP visits, hospital visits, hospitalisations, specialist visits, emergency department visits.
Baseline conditions: Chronic cardiovascular disease, hypertension, diabetes mellitus severity and complications, hyperlipidemia, lifestyle cardiovascular disease risk factors (smoking, obesity), stage of CKD, other kidney disorders, liver disease, chronic obstructive pulmonary disease, Charlson Comorbidity Index score.

[e] Censored at the earliest of death, disenrolment, exclusion criteria during follow-up, or end of the study period. Note that patients can be in more than 1 cohort at any given time based on index medication start date. Treatment change is not a censoring event. It is anticipated that many patients will have tried medications in more than 1 of the 4 cohort medication classes.

9.2.2.1. Index date (cohort entry date)

The index date will be defined as the date on which each identified new user receives the index prescription for the study medication. Index dates and cohort entry eligibility will be evaluated separately and independently for each medication-specific cohort; thus, an individual may have separate index dates for each medication-specific cohort.

9.2.2.2. Baseline and lookback period

To characterise the new-user cohorts at the time of study drug initiation, information available in the 365 days during the lookback (pre-index) period on or before the index date will be collected (including the index date, unless otherwise specified). All cohort members are required per the inclusion criteria to have at least 12 months of data before the index date (baseline period). Nevertheless, for comedications for diseases other than diabetes, the lookback period will be limited to 180 days before or at the index date. Comedications for which days supplied overlap or end at the index date will be described. In addition, the lookback period for health care resource utilisation will be limited to 180 days before the index date. Longer lookback periods for a small number of specific covariables may be used and adapted in each data source (e.g., kidney transplant, CKD, diabetes). The list will be detailed in the SAP and will be adapted to each data source considering coding practices, availability of laboratory results, and the time periods in which they are available as well as the general duration and availability of lookback periods.

9.2.2.3. Follow-up

In each of the 2 study periods, before and after finerenone approval, follow-up will start the day after the index date and will continue until the first occurrence of 1 of the following censoring criteria:

- End of the study period, defined as 30 June 2021 for study period I and the end of the study period (30 September 2024) for study period II
- Disenrollment from the database or emigration from the database catchment area (see Section 9.3.2)
- Development of kidney failure during follow-up
- Development of kidney cancer
- Death, identified from health system enrolment data or national death registries, as appropriate in each data source

It is expected that the length of follow-up time will vary among the data sources depending on the dates of finerenone availability

9.2.3. Selection criteria

Eligibility for each medication-specific cohort will be evaluated separately. Patients may be considered for eligibility for each medication-specific cohort in both study periods. For each specific medication in each study period, patients will be identified at the first use of a drug in the medication class during the study period, and the date of the observed first use will be the index date. Eligibility will be evaluated with the following inclusion and exclusion criteria.

9.2.3.1. Inclusion criteria

- Active registration or continuous enrolment for at least 12 months in 1 of the selected data sources before the index date
- No recorded prescription or dispensing of any medication in the class during the 12 months before the index date
- Age 18 years or older as of the index date
- Diagnosis of T2D on or before the index date (see Section 9.3, Variables)
- Diagnosis of CKD on or before the index date (see Section 9.3, Variables)

9.2.3.2. Exclusion criteria

- Type 1 diabetes identified by appropriate algorithms in each participating data source
- Kidney cancer on or before the index date
- Kidney failure
    - Maintenance dialysis on or before the index date
- Kidney transplantation on or before the index date

9.2.4. Representativeness

Exclusion criteria have been minimised with the intent of ensuring that the patients included in the study cohorts are as similar as possible to patients with CKD and T2D starting the study medications in real-world settings. The data sources include the population of either the entire country (Denmark) or of a specific region of the country (Valencia, Spain) or are representative of the general population of the country in terms of age and sex (CPRD, UK; PHARMO, The Netherlands). Optum (US) comprises employer-based health insurance and Medicare Advantage members; retired patients are overrepresented in the database, as a larger proportion of the database is aged 65 years or greater compared with the US population, although the Medicare Advantage beneficiaries may not be representative of the entire US Medicare population. The Japan Chronic Kidney Disease Database Extension (J-CKD-DB-Ex) is a longitudinal tertiary hospital–based data source, and younger patients with advanced CKD are more likely to be referred to and managed in university hospitals (37).

9.3. Variables

9.3.1. Exposure definition

Exposures of the study medications will be identified from prescriptions in the electronic health record (EHR) or administrative data for prescription or dispensing of medications, depending on the data source. The exposures will be defined as follows separately for each study period:

- New use of study drug. The date of the first observed prescription record or prescription dispensing for a drug in 1 of the study classes—an SGLT2i, GLP-1 RA, sMRA, finerenone,

or other non-steroidal MRA—during the study period will be considered the *index date,* and follow-up will start the day after. For SGLT2i, GLP-1 RA, sMRA, or other non-steroidal MRA, any medication within the corresponding class will be eligible. Finerenone, although also a non-steroidal MRA—and since it is the only MRA drug with the approved indication to reduce the risk of kidney and cardiovascular complications—will constitute a separate class. Patients without use of the study drug or any drug in that class in the 365 days before the index date (e.g., a washout period) will be considered new users of the study drug.

- Current use periods of the study drug will be defined from the day after the index date to the end of supply for consecutive prescriptions/dispensings plus a grace period of 30 days. For consecutive prescriptions/dispensings of the study medication separated by gaps of 30 days or less, time from current use will include the gaps between prescriptions/dispensings.
- Patients may have multiple current use periods during follow-up if their treatment is interrupted and then restarted after a gap of more than 30 days.
- Treatment discontinuation will be defined by the date corresponding to the end of current use.

For each patient's current use period of the study drug, number of prescriptions/dispensings, and duration of the current use period will be recorded. Duration of exposure will be based on the duration of current use periods. Categories of duration will be defined based on available data.

Dose will be the dosage at the index date. When the dose is missing, the dose will be estimated from the available recorded information (e.g., strength, number of units, amount of drug prescribed, days' supply).

A list of all study drugs, with Anatomical Therapeutic Chemical (ATC) codes, is included in Table 3 by drug class. Fixed-dosed combinations of glucose-lowering drugs and the study drugs are also included. For study drugs without ATC code and/or for data sources that use other coding systems than ATC codes, a detailed description of the respective codes/coding systems used to define exposure for the respective study drugs will be provided in the SAP.

Table 3: List of study drugs by class and ATC code

Medication class	Drug substance	ATC code
SLGT2i	dapagliflozin	A10BK01
	canagliflozin	A10BK02
	empagliflozin	A10BK03
	ertugliflozin	A10BK04
	ipragliflozin	A10BK05
	sotagliflozin	A10BK06
	luseogliflozin	A10BK07
	tofogliflozin	Not available
	dapagliflozin and metformin	A10BD15
	dapagliflozin, metformin, and saxagliptin	A10BD25

Medication class	Drug substance	ATC code
	dapagliflozin and saxagliptin	A10BD21
	empagliflozin and linagliptin	A10BD19
	empagliflozin and metformin	A10BD20
	canagliflozin and metformin	A10BD16
	ertugliflozin and metformin	A10BD23
	ertugliflozin and sitagliptin	A10BD24
	canagliflozin and teneligliptin	Not available
	ipragliflozin and sitagliptin	Not available
GLP-1 RA	exenatide	A10BJ01
	liraglutide	A10BJ02
	lixisenatide	A10BJ03
	albiglutide	A10BJ04
	dulaglutide	A10BJ05
	semaglutide	A10BJ06
	lixisenatide and insulin glargine	A10AE54
	Liraglutide and insulin degludec	A10AE56
sMRA	spironolactone	C03DA01
	potassium canrenoate	C03DA02
	canrenone	C03DA03
	eplerenone	C03DA04
Finerenone	finerenone	C03DA05
Other nsMRA[a]	esaxerenone	Not available yet
	aparenone	Not available yet

ATC = Anatomical Therapeutic Chemical; GLP-1 RA = glucagon-like peptide-1 receptor agonists; nsMRA = mineralocorticoid receptor antagonists; sMRA = steroidal mineralocorticoid receptor antagonists; SLGT2i = sodium-glucose cotransporter 2 inhibitors.

[a] This class of drugs will be included in only in the Japan data source.

