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Hiddo J L Heerspink
University of Groningen
Janet B McGill
Washington University School of Medicine in St. Louis
et al.

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Rationale and design of a randomised phase III registration trial investigating finerenone in participants with type 1 diabetes and chronic kidney disease: The FINE-ONE trial

Hiddo J.L. Heerspink [a,*], Andreas L. Birkenfeld [b,c,d], David Z.I. Cherney [e], Helen M. Colhoun [f], Linong Ji [g], Chantal Mathieu [h], Per-Henrik Groop [i], Richard E. Pratley [j], Sylvia E. Rosas [k], Peter Rossing [l,m], Jay S. Skyler [n], Katherine R. Tuttle [o], Robert Lawatscheck [p], Charlie Scott [q], Robert Edfors [r], Markus F. Scheerer [s], Peter Kolkhof [t], Janet B. McGill [u]

[a] Clinical Pharmacy and Pharmacology, University of Groningen University Medical Centre Groningen, PO Box 30.001, 9700 RB Groningen, Netherlands
[b] Institute for Diabetes Research and Metabolic Diseases of the Helmholtz Centre Munich at the University of Tübingen, Otfried Müller Street 47, 72076 Tübingen, Germany
[c] German Centre for Diabetes Research (DZD), Neuherberg, Germany
[d] Department of Internal Medicine, Division of Endocrinology, Diabetology and Nephrology, Eberhard Karls University Tübingen, Tübingen, Germany
[e] Division of Nephrology, University Health Network, Toronto General Hospital, University of Toronto, 585 University Ave, 8N-845, Toronto, Ontario M5G 2N2, Canada
[f] Institute of Genetics and Cancer, College of Medicine and Veterinary Medicine, University of Edinburgh, Edinburgh EH4 2XU, UK
[g] Departments of Endocrinology and Metabolism, Peking University People's Hospital, Peking University Diabetes Centre, No 11, Xizhimen South Street, Beijing 100044, China
[h] Clinical and Experimental Endocrinology, Katholieke Universiteit Leuven, 3000 Leuven, Belgium
[i] Department of Nephrology, University of Helsinki and Helsinki University Hospital, Biomedicum Helsinki (C318b), Haartmaninkatu 8, FIN-00290 Helsinki, Finland
[j] AdventHealth Translational Research Institute, Orlando, FL 32804, USA
[k] Kidney and Hypertension Unit, Joslin Diabetes Center, Harvard Medical School, One Joslin Place, Boston, MA 02215, USA
[l] Steno Diabetes Center Copenhagen, Borgmester Ib Juuls Vej 83, 2730 Herlev, Denmark
[m] Department of Clinical Medicine, University of Copenhagen, Blegdamsvej 3, 2200 Copenhagen N, Denmark
[n] Department of Medicine, University of Miami, Diabetes Research Institute, University of Miami Miller School of Medicine, Miami, FL 33136, USA
[o] Providence Inland Northwest Health, University of Washington School of Medicine, 105 W. 8th Avenue, Suite 250 E, Spokane, WA 99204, USA
[p] Cardiology and Nephrology Clinical Research, Bayer AG, Research & Development, Pharmaceuticals, Clinical Development, Building S101, 13342 Berlin, Germany
[q] Data Science and Analytics, Bayer PLC, Research & Development, Pharmaceuticals, 400 South Oak Way, Reading RG2 6AD, UK
[r] Cardiovascular Studies & Pipeline, Medical Affairs & Pharmacovigilance, Pharmaceuticals, Bayer AG, Building S102, 13342 Berlin, Germany
[s] Medical Affairs & Pharmacovigilance, Pharmaceuticals, TA CardioRenal & Heart Disease, Bayer AG, Building S102, 04/160, 13353 Berlin, Germany
[t] Research and Development, Pharmaceuticals, Cardiovascular Precision Medicines, Bayer AG, 42113 Wuppertal, Germany
[u] Division of Endocrinology, Metabolism & Lipid Research, Washington University in St. Louis, School of Medicine, 660 S. Euclid, Campus Box 8127, St. Louis, MO 63110, USA

