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Authors
Desai, Nihar R
Navaneethan, Sankar D
Nicholas, Susanne B
et al.

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Design and rationale of FINE-REAL: A prospective study of finerenone in clinical practice☆

Nihar R. Desai [a,*], Sankar D. Navaneethan [b], Susanne B. Nicholas [c], Kevin M. Pantalone [d], Christoph Wanner [e], Stefanie Hamacher [f], Alain Gay [g], David C. Wheeler [h]

[a] Section of Cardiovascular Medicine, Yale School of Medicine, Yale New Haven Hospital, New Haven, CT, USA
[b] Section of Nephrology, Baylor College of Medicine, Houston, TX, USA
[c] David Geffen School of Medicine at University of California, Los Angeles, Los Angeles, CA, USA
[d] Endocrinology and Metabolism Institute Cleveland Clinic, Cleveland, OH, USA
[e] University Hospital Würzburg, Department of Medicine, Division of Nephrology, Würzburg, Germany
[f] ClinStat GmbH, Huerth, Germany
[g] Medical Affairs & Pharmacovigilance, Pharmaceuticals, Bayer AG, Berlin, Germany
[h] Department of Renal Medicine, University College London, London, UK

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ABSTRACT

Aims: Contemporary patterns of care of patients with chronic kidney disease (CKD) associated with type 2 diabetes (T2D) and the adoption of finerenone are not known. The FINE-REAL study (NCT05348733) is a prospective observational study in patients with CKD and T2D to provide insights into the use of the nonsteroidal mineralocorticoid receptor antagonist (MRA) finerenone in clinical practice.

Methods: FINE-REAL is an international, prospective, multicenter, single-arm study enrolling approximately 5500 adults with CKD and T2D in an estimated 200 sites across 22 countries. The study is anticipated to be ongoing until 2027.

Results: The primary objective is to describe treatment patterns in patients with CKD and T2D treated with finerenone in routine clinical practice. Secondary objectives include assessment of safety with finerenone. Other endpoints include characterization of healthcare resource utilization and occurrence of newly diagnosed diabetic retinopathy or its progression from baseline in patients with existing disease. A biobank is being organized for future explorative analyses with inclusion of participants from the United States.

Conclusions: FINE-REAL is the first prospective observational study with a nonsteroidal MRA in a population with CKD and T2D and is expected to provide meaningful insights into the treatment of CKD associated with T2D. FINE-REAL will inform decision-making with respect to initiation of finerenone in patients with CKD and T2D.

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* Corresponding author.
E-mail address: nihar.desai@yale.edu (N.R. Desai).

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1. Introduction

Type 2 diabetes (T2D) and chronic kidney disease (CKD) are rapidly growing public health burdens with high global prevalence.[1,2] T2D is the leading cause of kidney failure in the United States (US), with > 60 % of patients with kidney failure also having comorbid T2D.[3] The pharmacological standard of care for the treatment of CKD associated with T2D includes optimization of blood pressure control, lipid control, glycemic control, and the use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers.[4–6] Therefore, current and emerging treatments for patients with CKD and T2D primarily target hemodynamic and metabolic factors.[4–6] Nevertheless, a substantial residual risk for progression to kidney failure remains for patients on current standard of care.[7]

Finerenone, a selective, nonsteroidal, mineralocorticoid receptor antagonist (MRA), has been recently approved for the treatment of CKD associated with T2D in the US, European Union, and several other countries including China, India, and Japan.[8–10] The approvals were based on demonstrated efficacy in either the FIDELIO-DKD (NCT02540993) study alone, or in both the FIDELIO-DKD and FIGARO-DKD (NCT02545049) studies where finerenone reduced the risk of adverse cardiovascular and kidney outcomes compared with placebo in patients treated with maximum tolerated renin–angiotensin system (RAS) inhibition.[11–13] In both the FIDELIO-DKD and FIGARO-DKD studies, finerenone was well-tolerated with similar incidences of treatment-emergent adverse events (AEs) between the finerenone and placebo arms.[11,12] Hyperkalemia-related AEs were increased with finerenone; however, most instances were mild to moderate in severity with few treatment discontinuations.[11,12]