Current guidelines for the treatment of CKD among patients with T2D suggest starting treatment with either an ACEi or an ARB. If, despite of taking 1 of these treatments, patients remain at risk of kidney function impairment, an SGLT2i is recommended as additional therapy to either an ARB or an ACEi (ARB cannot be combined with ACEi). Moreover, it is recommended that all patients with CKD and T2D follow multifactorial risk reduction: blood pressure, glucose, and lipid control combined with lifestyle modifications such as smoking cessation, weight loss, and exercise (13).

In clinical practice, new users of the study medication classes (SGLT2i, GLP-1 RA, sMRA, finerenone, or other nsMRA) may receive a prescription in the context of (1) adding it as a single treatment regimen for CKD, as double therapy (if the patient is already being treated with an ACEi or an ARB) or as triple therapy (if the patient is already being treated with an ACEi or an ARB combined with an SGLT2i) or (2) switching from one drug indicated for CKD (e.g., finerenone) to the study drug as monotherapy or combination therapy. However, GLP-1 RA, sMRA, and other

nsMRA are not approved to treat CKD in patients with T2D, and it will not be feasible with the data available in the data sources to differentiate whether SGLT2i and GLP-1 RA are administered specifically for CKD or to improve glycaemic control or to decrease cardiovascular disease risk. Therefore, the concept of switching will have a restricted meaning and will imply that the overall treatment has been changed without changing the total number of drugs to treat diabetes and CKD. The classification of the index medication as an added-on or switched-to medication will be based on the use of the study medications (plus the use of ACEi and ARBs) during the 90 days before the index date and on the use of those medications at the index date and during the 90 days after the index date.

As an example, Table 4 shows how the pattern of finerenone initiation would be described considering the previous use of the study medications (plus ACEi and ARB) during those periods. All potential patterns of use will be described in the SAP.

Table 4: Example of classification of pattern of use of finerenone as index medication at the index date

Medication class	Use in the 90 days before index date	Use at index date and during the 90 days after	Pattern
SGLT2i	Yes	No	Switch
GLP-1 RA	No	No	Non-user
sMRA	No	No	Non-user
Non-steroidal MRA[a]	No	No	Non-users
ACEi	Yes	Yes	Add-on
ARB	No	No	Non-user

ACEi = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blockers; GLP-1 RA = glucagon-like peptide-1 receptor agonists; MRA = mineralocorticoid receptor antagonists; sMRA = steroidal mineralocorticoid receptor antagonists; SLGT2i = sodium-glucose cotransporter 2 inhibitors.

[a] Non-steroidal MRA drugs other than finerenone will only be identified in Japan.

9.3.2. Outcomes definition

The secondary objective of the study includes the following outcomes: treatment discontinuation, treatment switches, and add-on treatments during each study period. The detailed definitions for each outcome will vary by data source and will be specified in the SAP.

9.3.3. Covariate definition

Variables potentially associated with the use or not of the study medications—e.g., concomitant medications, comorbidities, lookback period duration—will be identified for all cohort members before or on the index date. A detailed description of definitions and code lists for all covariates that will be used in each data source will be specified in the SAP.

The following demographic characteristics will be evaluated as of the index date:

- Age
- Sex
- Race (as available in the data)
- Socioeconomic status (as available in the data)

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

- Markers of severity of T2D (as available in each data source)
    - Duration of T2D (as available in each data source)
    - Complexity of treatment for T2D (e.g., dual vs. monotherapy) and for CKD
    - Use of insulin
    - HbA1c (most recent recorded laboratory value in the 180 days before the index date, if available)
    - Hyperkalaemia defined as hospitalised hyperkalaemia or a potassium level greater than 5.5 mEq/l according to laboratory results as available in each data source
    - Retinopathy
    - Neuropathy
    - Amputations
    - The Diabetes Severity Complications Index (38, 39), as feasible in each data source
- Markers of severity of kidney dysfunction
    - Duration of CKD (all lookback period, as available in each data source)
    - Aetiology of CKD, as available in each data source (data source–specific diagnosis codes will be described in the SAP)
    - CKD stage or severity will be defined based on the eGFR, urine ACR levels, or stage-specific diagnosis codes (as available in each data source)
    - Hospitalisation episodes for acute kidney injury

The CKD stage will be defined using eGFR as recorded in the data source either by diagnosis codes or laboratory results. If eGFR is not recorded in the data source, it will be calculated using the creatinine-based 2021 CKD-EPI equation (without including cystatin-C) (40), which removes the black coefficient following recommendations from recent evidence and guidelines statements (41-44):

eGFR = 142 × min (Scr/ κ, 1)$^{a}_{1}$ × max (Scr/ κ, 1)$^{a}_{2}$ × c^{Age} × d [if female]

Where:

a_1 = −0.241 for females and −0.302 for males

a_2 = −1.200

c = 0.9938

d = 1.012

κ is 0.7 for female participants, and 0.9 is for male participants; min indicates the minimum of Scr/κ and 1, and max indicates the maximum of Scr/κ and 1

The coefficient a_1 is used for levels of creatinine less than or equal to 0.9 mg per decilitre for male participants and 0.7 mg per decilitre for female participants. The coefficient a_2 is used for levels of creatinine greater than 0.9 mg per decilitre for male participants and 0.7 mg per decilitre for female participants

The Jm-EPI-CKD formula will be used in Japan (45, 46).

CKD stage based on eGFR categories (mL/min/1.73 m^2) will be defined as follows:
Stage 1: > 90, normal or high
Stage 2: 60-89, mildly decreased
Stage 3a: 45-59, mildly to moderately decreased
Stage 3b: 40-44, moderately to severely decreased
Stage 4: 15-29, severely decreased
Stage 5: < 15 OR treated by dialysis, kidney failure (this stage will be an exclusion criterion [Section 9.3.3.2])

- For those patients without eGFR values available, if recorded CKD diagnosis codes indicate CKD stage, the stage will be recorded.
- CKD may also be based on albuminuria measured with ACR (1). For those patients with ACR values available, the following albuminuria categories will be assigned (ACR mg/g is approximately equivalent to AER mg/d):
A1: < 30, normal to mildly increased
A2: 30-300, moderately increased (formerly “microalbuminuria”)
A3: > 300, severely increased (includes nephrotic syndrome, > ~ 2000). The ACR categories will be used if available, as they provide additional information regarding cardiovascular disease risk and kidney prognosis (13). However, for CKD staging, only eGFR values will be used.
- If eGFR, ACR, and stage-specific diagnosis codes are not present, the patient will be classified as CKD stage unspecified.

- Gout

The following comorbidities will be ascertained:

- Macrovascular complications: coronary heart disease, cerebrovascular disease, peripheral vascular disease

- Cardiovascular risk factors: hypertension, hypercholesterolaemia
- Congestive heart failure
- Severe liver disease
- Other comorbidities measured by the Charlson or similar comorbidity indices (47) (48) or as single entities

The following lifestyle factors will be defined, as available in each data source:

- Body mass index (BMI) or evidence of obesity, as available in each data source
- Smoking status, as available in each data source
- Alcohol abuse and alcohol abuse–related conditions, as available in each data source

History of study medication classes and other treatments for CKD (other than the index medication class for each medication-specific cohort), measured both in the 90 days before and including the index date and > 90 days but within 365 days before the index date:

- SGLT2i and fixed-dose combinations
- GLP-1 RA and fixed-dose combinations
- sMRA
- Finerenone
- Other non-steroidal MRA (only applicable in Japan where esaxerenone is available)
- ACEi and/or ARB

The following comedications and health care utilisation measures will be identified in the 180 days before and including the index date.

- Medications for T2D other than the index medication
    - Metformin and fixed-dose combinations
    - Sulfonylureas and fixed-dose combinations
    - Sulfonamides
    - Alpha glucosidase inhibitors
    - Thiazolidinediones
    - Dipeptidyl peptidase-4 inhibitors (DPP-4i) and fixed-dose combinations
    - Repaglinide
    - Nateglinide
    - Mitiglinide
    - Imeglimin (Japan only)

- Cardiovascular medications
    - ACEi or ARB
    - Antihypertensives/diuretics other than ACEi or ARB
    - Beta blockers
    - Direct renin inhibitors
    - Angiotensin receptor-neprilysin inhibitor
    - Statins
    - Non-dihydropyridine calcium channel blockers
    - Anticoagulants
    - Aspirin and other antiplatelets (e.g., clopidogrel, ticlopidine, prasugrel)
    - Digoxin
    - Nitrates and other vasodilators
    - Lipid-lowering drugs other than statins
- Other medications
    - Anti-inflammatory drugs
    - Antibiotics, antifungals, antituberculars
    - Acetaminophen
    - Anticonvulsants
    - Chemotherapeutic agents
- General practitioner visits
- Hospital visits and hospital admissions
- Specialist visits
- Emergency department visits

9.3.3.1. Variables defining eligibility

The following characteristics will be defined to determine eligibility for the study cohort.