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ABSTRACT

Aims: Despite guideline-recommended treatments, including renin angiotensin system inhibition, up to 40 % of individuals with type 1 diabetes develop chronic kidney disease (CKD) putting them at risk of kidney failure. Finerenone is approved to reduce the risk of kidney failure in individuals with type 2 diabetes. We postulate that finerenone will demonstrate benefits on kidney outcomes in people with type 1 diabetes.

Methods: FINE-ONE (NCT05901831) is a randomised, placebo-controlled, double-blind phase III trial of 7.5 months' duration in ~220 adults with type 1 diabetes, urine albumin/creatinine ratio (UACR) of ≥ 200–< 5000 mg/g (≥ 22.6–< 565 mg/mmol) and eGFR of ≥ 25–< 90 ml/min/1.73 m^2.

Results: The primary endpoint is relative change in UACR from baseline over 6 months. UACR is used as a bridging biomarker (BB), since the treatment effect of finerenone on UACR was associated with its efficacy on kidney outcomes in the type 2 diabetes trials. Based on regulatory authority feedback, UACR can be used as a BB for kidney outcomes to support registration of finerenone in type 1 diabetes, provided necessary criteria are met.

* Corresponding author.
E-mail address: h.j.lambers.heerspink@umcg.nl (H.J.L. Heerspink).

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Secondary outcomes include incidences of treatment-emergent adverse events, treatment-emergent serious adverse events and hyperkalaemia.
Conclusions: FINE-ONE will evaluate the efficacy and safety of finerenone in type 1 diabetes and CKD. Finerenone could become the first registered treatment for CKD associated with type 1 diabetes in almost 30 years.
Trial registration: ClinicalTrials.gov NCT05901831.

1. Introduction

Type 1 diabetes results from an autoimmune disorder characterised by destruction of pancreatic beta cells leading to insulin deficiency and the need for lifelong insulin treatment [1]. In 2022, an estimated 8.75 million individuals worldwide were living with type 1 diabetes, of whom approximately 1.9 million were living in low-income and lower-middle-income countries [2]. Chronic kidney disease (CKD) is a complication of diabetes and affects up to 40 % of people with type 1 diabetes [3–5]. Its prevalence increased by > 20 % from 2007 to 2017 [6]. People with type 1 diabetes and CKD are at higher risk of experiencing kidney failure and cardiovascular disease and have a shorter life expectancy than people with type 1 diabetes without CKD [7]; therefore, adequate measures to identify CKD early and treat it appropriately are important management goals [8].

The adoption of renin angiotensin system (RAS) blockade initially with angiotensin-converting enzyme inhibitors (ACEis) and later angiotensin receptor blockers (ARBs) as a standard of care has slowed CKD progression in people with type 1 diabetes and led to a reduction in the incidence of kidney failure since the 1990s; however, no further therapeutic advancements have occurred since then [5,7]. These trends underscore the high unmet need in type 1 diabetes and CKD and the necessity for novel kidney-protective medications for such persons. New therapies have become available for people with type 2 diabetes and CKD, including sodium–glucose cotransporter 2 inhibitors and the selective non-steroidal mineralocorticoid receptor antagonist (MRA) finerenone. Despite these therapies being potentially beneficial for people with type 1 diabetes and CKD, such persons were excluded from past clinical trials; therefore, these therapies have not been approved in type 1 diabetes.