Based on the results of these studies, marketing authorization for finerenone was granted by the US Food and Drug Administration (FDA) in July 2021 and the European Medicines Agency (EMA) in February 2022 for the treatment of adults with CKD and T2D.[8,10,14] In addition, finerenone is now included as a recommended treatment for CKD associated with T2D in the most recent guidance from the American Diabetes Association (ADA), the American Association of Clinical Endocrinologists, and in the ADA-Kidney Disease: Improving Global Outcomes (KDIGO) consensus report on diabetes management in CKD.[6,15] In addition, finerenone has been acknowledged as an advancement in delaying the progression of CKD in T2D by the American Heart Association.[16] Patients enrolled in randomized clinical trials may differ from those encountered in routine clinical practice. Little is known about contemporary patterns of care of patients with CKD and T2D and the adoption of finerenone. The choice and order of treatments by clinicians may also be influenced by intrinsic factors (patient characteristics such as comorbidities), background therapy, and local healthcare factors (such as medication reimbursement). Therefore, long-term efficacy and safety data from patients treated in clinical care are needed to inform clinicians and public health organizations on the most appropriate treatment pathway for patients and the management of AEs, particularly hyperkalemia. The FINE-REAL study (a non-interventional study providing insights into the use of finerenone in a routine clinical setting) aims to address this clinical need and will provide insights on characteristics and treatment patterns of patients with CKD and T2D treated with finerenone in routine clinical practice. This manuscript will outline the FINE-REAL study design and analysis plan.

2. Materials and methods

2.1. Study design

FINE-REAL is an international, prospective, observational, multicenter, single-arm study. The study is registered with www.clinicaltrials.gov (NCT05348733). FINE-REAL aims to assess real-world data to describe patient characteristics, treatment patterns, and clinical outcomes in patients with CKD and T2D treated with finerenone (10 or 20 mg). The study will be conducted in approximately 22 countries (Belgium, Brazil, Canada, Chile, China, Colombia, Denmark, France, Germany, Italy, Luxembourg, Mexico, Netherlands, Saudi Arabia, Singapore, Slovenia, South Korea, Spain, Switzerland, Taiwan, Thailand, and the US) with a planned enrollment of approximately 5500 participants. Sample size was determined based on feasibility assumptions (e.g., included countries, available sites, and sites' capacities) and corresponding precision calculations. The first participant was enrolled on June 13, 2022 and the estimated last patient last visit date is September 1, 2027.

FINE-REAL is an observational study whereby patients initiated on finerenone in accordance with the country/region-specific marketing authorization as part of a patient's standard of care will be enrolled. Documented approval from appropriate independent ethics committees/institutional review boards will be obtained for all participating centers in applicable countries prior to study start. The study will be carried out within an approved drug indication in accordance with the guidelines and regulations from the EMA, FDA, and applicable local laws and regulations. All study participants will provide informed consent; consent forms are subject to approval following review by appropriate independent ethics committees/institutional review boards according to country-specific requirements. Patients may withdraw from the study at any time. National and international data protection laws as well as regulations on observational studies will be followed. Electronic records used for capturing patient documentation will be validated according to the FDA Code of Federal Regulations Title 21, Part 11.[17] These regulations describe the criteria to be met for e-signatures to be considered reliable and generally equivalent to paper records and handwritten signatures. These regulations mandate access controls to ensure that only authorized individuals can use the system. In addition, a computer-generated audit trail must be in place to record the date and time of any actions to create, modify, or delete electronic records. Patients will only be identified with a unique central patient identification code; only the patient's treating physician and/or authorized site personnel will be able to identify the patient based on the patient identification code.