- Active registration will be defined separately for each included data source. In Optum, active registration will imply continuous enrolment in the health plan with medical and pharmacy coverage. In CPRD, it will imply registration in a primary care practice with up-to-standard data. In VID, it will imply continuous enrolment in the health plan with medical and pharmacy coverage, and residence in the region. In Denmark, it will imply residency in the country and coverage by the laboratory databases. In PHARMO, it will imply up-to-standard data in the PHARMO Database Network.

- T2D diagnosis at any point before (and including) the index date
    - Algorithms to identify T2D will be adapted to the type and availability of data in each data source and will be specified in the statistical analysis plan (SAP). In CPRD, patients with T2D will be identified based on a combination of outpatient and inpatient codes for T2D, T1D, diabetes unspecified, and GP prescriptions for insulin and non-insulin glucose-lowering drugs using an adapted definition from Holden et al. (49). In Denmark, patients with T2D will be identified based on a combination of community pharmacy prescription data, hospital codes, and primary care procedure codes (50). In Optum, VID, and J-CKD-DB-Ex, algorithms will be developed. In PHARMO, patients with T2D will be identified based on a combination of GP-recorded diagnoses and prescriptions for drugs used in diabetes.
- CKD stages 2-4 related to eligibility will be defined according to the presence of the following criteria at any point before (and including) the index date:
    - A diagnosis code indicating CKD stage 2, 3, 4, or stage unspecified

    OR

    - Two urine ACR test results ≥ 30 mg/g separated by at least 90 days and no more than 540 days. Depending on test availability in the different data sources, equations for converting urine protein–creatinine ratio and dipstick protein to ACR may be used (51).

    OR

    - Two different eGFR test results ≥ 15 mL/min/1.73 m^2 AND < 60 mL/min/1.73 m^2 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. If an eGFR value is not reported, but sufficient information to calculate one is present, it will be calculated. See Section 9.3.3 on the criteria used to derive eGFR values from creatinine results using the creatinine-based 2021 Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) equation (40). For Japan, a specific Jm-CKD-EPI formula will be used (45, 46).

9.3.3.2. Variables defining exclusion criteria

Exclusion diagnoses will be identified based on recorded GP diagnoses or hospital outpatient or inpatient diagnoses or laboratory results during the lookback period or on the index date. Definitions of specific variables will be adapted to the type and availability of data in each data source.

- Kidney failure: Substantially impaired kidney function for exclusion purposes will be defined as meeting any of the following before or at the index date:
    - Two different eGFR test results < 15 mL/min/1.73 m^2 separated by at least 90 days and no more than 540 days
    - Dependence on dialysis (at least 3 sessions during the baseline period)

    - A diagnosis code indicating kidney failure or CKD stage 5 (ICD-10 code N18.5)
    - Kidney transplant (ICD-10 code Z94.0)
- Kidney cancer (ICD-10 code C64)
- Type 1 diabetes mellitus (Note: In some data sources, T1D status will already be accounted for as part of the T2D inclusion criterion; in other data sources, T1D status will be defined separately. Data source–specific criteria will be included in the SAP.)

9.4. Data sources

The study will be conducted initially using data from data sources in 6 countries—Denmark, Japan, the Netherlands, Spain, the UK, and the US—using a common SAP adapted to specifications in each data source, with oversight by the study coordinating centre, which will compile aggregated results from each data source into study reports. Data sources included in the study may be revised during the course of the study, including the addition or removal of data sources. The main features of each of the proposed data sources are summarised in Table 5. The following sections describe in more detail the information on laboratory, diagnosis, procedure, and treatment data as well as patient characteristics captured in each data source proposed.

Table 5: Main features of the preselected databases for the FINEGUST study

Feature	Denmark, National Health Registers	Netherlands, PHARMO	Spain, VID	UK, CPRD	US, Optum CDM	Japan Chronic Kidney Disease Database (J-CKD-DB-Ex)
Country population[a]	5,822,763	17,407,585	Valencia, 5.057.353[b]	67,025,542	332 million[c]	125,710,000[d]
Database population	5.8 million	4 million	5 million	14 million (GOLD plus Aurum)	68 million (15-20 annual covered lives)	
Database type	National health record databases capable of linkage with other databases through a unique personal identification number	Primary health care electronic medical record database plus partial linkage to other data	Regional health record databases capable of linkage with other databases through a unique personal identification number	Primary health care electronic medical record database plus partial linkage to HES and other data	Administrative health claims from commercial health plan and Medicare Advantage members	Hospital-based, longitudinal electronic medical record database
Drug dictionary codes/therapeutic classification	ATC	ATC	ATC	dm + d and Gemscript	NDC codes	National drug code in Japan, HOT codes

Feature	Denmark, National Health Registers	Netherlands, PHARMO	Spain, VID	UK, CPRD	US, Optum CDM	Japan Chronic Kidney Disease Database (J-CKD-DB-Ex)
Disease and procedure coding system(s)	ICD-10 Procedure codes: NCSP	ICD-9-CM/ICD-10, ICPC	ICD9-CM, ICD-10-ES	SNOMED CT and local EMIS® codes and Read codes	ICD-9-CM/ICD-10-CM CPT, HCPCS	ICD-10

ATC = Anatomical Therapeutic Chemical Classification System; CDM = Clinformatics DataMart; CPRD = Clinical Practice Research Datalink; CPT = Current Procedural Terminology; dm + d = *Dictionary of Medicines and Devices;* EMIS = Egton Medical Information Systems; GOLD = General Practitioner Online Database; HCPCS = Healthcare Common Procedure Coding System; HES = Hospital Episode Statistics; HOT = Standard master (HOT codes) for pharmaceutical products; http://www2.medis.or.jp/master/hcode/; ICD-10 = *International Classification of Diseases, 10th Revision*; ICD-10-CM = *International Classification of Diseases, 10th Revision, Clinical Modification*; ICD-9-CM = *International Classification of Diseases, 9th Revision, Clinical Modification*; NCSP = NOMESCO Classification of Surgical Procedures; ICPC = International Classification of Primary Care; NDC = National Drug Code; Optum CDM = Optum Clinformatics DataMart; PHARMO = PHARMO Database Network of the PHARMO Institute for Drug Outcomes Research (the Netherlands); SNOMED CT = Systematized Nomenclature of Medicine – Clinical Terms; UK = United Kingdom; US = United States; VID = Valencia Health System Integrated Database.

[a] Population data from (52), except for the Valencia region of Spain.

[b] Population data from the Valencia regional government (https://pegv.gva.es/auto/produccion/web/PMH/UC/2020/ultimesxifres.html).

[c] Population data from the US census on 17 May 2021 (https://www.census.gov/popclock/).

[d] Population data from Statistics Bureau of Japan (https://www.stat.go.jp/english/data/handbook/c0117.html)

9.4.1. Danish National Health Registers, Denmark

Denmark has a tax-funded health care system that ensures easy and equal access to health care for all its citizens, and all contacts with the system are recorded in administrative and medical registers (53). Denmark's population was 5,850,189 individuals as of 01 June 2021 (54). Health care coverage includes visits to general practitioners (GPs) and specialists, hospital admissions, and outpatient visits. The costs of most medicines used outside the hospital setting are partially reimbursed by the Danish health system (55). The civil registration system in Denmark allows personal identification of each person in the entire Danish population through a 10-digit personal identifier ("central pharmaceutical reference [CPR] number") assigned to all Danish residents, which enables linkage between all Danish registers, such as the Danish National Patient Register, the Danish National Prescription Registry, the Danish National Laboratory Database, the Danish Cancer Registry, and the Danish Register of Causes of Death (55, 56). Data collected in these registers are available to external investigators for research purposes, such as for post-authorisation safety studies and drug utilisation studies. The research process requires collaboration with a local university or an investigator affiliated with a research institute to access the data and ethics committee notification or approval to handle the data.

The Danish National Patient Register includes data on all hospital admissions since 1977 and on hospital outpatient clinic visits to specialists and emergency department visits since 1995. Hospital discharge diagnoses and information on surgical procedures, in-hospital deaths, and some selected drugs are recorded. Since January 1994, hospital discharge diagnoses have been coded using

International Classification of Diseases, 10th Revision (ICD-10) codes. Diagnoses for conditions that do not require hospitalisation are captured only as secondary diagnoses when patients are hospitalised for another condition or as visits to a hospital outpatient clinic; thus, visits with a GP are not captured (56). The National Health Board records all procedures occurring in public hospitals through procedure codes used in Demark.