Overactivation of the mineralocorticoid receptor (MR) has been shown in preclinical models to contribute to fibrosis and inflammation and can lead to progressive kidney function loss [9]. Small clinical studies have demonstrated that the non-selective steroidal MRA spironolactone reduces albuminuria by approximately 30–60 % [10,11]. While spironolactone has indications in hypertension and heart failure with reduced ejection fraction, it is not approved for the treatment of any type of CKD due to a lack of randomised controlled trial data and an unfavourable efficacy/safety profile concerning acute kidney injury and hyperkalaemia [12–14]. Finerenone, a selective non-steroidal MRA, blocks MR overactivation in kidney epithelial cells (thereby counteracting sodium retention) and in several non-epithelial cells, including cardiac, vascular, glomerular and infiltrating immune cells (thereby counteracting inflammation, fibrosis, hypertrophy and remodelling) [9,15]. Based on results from the pooled FIDELITY analysis, the benefit-to-risk profile of finerenone has been well described in over 6500 people with type 2 diabetes and CKD randomised to finerenone on top of optimised RAS therapy in the FIDELIO-DKD and FIGARO-DKD studies [16–18].

Finerenone was associated with a consistent reduction in the urine albumin/creatinine ratio (UACR) as well as a decreased risk of adverse kidney and cardiovascular events in the pooled FIDELITY analysis [19]. Based on (1) the efficacy of finerenone on kidney outcomes in people with type 2 diabetes and CKD [16,17,19]; (2) analysis from a landmark trial of captopril (Lewis, et al [1993]) [20] demonstrating that in people with type 1 diabetes and CKD, an early reduction in albuminuria with captopril was associated with a reduction in the risk of adverse kidney outcomes (Fig. 1); and (3) earlier studies demonstrating that

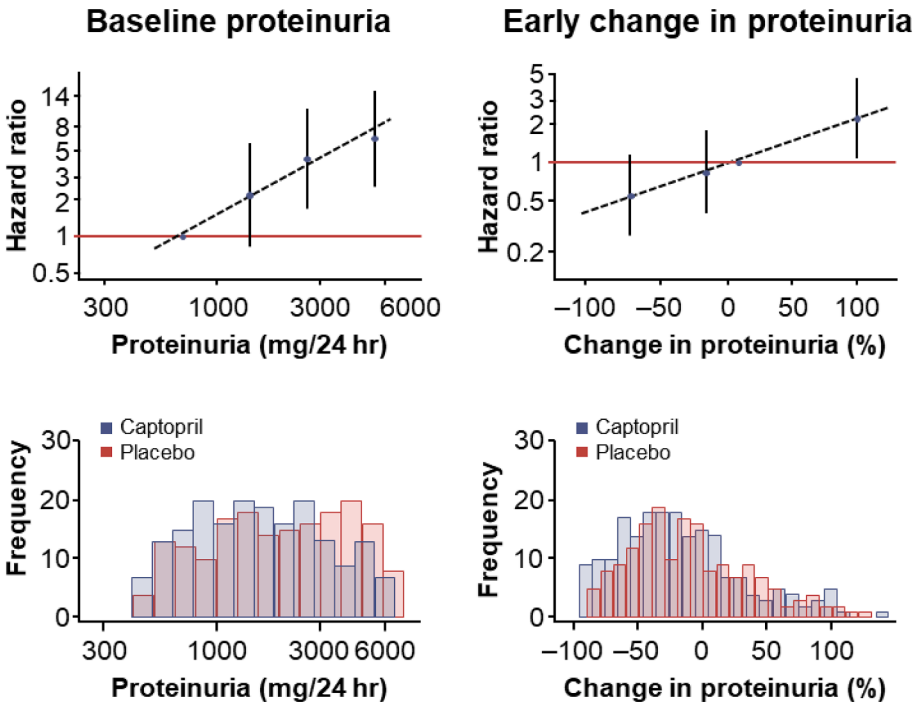


Fig. 1. CSG-Captopril trial: in patients with type 1 diabetes, proteinuria predicts kidney failure, and early reduction in proteinuria is associated with kidney protection. Analyses adjusted for age, sex, race, systolic BP, eGFR and albuminuria. BP, blood pressure; eGFR estimated glomerular filtration rate.