2.2. Study participants and data collection

Eligible individuals will be ≥18 years of age with a diagnosis of CKD associated with T2D and initiating treatment with finerenone in accordance with the local label. Baseline information (defined as data collected ≤1 month prior to the first dose of finerenone) will be recorded retrospectively with the status at the initial study visit. It is anticipated that follow-up visits will occur approximately every 3 months for the first year of treatment with finerenone (Fig. 1). The end-of-observation visit will be documented 12 months after the start of finerenone treatment in cases where finerenone therapy is still ongoing, or about 30 days after the end of finerenone treatment if treatment with finerenone is <12 months, or after death, withdrawal of informed consent, or loss-to-follow-up, whichever occurs first. A summary of data to be captured at all visits is shown in Table 1. A temporary treatment pause of finerenone is defined as ≤6 months; in such instances, patients will remain in the study and be followed up as planned. Finerenone treatment pauses of >6 months are considered as permanent treatment discontinuation.

2.3. Study objectives

The primary objective of the FINE-REAL study is to describe treatment patterns in patients with CKD and T2D treated with finerenone in routine clinical practice (Table 2). Variables for determining this primary objective include the clinical characteristics of underlying CKD associated with T2D (such as hypertension, ischemic cardiovascular events, chronic heart failure, and atrial fibrillation), the type and duration of concomitant secondary medications (such as glucose-lowering agents including sodium–glucose cotransporter 2 inhibitors [SGLT2is] and glucagon-like peptide-1 receptor agonists [GLP-1 RAs],

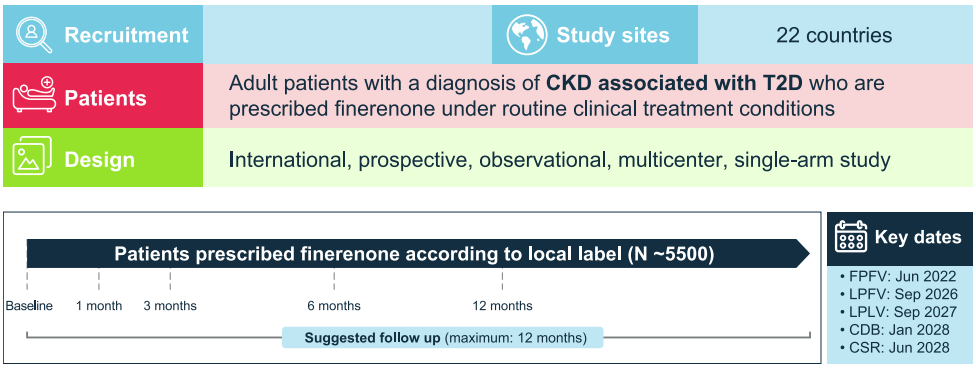

Fig. 1. Design of the FINE-REAL study.
Abbreviations: *CDB* clean database, *CKD* chronic kidney disease, *CSR* clinical study report, *FPFV* first patient first visit, *LPFV* last patient first visit, *LPLV* last patient last visit, *T2D* type 2 diabetes.

Table 1
Data collection at baseline, follow-up visits, and end of study.

	Baseline visit	Follow-up visit(s) including the final visit
Date/type of visit	X	X
Eligibility/informed consent	X	
Demographics		
Year of birth, sex, ethnic group, race (black/non-black)[a], smoking status, and alcohol consumption	X	
Vital signs		
Weight, height, and blood pressure	X	
Disease history	X	
Comorbidities (medical history, concomitant diseases)	X	
Concomitant medication		
Glucose-lowering agents, lipid-lowering treatment, RAS inhibitors, MRA[b], digoxin, β-blockers, diuretics, potassium supplements, potassium binders, herbal therapy, traditional Chinese medicine, anti-thrombotic treatment, vaccination against SARS-CoV-2, and NSAIDs	X	X
Exposure/treatment	X	X
Laboratory parameters		
Collected at baseline: eGFR, liver function (AST and ALT), hemoglobin, serum sodium, HbA1c, fasting blood glucose, and UACR Collected at baseline and post-baseline: serum creatinine, serum or plasma potassium, urine test results	X	X
AEs	(X)	X[c]
Hyperkalemia		X
End of observation		X
Healthcare resource utilization (inpatient/ outpatient/emergency department visits)	X	X
Diabetic retinopathy assessment	X	X
Sampling of blood and urine samples for biobanking (for patients in the US only)	X	X