The Danish National Prescription Registry contains data on all drugs sold in primary care or purchased for use in Danish hospitals, but the drugs used during hospital admissions or drugs supplied directly by hospitals or treatment centres (e.g., chemotherapeutic agents) are not captured on the individual level (53). However, from 2020 through 2021 onwards, information on those drugs is expected to be available via a new hospital prescription register. The database will be available at the beginning of 2022.

In the Danish National Health Registers, information on oral medications dispensed from hospital (either for hospitalised and non-hospitalised patients) and ambulatory pharmacies is available, including ATC code, product name, strength, date of dispensing, and amount dispensed.

Results of laboratory tests are available in Denmark for both outpatient and inpatient settings through the Register of Laboratory Results for Research (LAB_F database) (57). The LAB_F database contains hundreds of millions of stored laboratory test results for most individuals living in Denmark from every blood sample taken in any public or private hospital or by any GP or privately practising specialist physician and submitted to any clinical chemistry department located in Denmark's register-covered regions. The LAB_F database covers all 5 Danish regions (the Central Denmark, North, South, Zeeland, and Capital regions). The time coverage of the database varies by region, but the coverage is complete for all regions from 2014/2015 onwards, but regional data were available since the 1990s. The lag time (i.e., the time from a patient encounter to the time when data are available for research) between the introduction of a new test and its capture in the database is 1 to 2 months. The lag time is different for the different registers and ranges between 3 and 6 months. The Danish Health Data Board, which will be used to access data for FINEGUST, receives data updates from all the data sources on an almost daily basis. The time-limiting issue concerns obtaining all relevant permissions, which may take 3 to 6 months.

9.4.2. PHARMO Database Network of the PHARMO Institute for Drug Outcomes Research, The Netherlands

The medical record linkage system of the PHARMO Database Network of the PHARMO Institute for Drug Outcomes Research (the Netherlands) (PHARMO) is a population-based data tracking system that includes complete patient-level information on patient demographics; mortality; in-hospital and ambulatory drug dispensing; hospital diagnoses; and clinical laboratory, pathology, and GP information for 4 million community-dwelling inhabitants of a well-defined area in the Netherlands (https://www.pharmo.nl/what-we-have/pharmo-database-network/) (58). The average follow-up is 10 years. The data collection period and catchment area differ across databases in the network, and the databases overlap to varying degrees.

General practice data: The General Practitioner Database includes data from electronic patient records registered by GPs. Primary care data are available for a portion of the population: approximately 3.2 million inhabitants (approximately 20% of the Dutch population). The overlap between the In-patient Pharmacy Database and primary care data is small, thus limiting the number

of inpatient medication users for whom a proxy for the indication might be sought. The data recorded include diagnoses and symptoms, laboratory test results, specialist referrals, and drug prescriptions. The prescription information includes the date, type of product, strength, dosage regimen, quantity, and route of administration. The treatment indication is not recorded as directly associated with the medication records, but it can be ascertained through concomitant diagnoses. Free-text comments may provide valuable information to identify diagnoses or the indication but are available for only some patients and are not mandatory to be recorded by the GP. Information on lifestyle factors (e.g., BMI, smoking status, alcohol consumption) is available if it has been recorded in the GP records.

Hospitalisation data: The Hospitalisation Database includes discharge dates, discharge diagnoses, and procedures for hospitalisations longer than 24 hours (or shorter if the patient required a bed). Hospital discharge diagnoses are available from the Dutch National Basic Hospital Care Registration (Landelijke Basisregistratie Ziekenhuiszorg [LBZ]) and are recorded using ICD-10 codes. Procedures are coded according to the Dutch Hospital Data Foundation registration system.

Prescription data: The Out-patient Pharmacy Database includes products prescribed by GPs or specialists and dispensed in outpatient pharmacies that cover approximately 3.8 million residents. This information includes product, date, strength, dose, quantity, administration route, prescriber specialty, and cost. The In-patient Pharmacy Database includes data on dispensings from hospital pharmacies given during hospitalisations. This information includes type of drug, start and end dates of use, strength, dose, and administration route. Drugs are coded using the ATC classification system.

Laboratory test values: Laboratory test results are available for a catchment area representing 1.2 million residents. The Clinical Laboratory Databases include results of tests ordered by GPs and specialists. Kidney outcomes and hyperkalaemia can be identified based on diagnosis and procedure codes recorded in the Hospitalisation Database and/or combined or supplemented with laboratory test values available from the clinical laboratory records. These tests are those ordered in primary or secondary care settings. However, if the tests are ordered from primary care, the results are also captured in the GP records covering a larger population. The overlap between the Clinical Laboratory Database and Out-patient Pharmacy Database is approximately 20%. Thus, approximately 800,000 patients would have both laboratory results and prescription information available.

Lifestyle data: Information on lifestyle variables (e.g., BMI, smoking, alcohol consumption) is available in the General Practitioner Database if recorded by GPs in the electronic medical records.

9.4.3. Valencia Health System Integrated Database, Spain

Valencia is a region in Spain with a population of approximately 5 million people. Over 98% of the population is covered by the Valencia Health System (VHS), which is a public system. VHS is the data custodian and provider of several health care data sets that can be linked at the individual level by a single personal identification number and that constitute VID (59). VID provides exhaustive longitudinal information, including sociodemographic and administrative data (e.g., sex, age, nationality), clinical (e.g., diagnoses, procedures, diagnostic tests, imaging), pharmaceutical (e.g., prescription, dispensation), and health care utilisation data from hospital care, EDs, specialised care (including mental health and obstetrics care), primary care, and other public health services.

VID also includes a set of associated population databases and registers of significant care areas, such as cancer, rare diseases, vaccines, congenital anomalies, microbiology, and others, as well as public health databases from the population screening programmes. The database uses standard coding systems (ICD for procedures and diagnoses and ATC for prescription drugs). This comprehensive database has been used in several projects to evaluate the adherence, safety, and effectiveness of medication in a real-world setting (60-68).

The data sets in VID are as follows:

The Population Information System (SIP) is a regionwide database that provides basic information on VHS coverage (e.g., dates and causes of VHS entitlement or disentitlement, insurance modality, pharmaceutical copayment status, assigned Healthcare Department, Primary Healthcare District, primary care physician) as well as some sociodemographic data, such as sex, date of birth, nationality, country of origin, previous year's income stratum, employment status, social exclusion risk, geographic location, address, and other administrative data. Importantly, the SIP database includes the date of death captured from the mortality registry. The SIP database is paramount to VID, as it is the source of the individual, exclusive, and permanent identifier number associated with each individual (the SIP number) that is then used throughout the rest of the databases, thereby allowing data linkage across the multiple databases in the network.

The Ambulatory Medical Record (ABUCASIS) is the electronic medical record for primary and specialised outpatient activity, with 96% population coverage since 2009. ABUCASIS is the integration of 2 main modules—the Ambulatory Information System (SIA) and the Pharmaceutical Module (GAIA)—which include paediatric and adult primary care, mental health care, prenatal care, and specialist outpatient services, as well as providing information about dates, visits, procedures, laboratory test results (e.g., serum potassium, serum creatinine, eGFR, ACR, HbA1c, arterial and venous blood gases), diagnoses, and clinical and lifestyle information. ABUCASIS also includes information on several health programmes (e.g., healthy children, vaccines, pregnancy, notifiable diseases), the primary care nurse clinical record, and the health-related social assistance record. The SIA module uses the *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM) for coding diagnoses (and, partially, ICD-10-ES [*International Classification of Diseases, 10th Revision, Spanish Version*] from 2019). The SIA also uses the Clinical Risk Groups system to stratify the morbidity of the entire population.

The GAIA Pharmaceutical module stores data on all outpatient pharmaceutical prescriptions and dispensings, including both primary care and outpatient hospital departments, using the ATC classification system and the National Pharmaceutical Catalogue, which allow the identification of the exact content of each dispensing. GAIA does not include in-hospital medication or medication administered in the Accident & Emergency Department (AED). GAIA provides detailed information on prescriptions issued by physicians, such as treatment duration and dosage. GAIA includes a comprehensive e-prescription paper-free system connected to all community pharmacies in the region that permits the linkage of individual prescriptions and dispensings through a specific prescription identification number. This linkage enables a refined estimation of common and relevant research entities, such as medication adherence.