Table 1
Key eligibility criteria.

Inclusion criteria	Exclusion criteria
• Age ≥ 18 years (or the legal age of consent according to local legislation) • Type 1 diabetes (continuously treated with insulin, started ≤ 1 year from diagnosis). If onset was after age 35, documentation of the presence of at least one of the following: – Documented presence of circulating type 1 diabetes–associated autoantibodies – History of hospitalisation for diabetic ketoacidosis – Documented plasma C-peptide below the limit of detection with standard assay (with concurrent blood glucose > 100 mg/dl)	• Type 2 diabetes • Other known causes of CKD than type 1 diabetes
	• Kidney transplantation • Mean BP > 160/100 mmHg or mean systolic BP < 90 mmHg at screening • Hospitalisation due to a CV event ≤ 4 weeks prior to screening (heart failure decompensation, acute coronary syndrome, stroke, transient ischemic attack, acute limb ischemia) • Acute kidney injury requiring dialysis ≤ 24 weeks prior to screening • Symptomatic heart failure with reduced ejection fraction with class 1A indications for MRAs
• HbA_{1c} at screening < 10.0 % (<86 mmol/mol) (central assessment)[a]	• Concomitant dual therapy with both an ACEi and an ARB which cannot be discontinued for the purpose of the study ≥ 8 weeks prior to screening
• Serum potassium ≤ 4.8 mmol/l at screening (local assessment)[a]	• Current or previous (≤ 8 weeks prior to screening) treatment with a SGLT2/1 inhibitor or GLP1 receptor agonist
• Clinical diagnosis of CKD at screening: – eGFR of ≥ 25 to < 90 ml/min/1.73 m^{2}[a] – UACR of ≥ 200 to < 5000 mg/g (≥ 22.6 to < 565 mg/mmol) and documentation of elevated albuminuria or proteinuria in medical records ≥ 3 months prior to screening[a,b] • On a stable dose (preferably without any change in dose for ≥ 4 weeks prior to screening) of ACEi or ARB	• Concomitant therapy with an MRA (eplerenone, spironolactone, canrenone, esaxerenone), any renin inhibitor, ARNI (sacubitril/valsartan combination) or potassium-sparing diuretic which cannot be discontinued ≥ 8 weeks prior to screening)

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BP, blood pressure; CKD, chronic kidney disease; C-peptide, connecting peptide; CV, cardiovascular; eGFR estimated glomerular filtration rate; GLP, glucagon-like peptide; MRA, mineralocorticoid receptor antagonist; SGLT, sodium–glucose cotransporter; UACR, urine albumin/creatinine ratio.

[a] One reassessment is allowed during the screening period.

[b] Quantitative or semiquantitative record documented in the participant's record. If no documentation of elevated albuminuria or proteinuria is available in the medical history, the pre-screening UACR assessment could be used instead. The pre-screening UACR is optional and is collected under a separate simplified informed consent to identify potential eligible study participants.

spironolactone reduces UACR in people with type 1 diabetes and CKD [10,11], it is postulated that finerenone will also reduce UACR, and thereby slow CKD progression in people with type 1 diabetes and CKD. In this setting, where elevated UACR is associated with a higher risk of kidney failure and finerenone decreases UACR as well as the risk of kidney failure, UACR may serve as a bridging biomarker (BB) to translate the obtained efficacy evidence of finerenone from people with type 2 diabetes and CKD to those with type 1 diabetes and CKD [21].

The aim of the FINE-ONE study is to assess the efficacy and safety of finerenone, in addition to the standard of care consisting of ACEi or ARB treatment, compared with placebo in people with type 1 diabetes and CKD. The rationale for using UACR as a BB to support future regulatory approval of finerenone in type 1 diabetes and the design of the FINE-ONE study are presented here.