Abbreviations: *AE* adverse event, *ALT* alanine transaminase, *AST* aspartate aminotransferase, *CKD-EPI* Chronic Kidney Disease Epidemiology Collaboration, *eGFR* estimated glomerular filtration rate, *HbA1c* glycated hemoglobin, *MRA* mineralocorticoid receptor antagonist, *NSAID* non-steroidal anti-inflammatory drug, *RAS* renin-angiotensin-system, *SARS-CoV-2* Severe Acute Respiratory Syndrome Coronavirus-2, *UACR* urinary albumin-to-creatinine ratio.
[a] Assessment of race required for calculation of eGFR using the CKD-EPI 2009 formula.[35]
[b] Another MRA should not be given together with finerenone, however, we are interested to know if a patient was exposed before the initiation of finerenone.
[c] AEs (up to 30 days after the final treatment with finerenone).

Table 2
List of primary, secondary, and exploratory study objectives and endpoints.

Study objectives and endpoints
Primary objective: To describe treatment patterns in patients with CKD and T2D treated with finerenone, based on: Clinical characteristics of patients with CKD and T2D Reasons for introducing finerenone Reasons for discontinuation of finerenone Planned and actual duration of treatment with finerenone Dosing of finerenone Use of secondary therapies in patients with CKD and T2D
Secondary objective: To evaluate overall reported safety of finerenone in treated patients and hyperkalemia, based on: Reported AE/SAEs Reported hyperkalemia Reported hyperkalemia leading to permanent study drug discontinuation Reported hyperkalemia leading to dialysis Reported hyperkalemia leading to hospitalization
Further objective: To assess healthcare resource utilization and diabetic retinopathy, based on: Reported visits with healthcare providers (reasons, duration, and outcomes) Outpatient visit (including but not limited to emergency room department visits), inpatient stay Reported diabetic retinopathy and its progression if existing at time of ICF signature
Exploratory objective Identification of baseline risk factors associated with AEs Establishment of a biobank to support future analyses[a]

Abbreviations: *AE* adverse event, *CKD* chronic kidney disease, *ICF* informed consent form, *SAE* serious adverse event, *T2D* type 2 diabetes.
[a] US patients only.

statins, RAS inhibitors, previous MRA use, digoxin, anti-thrombotic treatments, diuretics, and vaccination against Severe Acute Respiratory Syndrome Coronavirus-2), and planned and actual duration of treatment with finerenone (including dose and frequency of finerenone treatment and reasons for initiating and discontinuing finerenone). Secondary objectives include assessment of safety with finerenone with a focus on hyperkalemia. Further endpoints include characterization of healthcare resource utilization and occurrence of newly diagnosed diabetic retinopathy or progression from baseline of existing diabetic retinopathy. An exploratory objective is to identify baseline risk factors associated with AEs. A US-specific prespecified exploratory objective is to collect blood and urine samples to establish a biobank for future analyses; it is anticipated that up to 1000 of all enrolled participants will be from the US, of whom approximately 200 will have samples collected for the biobank.

2.4. Data collection, management, and analysis

Investigators/treating physicians will collect historical data from existing medical records. Treatment-related data will be collected during all study visits. A contract research organization will be selected and assigned for the Electronic Data Capture system development. Documentation of all variables and covariates by all participating sites will be standardized. After data entry, missing or implausible data will be queried, and the data will be validated. In addition, a check for multiple documented patients will be performed. A medical review of the data will be performed to verify the data from a medical perspective for plausibility, consistency, completeness, and to identify potential issues that could affect the robustness or the progress of the study.

All documented therapies will be coded using the latest version of the World Health Organization Drug Global available at the time of database lock. Clinical diagnoses/diseases/event terms will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA).

Statistical analyses will be of an explorative and descriptive nature as the FINE-REAL study is not intended to test a pre-specified statistical hypothesis. The primary objective will be analyzed using descriptive statistics. The mean and median length of follow-up together with the patient-years will be presented for the primary objective. Demographic and other baseline characteristics, including clinical characteristics of the underlying CKD associated with T2D, will be described by frequency tables or summary statistics. Medical history conditions will be displayed by a frequency table. Prior and concomitant medication will be presented by frequency tables or summary statistics. The standard of care for CKD (including SGLT2is/GLP-1RAs, MRAs, and RAS inhibitors) will be tabulated by patient frequencies.