The Hospital Medical Record (ORION) provides comprehensive information covering all areas of specialised care from admission, outpatient consultations, hospitalisation, emergencies, diagnostic services (e.g., laboratory tests, imaging, microbiology, pathology), pharmacy, surgical block

(e.g., day surgery, critical care), prevention and safety, social work, at-home hospitalisation, and day hospitalisation. ORION is currently in the process of being integrated for the whole region, with several databases already fully integrated and available for all hospitals, including the Minimum Basic Data Set at Hospital Discharge (MBDS) and the AED clinical record. Other information, such as inpatient drug prescriptions, laboratory results for hospitalised patients, and plasma level determinations are captured in ORION but are still hospital based (i.e., not linked to VID).

The MBDS (Minimum Basic Data Set) is a synopsis of clinical and administrative information on all hospital admissions and major ambulatory surgery in VHS hospitals, including public-private partnership hospitals (approximately 450,000 admissions per year in the region). The MBDS includes admission and discharge dates, age, sex, geographic area and zone of residence, primary diagnosis at discharge, up to 30 secondary diagnoses (comorbidities or complications), clinical procedures performed during the hospital episode, and the diagnosis-related group(s) assigned at discharge. The MBDS used the ICD-9-CM system for coding through December 2015 and ICD-10-ES thereafter. The MBDS was extended in 2015 to include the "present on admission" diagnosis marker and information on tumour morphology.

The AED clinical record was launched in 2008 and collects triage data, diagnoses, tests, and procedures performed in public EDs. As with the MBDS, the coding system used was ICD-9-CM until December 2015 and ICD-10-ES thereafter. Diagnosis codification has been increasing from approximately 45% of all ED visits between 2008 and 2014 up to approximately 75% in 2017, largely due to the progressive incorporation of hospital coding.

In all databases in VID, individual data are collected daily as a part of the routine clinical care provided to patients. Some data sets are updated daily and available for research immediately. In other data sets, such as the MBDS and AED, the data are subject to a consolidation and quality-check process before they are available for research; in these cases, data from the last quarter before the data extraction may be missing or not yet consolidated.

Linkage to a mortality register in VID is possible.

In VID, it is not possible to conduct source validation studies (patient consent would be required).

An average of 6 months since the approval of the Data Commission and the availability of data is expected.

9.4.4. The Japan Chronic Kidney Disease Database (J-CKD-DB)

The Japan Chronic Kidney Disease Database (J-CKD-DB) is a large-scale, nationwide comprehensive clinical database of patients with CKD based on EHR data from 21 participating university hospitals nationwide (37, 69). Using a standardised method for information exchange (Standardized Structured Medical Information eXchange; SS-MIX2) (70), the J-CKD-DB efficiently compiles clinical data on patients with CKD across hospitals, regardless of differences in EHR systems. It includes automatically extracted data from all patients, regardless of whether they are under the care of nephrology or other specialities, aged 18 years or older with CKD in Japan (proteinuria $\geq$ 1 + [dipstick test] and/or eGFR < 60 mL/min/1.73 m^2).

Initiated in December 2014, the database contains information on all inpatient and outpatient encounters, prescriptions, diagnostic codes, and laboratory measurements (71).

The J-CKD-DB comprises 2 databases:

- J-CKD-DB, the older database, containing cross-sectional data
- J-CKD-DB Extension (J-CKD-DB-Ex), containing longitudinal data, with ~200,000 cases of CKD

These data sources have been previously used in comparative and effectiveness analyses.

9.4.5. Optum Clinformatics® DataMart (CDM)

Optum Clinformatics DataMart (CDM) is a database comprising administrative health claims for members of a large national managed care company affiliated with Optum. CDM comprises commercial health plan data and Medicare Advantage members with service dates beginning January 2007 to the present. The population is geographically diverse, spanning all 50 states plus the District of Columbia and covering approximately 3% to 4% of the US population. The database includes approximately 15 to 20 million annual covered lives, for a total of approximately 68 million unique lives over the available period.

Pharmacy claims include drug name, dosage form, drug strength, fill date, days' supply, financial information, and de-identified patient and prescriber information, allowing longitudinal tracking of medication refill patterns and changes in medications. Medical claims or encounter data are collected from all available health care sites (e.g., inpatient hospital, outpatient hospital, emergency department, physician's office, surgery centre) for virtually all types of provided services, including specialty, preventive, and office-based treatments. These administrative claims are submitted for payment by providers and pharmacies and are verified, adjudicated, adjusted, and de-identified prior to inclusion in CDM. Data are included for only those covered lives with both medical and prescription drug coverage to enable users to evaluate claims related to the complete health care experience. The data are ICD-10-CM compliant.

Additionally, the CDM includes results for outpatient laboratory tests processed by large national vendors under contract with the managed care organisation. In addition to medical claims, pharmacy claims, and laboratory test results, CDM includes data tables related to member inpatient confinements, member enrolment, and provider data.

The data are updated quarterly, with a lag time of approximately 9 months.

9.4.6. Clinical Practice Research Datalink (CPRD)

In the UK, nearly all residents are registered at general medical practices that use electronic medical records. Some of those records are available for research in CPRD, which contains diagnostic and prescribing information recorded by GPs as part of their routine clinical practice. CPRD data are divided into 2 databases—CPRD GOLD and CPRD Aurum—that differ in the system software used. As of June 2021, CPRD GOLD contains data for 20.3 million patients with research-quality data, 3.1 million of whom are registered in a contributing practice and considered active. CPRD GOLD includes practices from England, Wales, Northern Ireland, and Scotland. As of June 2021, CPRD Aurum contains data for 40.0 million patients with research-quality data, 13.4 million of whom are registered in a contributing practice (1,489 contributing practices) and considered active; 99% of the practices are from England (72). The patients in both databases are representative of the UK population in terms of age and sex.

In the UK, GPs serve as the gatekeepers for all medical services. Detailed information on prescriptions written by GPs, including prescribed dose and duration, is routinely recorded. CPRD also contains information on lifestyle factors, with a variable proportion of missing values. In contrast, pharmaceutical exposures and comorbidities are based on outpatient prescriptions and diagnoses and are expected to be complete.

The CPRD Aurum online database contains data collected in primary care practices that participate in CPRD. These data are at least partially linkable with other health care data sets (e.g., hospitalisation data, national mortality data). Updated, valid, linked data are available through the CPRD Division of the UK Medicines and Healthcare Products Regulatory Agency.

Most CPRD Aurum practices (93%) are linked to the following external data resources:

- Office for National Statistics (ONS): death registration data (date, place, and causes of death)
- Hospital Episode Statistics (HES): data on admitted patient care, outpatient hospital care, accident and emergency care, diagnostic imaging, and patient-reported outcome measures
- National Cancer Registration and Analysis Services
- Patient-level and practice-level socioeconomic deprivation data

Linkage to HES enables access to the hospitalisation data, i.e., admission date, discharge diagnoses, and procedure codes (73). Linkage to the National Death Register at ONS can be used to ascertain date and cause(s) of death and to validate the mentions of death in the GP records. Death rates by age group and various causes of death, including ischaemic heart disease, are comparable between linked CPRD data and official rates for England and Wales, and the subset of linked CPRD practices seems to be a representative sample of the general population (74). In CPRD, participating GPs are required to record in the database the date of death. However, evidence indicates that without the ONS linkage, the GP-recorded date of death is not always accurate (75). Moreover, cause of death is recorded in CPRD with a variable degree of completeness. Data in HES and ONS are updated every 6 months, but the lag time can be more than 1 year.

Detailed information on prescriptions written by GPs, including prescribed dose and duration, is routinely recorded in the data source. In CPRD Aurum, observations are coded using a combination of SNOMED CT (Systematized Nomenclature of Medicine–Clinical Terms; UK edition) (76), Read version 2 (77), and local EMIS (Egton Medical Information Systems) Web® codes. The Drug Dictionary contains information on drug and device prescriptions recorded in EMIS Web®. This information is coded using the *Dictionary of Medicines and Devices* (dm+d), which exists within the SNOMED CT terminological structure (78).

Because GPs serve as the gatekeeper for all medical services in the UK, any visit to a specialist or hospital requires communication back to the GP, who enters that information into the patient's medical record. The validity of the former General Practice Research Database, upon which CPRD was founded, is well established as a reliable data source for drug safety studies in numerous therapeutic areas (79, 80).