2. Subjects, materials and methods

2.1. Study design

FINE-ONE is a randomised, prospective, double-blind, global, multicentre, phase III study in people with type 1 diabetes and CKD. The primary objective is to demonstrate whether the addition of finerenone to standard of care is superior to placebo in reducing UACR over 6 months in people with type 1 diabetes and CKD. It is anticipated that about 440 participants will be screened to reach the required total of approximately 220 randomised participants. The study protocol, any protocol amendments and informed consent forms are subject to approval following review by independent review boards and independent ethics committees according to country-specific requirements. FINE-ONE is being conducted in compliance with the principles of the Declaration of Helsinki and in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice. All study participants will provide written informed consent prior to study enrolment. The study is registered within https://www.ClinicalTrials.gov (NCT05901831).

2.1.1. Study participants

Eligible individuals will be ≥ 18 years of age at screening, with a diagnosis of type 1 diabetes defined as continuous treatment with insulin, started within 1 year from diagnosis. If the onset of type 1 diabetes occurred after the participant was aged over 35 years, one or more of the following must also be documented: presence of type 1 diabetes-associated autoantibodies, history of hospitalisation for diabetic ketoacidosis or plasma C-peptide below the limit of detection of a standard assay (with concurrent blood glucose > 100 mg/dl). Participants must also be on treatment with a stable dose of ACEi or ARB (no dose changes for at least 4 weeks prior to screening). Eligible individuals must have, by central assessment, a glycated haemoglobin (HbA_{1c}) of < 10.0 % (< 86 mmol/mol), an estimated glomerular filtration rate (eGFR) of ≥ 25 to < 90 ml/min/1.73 m^2 and a UACR of ≥ 200 to < 5000 mg/g (≥ 22.6 to < 565 mg/mmol). Key eligibility criteria are detailed in Table 1. A screening visit will occur ≤ 14 days before randomisation.

2.1.2. Randomisation and study treatment

Participants will be randomised 1:1 to finerenone or matching placebo to finerenone (Fig. 2). Starting on Day 1, finerenone (or matching placebo) will be administered orally in addition to standard of care (either an ACEi or ARB). The starting dose will depend on the participant's eGFR level: a lower dose of 10 mg once daily (OD) if eGFR is ≥ 25 to < 60 ml/min/1.73 m^2 or the higher (target) dose of 20 mg OD if eGFR is ≥ 60 ml/min/1.73 m^2.

After 30 days, finerenone will be uptitrated to the 20 mg target dose provided the locally determined serum/plasma potassium concentration is ≤ 4.8 mmol/l and eGFR decrease is < 30 % compared with the value measured at the prior visit. Corresponding sham uptitrations will be performed for placebo. Downtitration from a 20 mg to a 10 mg dose is