Cumulative incidences and incidence rates will be estimated for secondary endpoints and corresponding two-sided 95 % confidence intervals (CIs) will be provided. Assuming an incidence proportion of 50 %, the precision width will not exceed 2.6 % for a sample size of 5500 patients. Lower proportions will minimize the precision width. AEs will be classified using the MedDRA preferred terms (PTs) (latest version). A summary of AEs will be presented by primary System Organ Class and MedDRA PT. In addition, frequency tables for hyperkalemia-related events will be provided and cumulative incidences will be provided in the form of Aalen-Johansen estimates and curves. The occurrence, duration, treatment, severity, and outcome of AEs, serious AEs, and adverse reactions will be summarized for the overall population. For the diabetic retinopathy-related endpoints, frequency tables describing the severity will be presented. All analyses will be performed for the overall population and separately for each participating country if patient numbers are sufficient and if required for local reasons. Where possible, data will be stratified by subgroups (e.g., age, sex, and other baseline characteristics).

3. Discussion

Finerenone has been studied in a large, interventional, clinical trial program,[11,12] after which regulatory approvals were granted for use in patients with CKD and T2D.[8–10] In the FIDELIO-DKD trial, finerenone significantly reduced the risk of the composite kidney outcome (time to kidney failure, sustained ≥40 % decrease in estimated glomerular filtration rate from baseline, or death due to kidney disease) by 18 % (hazard ratio [HR] = 0.82; 95 % CI 0.73–0.93; $P = 0.001$).[11] In the FIGARO-DKD trial, finerenone significantly reduced the composite cardiovascular outcome (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure) by 13 % compared with placebo (HR = 0.87; 95 % CI 0.76–0.98; $P = 0.03$).[12] However, clinical experience and guidance with initiation of finerenone in patients with CKD and T2D is lacking in many regions. FINE-REAL is the first prospective observational study investigating the use of a nonsteroidal MRA (finerenone) in routine clinical care and will identify clinically relevant treatment patterns in patients with CKD and T2D. Furthermore, FINE-REAL will allow for the identification of potential differences between real-world prescribing and current/future guideline recommendations from the ADA, European Society of Cardiology, the European Association for the Study of Diabetes, the Kidney Disease Outcomes Quality Initiative, and the KDIGO working group.

In addition to monitoring treatment patterns, FINE-REAL will provide the opportunity to assess incidence of hyperkalemia and its management in the clinic. Uptake of nonselective, steroidal MRAs, such as spironolactone, in clinical practice has been limited due to concerns of hyperkalemia which also influences time on treatment.[18,19] Finerenone is a selective, nonsteroidal MRA and was associated with significantly reduced hyperkalemia compared with spironolactone in the phase II randomized Mineralocorticoid Receptor Antagonist Tolerability Study–Diabetic Nephropathy (ARTS) trial.[20] The distinct effects of finerenone versus steroidal MRAs observed in the ARTS trial may be due to differences in molecular structure and MRA activity.[21] Guidance from the US and European labels for finerenone recommend withholding finerenone if serum potassium exceeds 5.5 mEq/L (5.5 mmol/L) and restarting treatment with finerenone 10 mg when serum potassium is ≤5.0 mEq/L (5.0 mmol/L).[8,10] The FINE-REAL study will capture hyperkalemia events leading to finerenone discontinuation and allow for assessment of adherence to the hyperkalemia-related recommendations in the product labels.

CKD associated with T2D is associated with high healthcare resource utilization. In 2019, CKD and T2D-related expenditures were over 22.7 billion USD for Medicare beneficiaries.[22] Furthermore, the per-person cost was 47 % higher in patients with CKD and T2D versus those with T2D only.[22] In Europe, treatment costs for kidney failure, the majority of which are attributed to T2D, are high, typically exceeding €40,000 per patient.[23] In FINE-REAL, information related to hospital visits (reasons, duration, and outcomes) and outpatient, emergency, and inpatient events will be captured to characterize healthcare resource utilization associated with finerenone.