We propose using CPRD Aurum for the present study. CPRD Aurum includes more patients than CPRD GOLD, and almost all medical practices in CPRD Aurum have linkage to HES available. According to the most recent set of linkages released by CPRD (set 21) (81), linkage data in CPRD

GOLD cover approximately 74% of contributing CPRD GOLD practices in England and approximately 50% of contributing CPRD GOLD practices in the UK, for a total of 9,268,968 patients being eligible for linkage. In contrast, linkage data in CPRD Aurum cover approximately 99% of CPRD Aurum practices, all of which are in England, and 37,714,916 patients are currently eligible for linkage. Moreover, the number of practices contributing to CPRD GOLD is decreasing, while the number of practices contributing to CPRD Aurum is increasing. This trend is expected to accelerate in the future.

Research using CPRD data requires approval from the CPRD Independent Scientific Advisory Committee.

9.5. Study size

All patients meeting the study eligibility criteria will be included in the study cohorts. This is a descriptive study, and no formal comparisons between or within cohorts are planned. Given the large size of the data sources and that most study drug classes are commonly used among patients with CKD and T2D, the precision estimates included in the analysis (see Section 9.7) are expected to be adequate in study period I. In study period II, especially for finerenone, precision may vary depending on the uptake of the drug in each data source.

9.6. Data management

All conversion of the original data to analysis variables will be performed using SAS software version 9.4 or higher (SAS Institute, Inc.; Cary, North Carolina). In VID, Stata or R will be used. Routine procedures include checking electronic files, maintaining security and data confidentiality, following the SAP, and performing quality control checks of all programmes.

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 (i.e., storage on secure server), with periodic backup of files. A more complete description of the data management procedures will be included in the SAP.

9.7. Data analysis

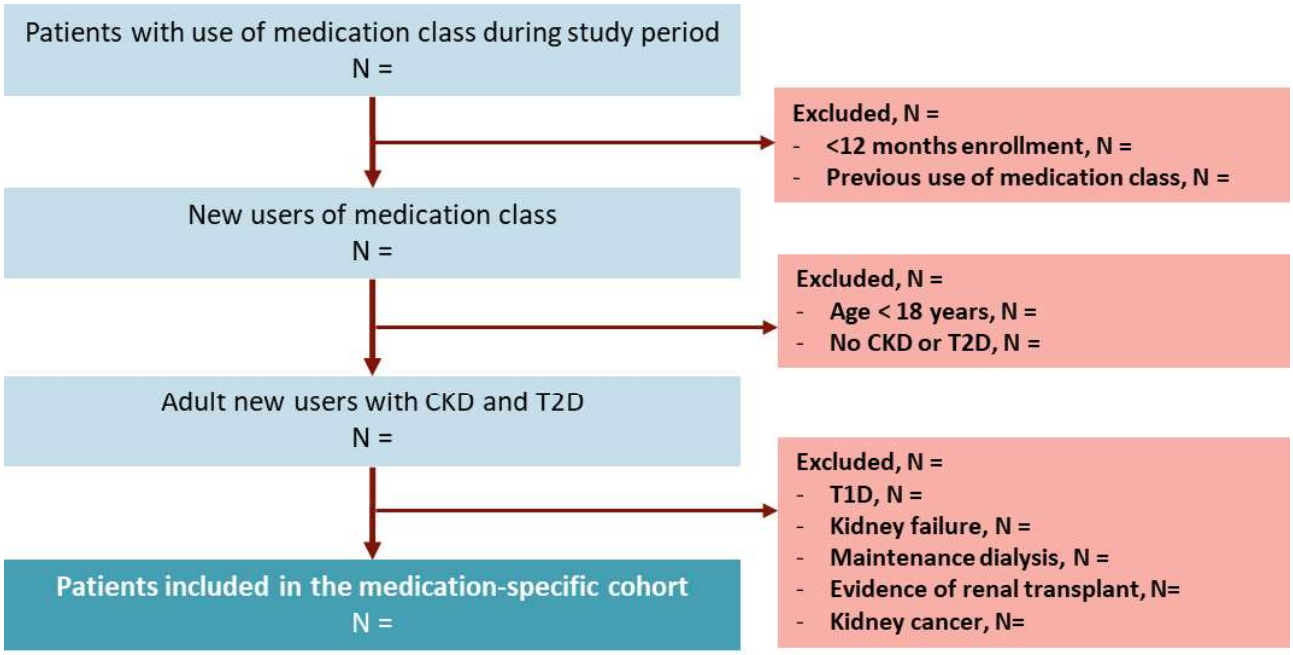
9.7.1. Pre-finerenone analysis (study period I)

Three new-user cohorts will be constructed for each data source—SGLT2i, GLP-1 RA, and sMRA—according to the criteria described in Section 9.2. A fourth new-user cohort—non-steroidal MRA—will be identified in Japan.

9.7.1.1. Included patients

The following parameters will be reported in each data source: attrition of patients due to study exclusion criteria, the number of eligible patients included in the different study cohorts, and the number of patients excluded for not meeting the inclusion criteria along with the reasons for exclusion (see shell figure in Figure 2). Counts and percentages of the reasons for censoring will also be reported.

Figure 2: Attrition of patients by application of eligibility criteria for each medication-specific cohort



CKD = chronic kidney disease; T1D = type 1 diabetes; T2D = type 2 diabetes.

9.7.1.2. Description of baseline characteristics

Results of the cohort selection process will be tabulated for each cohort in each data source.

Descriptive statistics will be presented for the variables listed in Section 9.3.3 separately for each medication-specific cohort in each data source.

- For categorical variables, the frequency distributions (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.

Due to country-specific data privacy standards, categorical variables with low counts will not be reported (they will be masked). For continuous variables, this is why the first and 99th percentile are being utilised over the minimum and maximum values. For categorical variables, low frequencies for a specific level will not be reported. However, considerations for back calculations will also need to be considered to make sure the results cannot be ascertained.

9.7.1.3. Drug utilisation analyses

The characteristics of the index medication classification in each of the medication-specific cohorts will be described at the index date as follows:

- Total number of new users

- Total length of study follow-up
- Characteristics of index prescription and dispensing: dose, dose frequency, strength, number of units, amount of drug prescribed, monotherapy, fixed-dose combination
- Characterisation of index medication in relation to existing therapy for CKD and diabetes
    - Added on to previous treatment
    - Switched to index medication

New users in each cohort will be followed from the index date through the end of follow-up to describe the following parameters:

- Number of prescriptions and dispensings over the study period (categorised)
- Duration of index current use episode, days
- Number of current episodes of index medication
- Number of gaps in treatment > 30 days with index medication
- Total duration of current use episodes of index medication
- Interruption of index medication
- Starting another study medication

Results for these variables will be summarised descriptively in a similar manner to the baseline demographics. All data-handling conventions and data source–specific limitations will be defined in the SAP.

9.7.1.4. Describe treatment changes over time

Periods of study drug use, changes in the index treatment, including treatment discontinuation, treatment switches/add-on treatments will be described in each new-user cohort.

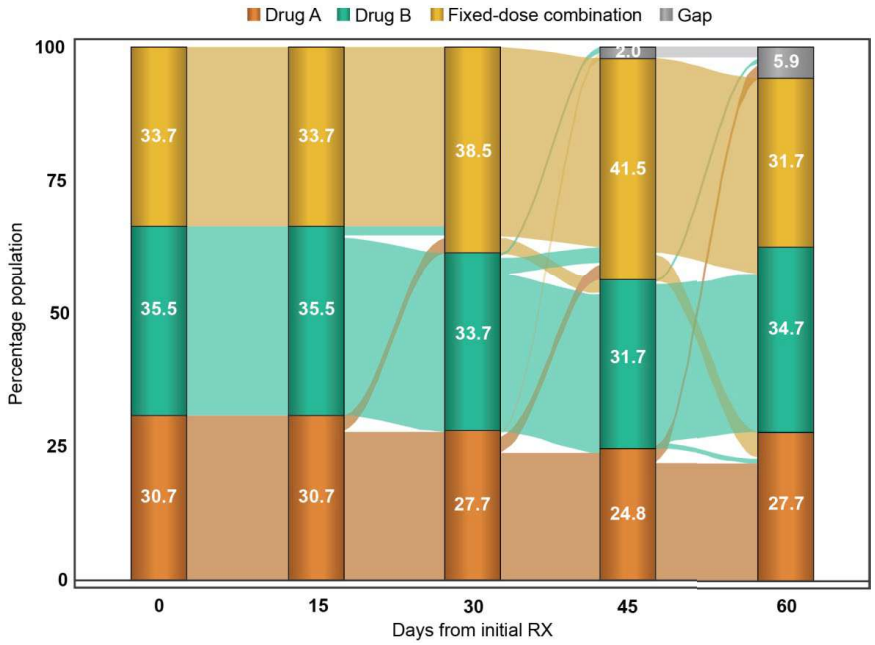
Changing treatment states over time will be displayed using shift tables and Sankey diagrams. Sankey diagrams will summarise and illustrate the proportion of patients who are in various treatment states at discrete checkpoints during follow-up and the movement between treatment states (82). Considered treatment states will include the following:

- Treated with index medication
- Untreated with index medication
- Lost to follow-up/end of study/censored
- Died (as available in each data source)

The Sankey diagram will use fixed checkpoints at defined intervals (e.g., every 90 or 180 days). Each medication-specific cohort in each study period will be displayed in separate Sankey diagrams.