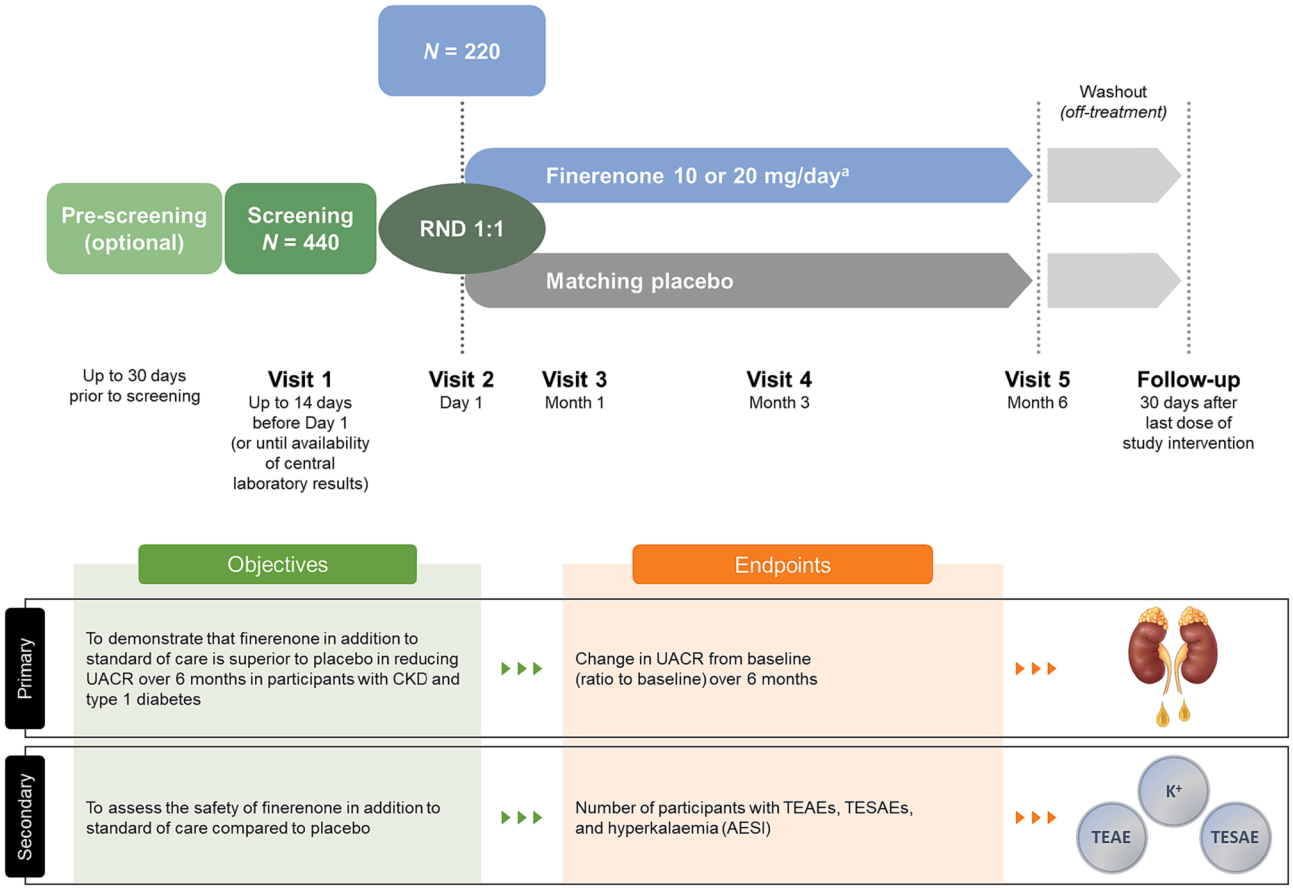


Fig. 2. Study design, objectives and endpoints. [a]Starting dose of finerenone: 10 mg OD if eGFR is $\geq$ 25 ml/min/1.73 m^2 and $<$ 60 ml/min/1.73 m^2 or 20 mg OD if eGFR is $\geq$ 60 ml/min/1.73 m^2 at screening visit. AESI, adverse event of special interest; CKD, chronic kidney disease; eGFR estimated glomerular filtration rate; K^+, potassium; OD, once daily; RND, randomisation; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event; UACR, urine albumin/creatinine ratio.

permitted for safety reasons at any time. Participants will continue study drugs until the end of treatment visits, unless there is withdrawal of consent or loss to follow-up.

2.1.3. Study follow-up

Visits following randomisation will occur at Months 1, 3 and 6 (the planned end of the study treatment). A follow-up/end-of-study visit will be scheduled at Month 7 (30 days after discontinuation of study treatment to assess off-drug effects; Fig. 2). Additional safety visits will take place 4 weeks (±7 days) after each uptitration or after restart of study drug following treatment interruption for $>$ 7 days. Blood and urine samples will be collected at study visits for assessment of UACR, eGFR and potassium. The total study duration for each participant will be approximately 7.5 months.