Diabetic retinopathy is a significant microvascular complication in T2D with no targeted pharmacological treatment available. In the ReFineDR (NCT04477707) and DeFineDR (NCT04795726) retrospective observational studies, a reported potential benefit favoring finerenone was a delay in progression of non-proliferative diabetic retinopathy.[24] The FINE-REAL study aims to expand on this exploratory and hypothesis-generating result by including new-onset diabetic retinopathy and its progression if existing at baseline as prespecified endpoints.

The establishment of a biobank is one of the objectives of FINE-REAL, which will allow for longitudinal analyses of genomics, proteins, and other prognostic markers and potentially correlating with clinical outcomes, such as hospitalization and mortality.[25] MR overactivation is associated with inflammation, fibrosis, and sodium retention in cardiorenal disease.[26,27] As a result, in patients with CKD and T2D, MR overactivation elevates the risk of CKD progression.[11,28] Finerenone inhibits MR overactivation and forms a complex with the MR that affects cofactor recruitment and binding to the MR.[26,29,30] Finerenone induces a distinct cardiac gene expression profile compared with a steroidal MRA, assessed ex vivo in a model of cardiac hypertrophy.[31] This difference may be driven by higher MR selectivity and altered pharmacological properties of finerenone influencing potency, tissue distribution, and inhibitory effects on inflammation and fibrosis compared with steroidal MRAs.[32,33] The establishment of a biobank will allow for the potential to expand on the preclinical genomic results with finerenone and allow for comparisons of similar analyses with steroidal MRAs.[34]

The FINE-REAL study is not without limitations. Due to its noninterventional study design and limitations inherent to observational studies, findings generated from FINE-REAL are subject to biases, such as selection bias, limitations related to availability of historical medical records, and differences in treatment or reporting owing to local

guidelines. In addition, although the study aims to include patients from a variety of geographic regions, there may be local limitations that reduce the representativeness of patients recruited, such as patient access to recruiting physicians (including differences in patient profile in specialized recruiting sites compared with local general practice), finerenone availability and reimbursement, and decisions relating to local standard of care. Strengths of the FINE-REAL study include its large target population of approximately 5500 patients, global participation of sites, and long duration of follow-up. In addition, the novel establishment of a biobank from a large sample size will support future analyses (i.e., longitudinal genomic analysis and changes in biochemical markers and urinary proteins over time) and provide further insight with respect to disease progression and clinical outcomes.

4. Conclusion

FINE-REAL will provide meaningful perceptions and insights into CKD associated with T2D treated with finerenone. Furthermore, FINE-REAL will capture AEs, particularly hyperkalemia, and identify how these are managed in routine clinical care. New onset and progression of microvascular complications, specifically diabetic retinopathy, is a prespecified endpoint due to the paucity of pharmacological treatments available for this complication. The establishment of a biobank will support future analyses to better characterize the mechanisms of disease and mechanism of action of finerenone. The FINE-REAL study will help to inform decision-making with respect to initiation of finerenone in patients with CKD and T2D. FINE-REAL will also provide insights into the dynamics of new therapy adoption across different geographies and health systems, a useful insight for international guidance and implementation.

CRediT authorship contribution statement

Nihar R. Desai: Conceptualization, Writing – review & editing, Supervision. **Sankar D. Navaneethan:** Writing – review & editing. **Susanne B. Nicholas:** Writing – review & editing. **Kevin M. Pantalone:** Writing – review & editing. **Christoph Wanner:** Writing – review & editing, Visualization, Supervision, Project administration. **Stefanie Hamacher:** Formal analysis, Writing – review & editing. **Alain Gay:** Conceptualization, Methodology, Validation, Resources, Writing – original draft, Writing – review & editing, Supervision. **David C. Wheeler:** Conceptualization, Methodology, Writing – review & editing, Supervision, Project administration.

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