An example Sankey diagram is shown in Figure 3.

Figure 3: Example of Sankey diagram showing changing treatment states over time



RX = prescription.
NOTE: This figure is just an indication of the method that will be used. The figure reflects the method as used in the original work (82). The method will be adapted to fit the goals of this study.

For this example figure, approximately one-third of the study population is on one of the 3 study drugs at any point in time, and there is minimal switching between the drugs. About 5% of a given cohort changed therapy, and gaps in therapy begin to appear 45 days after the index date (82).

Treated and untreated status will be determined by whether a patient is in any continuous current use period on the date of the checkpoint. Once a patient has died, they will be placed in a separate category and will remain in that state for each subsequent checkpoint. Patients may move between different treatment states at each checkpoint (e.g., starting as treated, then discontinuing treatment and becoming untreated or changing the index medication, then dying).

All patients still enrolled in their follow-up period and those who have died will be included in the denominator of each checkpoint. Patients who are lost to follow-up or censored will be subtracted from the denominator of checkpoints after the censoring date. The number of patients in the denominator of each checkpoint will be displayed. Patients who have died will remain in the denominator, as they will continue to be displayed as a treatment state at each checkpoint.

9.7.2. Post-finerenone analysis (study period II)

In each data source, 4 medication-specific new-user cohorts will be constructed—SGLT2i, GLP-1 RA, sMRA, and finerenone—according to the criteria described in Section 9.2. A fifth cohort—other non-steroidal MRA—will be identified in Japan. The analyses in this study period will be the same as the analyses in the pre-finerenone study period (see Section 9.7.1).

9.7.3. Temporal analysis

To address the secondary objectives evaluating temporal changes in baseline characteristics of the medication-specific cohorts in the pre-finerenone and post-finerenone periods, the descriptive statistics for the baseline characteristics of the medication class cohorts (Section 9.7.1.2) from study period I and study period II will be summarised and displayed separately for each data source in a tabular or graphical manner to be specified in the SAP. The differences in cohort characteristics at the 2 different time periods will be described. These analyses will be descriptive without formal comparisons between the 2 periods.

9.7.4. Other analyses

Pooling of data from the different data sources or combining descriptive estimates across data sources using meta-analysis methods will not be performed.

9.8. Statistical considerations

9.8.1. Missing data

Missing data approaches will be described in more detail in the SAP and will vary according to the different data sources.

For claims data sources, data are composed of coded health claims; the absence of a code for a particular characteristic will be interpreted as the patient not having the characteristic. We do not anticipate any explicitly missing data in the health care claims data sources. Some categorical demographic information derived from enrolment information (e.g., sex, race/ethnicity) may be categorised as unknown. These unknown categories will be reported as such in descriptive tables.

For EHR data sources, for lifestyle variables such as smoking or BMI, and for laboratory results, the percentage of missing data will be described.

Multivariable analyses requiring complete data and methods to account for missing data will not be performed in this analysis.

9.9. Quality control

Standard operating procedures or internal process guidance at each research centre 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, quality control procedures for programming, standards for writing analysis plans, and requirements for senior scientific review.

RTI as coordinating centre

All programming written by one study analyst will be reviewed independently by a different analyst, with oversight by a senior statistician. All key study documents, such as the analysis plan, abstraction forms, and study reports, will undergo quality control review, senior scientific review, and editorial review.

For RTI-HS, an independent Office of Quality Assurance (OQA) will 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 OQA according to established criteria in standard operating procedures and other applicable procedures.

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

CPRD

Bayer standard operating procedures will be followed during the conduct of the study. Programming and analysis plans will be reviewed by a second analyst.

Danish National Health Registers

Programming written by a main analyst will be partially reviewed by a second analyst. All key study documents will undergo quality review and senior scientific review.

J-CKD-DB-Ex

The Japanese Society of Nephrology and the Japan Association for Medical Informatics have constructed the J-CKD-DB using the SS-MIX2 system, which enabled the compilation of a large amount of electronic medical records from multiple medical institutions with a standardised data structure.

Data analysis will be performed by a specialist from the research partner. The ethical aspects and consideration will be reviewed by an independent ethics committee before conducting the study. The analysis will be performed as specified in the SAP. All key documents will undergo quality control review and scientific review by investigators of J-CKD-DB-Ex.

OPTUM

Bayer standard operating procedures will be followed during the conduct of the study. Programming and analysis plans will be reviewed by a second analyst.

PHARMO

Standard operating procedures at the PHARMO Institute 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, quality control procedures for programming, standards for writing analysis plans, and requirements for senior scientific review.

All programming written by the executing researcher will be reviewed independently by a senior researcher. All key study documents, such as the SAP and study reports, will undergo quality control and senior scientific review.

VID

FISABIO maintains a comprehensive research management system based on applicable national and international laws and regulations, by means of several standard operation procedures, including the ENCePP Code of Conduct for pharmacoepidemiology studies, as well as specific data integrity, storage, and processing procedures. The research team will devote the adequate qualified staff to project management tasks, programming and auditing, data management and quality checking, statistical planning, and reporting of results, and will ensure final senior scientific review in all key

stages of the project and for all deliverables. Double independent programming will be performed by a senior data analyst.

9.10. Limitations of the research methods

This study will utilise existing health care data from multiple countries and data sources. Using multiple data sources will allow evaluating of study parameters in diverse settings, populations, and health care systems. However, heterogeneity of the data types (e.g., EHR data, commercial insurance claims, population registries), coding systems, formularies, and data availability may result in key differences between data sources and will be discussed accordingly. The study will be conducted using a common protocol and SAP, and efforts will be made to harmonise approaches across all data sources.

Especially for US data sources, but potentially also others, the inclusion criterium of a minimum of 12 months continuous enrolment in the database, could result in selection bias.

As with all studies based in existing health care data sources, the data were generated for health care delivery or billing rather than research; thus, missing data or misclassification of study variables is possible.

Although prescribing and dispensing records will be used to define the study cohorts and evaluate drug utilisation, misclassification of exposure is still possible and may vary between data sources based on the structure (i.e., pharmacy dispensing vs. physician prescribing). In the US, patients may obtain drugs via retail plans available online instead of using claims-paid prescriptions, in which case, exposure would not be captured. Prescription data may not reflect actual exposure. A prescription issued or a prescription dispensed reflects the intent to use a drug, not actual patient use.

Definition and severity of CKD will be defined using diagnosis and procedure codes in all data sources. In some data sources (e.g., CPRD, VID, PHARMO), laboratory results are available and will be used to further refine the capture and staging of CKD. In data sources without laboratory results, the capture of CKD may not be as valid, and the validity may depend on the coding practices and coding settings (e.g., hospital coding vs. primary care coding; use of rule-out coding). Thus, the prevalence estimates and the severity of CKD may be heterogenous across the different data sources.

Lifestyle variables, such as BMI and smoking status, are not available in all data sources, particularly insurance claims databases. While ICD-10 diagnosis codes relating to obesity, nicotine dependence, and tobacco use are available, it is not known whether those codes are used consistently in all data sources. In this study, these variables are used for descriptive purposes only.

The data sources included are located in different geographical locations (US, Europe, UK, Japan), and the indication for finerenone differs as regulated by the FDA and the EMA. The FDA label allows treatment of patients with any level of kidney impairment, while the EMA label is restricted to patients with more severe kidney impairment (CKD stage 2 or greater). Thus, the current inclusion criteria may restrict the inclusion of patients being treated in the US according to the label.

9.11. Other aspects

Not applicable

10. Protection of human subjects

This is a non-interventional study using secondary data collection and does not pose any risks for patients. All data collected in the study will be de-identified with no breach of confidentiality with regard to personal identifiers or health information. Each database research partner will apply for an independent ethics committee review according to local regulations; in addition, RTI-HS as the coordinating centre will obtain approval or exemption from the RTI International (RTI) IRB.

Data protection and privacy regulations will be observed in collecting, forwarding, processing, and storing data from study participants.

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-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-HS will obtain approval for the study from the RTI IRB.

CPRD

The final study protocol will be submitted to the Independent Scientific Advisory Committee (ISAC) of CPRD as specified on CPRD's website (http://www.cprd.com/ISAC). CPRD requires that any study using CPRD data that will be published or for which results will be communicated to third parties must receive ISAC approval before proceeding.

Danish National Health Registers

Notification to Aarhus University (weeks) plus approval of data request according to the protocol from the Danish Health Data Board and Statistics Denmark are required. Depending on the level and type of data requested, obtaining approval may take from 3 to 12 months. Ethics committee approval is not required unless medical records are abstracted for validation purposes.

J-CKD-DB-Ex

The final study protocol will be submitted and reviewed by an independent ethics committee. The use of the de-identified data for conducting this study will be in compliance with the local regulations.

OPTUM

Optum CDM was designed to fully comply with HIPAA Privacy Rules. Optum Insight has performed extensive review of all data sources for CDM and applied several techniques to de-identify data. These techniques include:

- Removing all direct identifiers for an individual, including name, street address, social security number, phone numbers, and date of birth;
- Reducing the number of data elements that might be matched with an external data source or censoring their content.

In addition, access and use of the data is restricted by agreement with clients.

PHARMO

The study will be conducted in accordance with Good Epidemiology Practices. All data sources used are anonymous and are linked through probabilistic linkage using demographic variables of the patients. All other identifying information will be deleted after linkage of the various databases. This approach is approved by the Dutch Data Protection Authority ('College Bescherming Persoonsgegevens'). Confidentiality of patient records will be maintained at all times. All analyses of electronic records will be performed using appropriately de-identified data without access to personal identifying information. All study reports will contain aggregate data only and will not identify individual patients or physicians. Medical record abstraction, if available, will only be performed after receiving a waiver of authorisation from the relevant data holder's privacy board and approval from an IRB. At no time during the study will the sponsor receive patient identifying information except when it is required by regulations in case of reporting of adverse events. Approval from an internal compliance committee, which does not influence timelines, is required. If external registers are needed (e.g., Cancer Registry), approval from the database holder needs to be obtained, which can take up to 3 months. Most studies using the anonymised data from the PHARMO Database Network are not subject to ethics review, according to the Medical Research Involving Human Subjects Act. In the cases where ethics approval is required, the study protocol is submitted to an accredited medical research ethics committee in the Netherlands for review.

VID

Necessary steps and timelines to gain approval are as follows: 1) approval of the study protocol by an ethics committee (estimated time: 1 month); 2) the VHS Data Commission reviews these requests and approves (or otherwise) each specific data transfer for research purposes (timeline: 1 or 2 months); 3) the data are prepared for analysis (estimated timeline: 6 to 12 months).

11. Management and reporting of adverse events/adverse reactions

For studies in which the research team uses data from automated health care databases only, according to the International Society for Pharmacoepidemiology (83) 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 health care 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 (84).

According to the EMA Guideline on Good Pharmacovigilance Practices (GVP), Module VI – Management and Reporting of Adverse Reactions to Medicinal Products (84),

"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 (85). When reporting results of this study, the appropriate Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist will be followed (86). The Consolidated Standards of Reporting Trials (CONSORT) statement (87) refers to randomised studies, but provides useful guidance applicable to non-randomised studies as well.

The marketing authorisation holder and the investigators will agree upon a publication policy.

This study is classified as an EU-PASS and will consequently be registered in the ENCePP registry according to current rules and regulations.

[1] European Medicines Agency. Guideline on good pharmacovigilance practices (GVP). Module VI – Management and reporting of adverse reactions to medicinal products. 22 June 2012. Available at: 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

Table 6: List of stand-alone documents

Document name	Final version and date (if available)*
21956_FINEGUST_PIs and RPs_final_20220405.docx	**05 April 2022**
FOUNTAIN_EAC_member list.docx	**05 April 2022**
FOUNTAIN_EAC_Publication Committee member list.docx	**05 April 2022**

* Draft versions are indicated by <draft> in brackets and date. “TBD” indicates documents that are not available at the time of protocol creation but will be issued at a later stage.

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

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 post-authorisation 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: FINEGUST/**FINE**renone dru**G U**tilization **S**tudy and assessment of **T**emporal changes following availability of different treatment options in patients with chronic kidney disease and type 2 diabetes

EU PAS Register® number: **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]	☒	☐	☐	6
1.1.2 End of data collection[3]	☒	☐	☐	6

[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 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

No 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)	☒	☐	☐	4, 7
2.1.2 The objective(s) of the study?	☒	☐	☐	4, 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)	☒	☐	☐	4, 7, 8, 9.2.1
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Study is descriptive with no hypothesis testing planned

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)	☒	☐	☐	4, 9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	4, 9.1
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☐	☐	☒	
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

The analysis will include descriptive characteristics and drug utilization parameters.

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	9.1, 9.2
4.2.2 Age and sex	☒	☐	☐	9.2.3.1
4.2.3 Country of origin	☒	☐	☐	9.2
4.2.4 Disease/indication	☒	☐	☐	7, 9.1, 9.2
4.2.5 Duration of follow-up	☒	☐	☐	9.2.2
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, 9.2.3

Comments:

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

Comments:

The study does not include comparisons between drug groups. Descriptive characteristics of initiators of different study medications will be described at baseline and drug utilization over time will be measured and described. No safety outcomes are evaluated.

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?	☒	☐	☐	9.3.2, 9.7.1.3
6.2 Does the protocol describe how the outcomes are defined and measured?	☐	☒	☐	
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☒	☐	
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Details of how outcomes are defined and measured will be provided in the SAP. Outcomes are drug utilization parameters. No safety outcomes are included and no validation is planned.

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☐	☐	☒	
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☐	☐	☒	
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.10

Comments:

No formal comparisons between cohorts are planned. Measures of association or risk are not estimated

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

Comments:

Effect estimates will not be calculated, analyses are descriptive.

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:				

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

Comments:

Data will not be linked between data sources.

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?	☐	☒	☐	
10.3 Are descriptive analyses included?	☒	☐	☐	9.7.1.2, 9.7.1.3 9.7.1.4
10.4 Are stratified analyses included?	☐	☒	☐	
10.5 Does the plan describe methods for analytic control of confounding?	☐	☐	☒	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.8.1
10.8 Are relevant sensitivity analyses described?	☐	☐	☒	

Comments:

All patients meeting eligibility criteria will be included, no formal study size/precision estimation was estimated. No stratified analyses or sensitivity are planned. No comparative analyses will be performed so control of confounding is not included.

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)	☐	☒	☐	
11.2 Are methods of quality assurance described?	☒	☐	☐	9.9
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	9.9

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?	☐	☐	☒	
12.1.2 Information bias?	☐	☐	☒	
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).	☐	☐	☒	
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:

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

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	10

Comments:

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

Name of the main author of the protocol: PPD and PPD

Date: 21/April/2022

Please see the signed ENCePP Checklist here:

21956_FINEGUST_E
NCePP check-list_Sig

Signature:

Annex 3: Additional information

"Note to File" to clarify the protocol version:

Note to File_21956_FINEGUS

Annex 4: Description of updates and amendments

None

Annex 5: Signature pages

This protocol is electronically signed in the study management system

Title	FINEGUST/FINErenone druG Utilization Study and assessment of Temporal changes following availability of different treatment options in patients with chronic kidney disease and type 2 diabetes
Protocol version and date	V1.0, 11 MAY 2022
IMPACT study number	21956
Study type / Study phase	Observational ☒ PASS <Joint PASS: ☐ YES ☒ NO>
EU PAS register number	Study not yet registered
NCT number	Study not yet registered
Active substance	Finerenone; Kerendia (ATC: C03DA05)
Study Initiator and Funder	Bayer AG

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

Signatories

- PPD (Study Conduct Responsible)
- PPD (Study Content Owner)
- PPD (Study Medical Expert)
- PPD (Study Statistician)
- PPD (Study Epidemiologist)
- PPD (Study Safety Lead)

- PPD (Qualified Person responsible for Pharmacovigilance (QPPV))
- PPD (HEOR responsible)
- PPD (Study ODG Data Analyst)
- PPD (US Data Generation and Observational Studies)