2.1.4. Efficacy and safety assessments

Demographic characteristics and medical history will be recorded at screening. The evaluation of UACR will be performed at all scheduled visits using three first–morning–void urine samples, collected at the participant's home on the two consecutive days before each scheduled visit, and on the morning of the respective visit. Central laboratory assessments will be used for UACR. Safety will be assessed at all scheduled visits. Serum potassium will be monitored for safety assessments at all scheduled visits and determined both centrally and locally. Blood pressure will be assessed at screening and all follow-up visits.

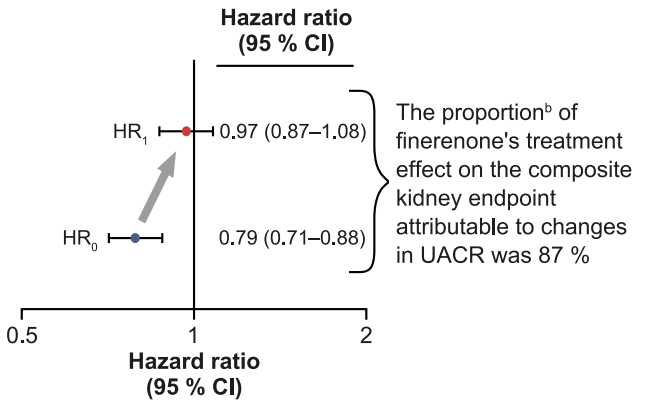
2.1.5. Primary objective

The primary objective of the study is to demonstrate that the addition of finerenone to standard of care is superior in reducing UACR over 6 months compared with placebo. The primary target outcome (estimand) to summarise this objective is the geometric mean ratio of the change in log(UACR) from baseline (ratio to baseline) over 6 months in adults, with a clinical diagnosis of type 1 diabetes and CKD, treated with finerenone (10 mg or 20 mg) versus placebo, in addition to standard of care. The estimand includes the effects of the intercurrent events (ICEs) of kidney failure, death and treatment discontinuation.

Change from baseline over 6 months of log(UACR) is used as the primary attribute. It is used as a BB to build upon the finerenone evidence obtained in people with type 2 diabetes and CKD and to expand to individuals with type 1 diabetes and CKD [21]. The use of UACR as a BB was supported by results from a restricted FIDELIO-DKD and FIGARO-DKD pooled population (UACR $\geq$ 200 mg/g and eGFR between 25 and 90 ml/min/1.73 m^2) demonstrating that the proportion of the treatment effect on the composite kidney endpoint (onset of kidney failure, a sustained decrease in eGFR $\geq$ 40 % over at least 4 weeks or kidney-related death) associated with changes in UACR was 87 % (Fig. 3).

2.1.6. Secondary outcomes

The secondary objective, as detailed in the Fig. 2, is to investigate the safety of finerenone compared with placebo. The secondary endpoints are to assess the number of participants with treatment-emergent adverse events (TEAEs) and treatment-emergent serious adverse events (TESAEs), with hyperkalaemia prespecified as an adverse event of special interest.



Proportion of treatment effect on 40 % kidney composite outcome (onset of kidney failure, a sustained decrease in eGFR ≥ 40 % over at least 4 weeks, or renal death) explained in the restricted[a] FIDELIO-DKD and FIGARO-DKD population

Variable	HR_1 adjusted analysis (95 % CI)	HR_0 unadjusted analysis (95 % CI)	Proportion explained[b] (%)
Time-varying log(UACR)	0.97 (0.87–1.08)	0.79 (0.71–0.88)	87.0

Fig. 3. UACR reduction associated with finerenone's treatment effect on the composite kidney endpoint (onset of kidney failure, a sustained decrease in eGFR ≥ 40 % over at least 4 weeks or kidney-related death) in a restricted[a] FIDELIO-DKD and FIGARO-DKD pooled population. [a]Restricted to patients with a UACR ≥ 200 mg/g (22.6 mg/mmol) and eGFR ≥ 25 and < 90 ml/min/1.73 m^2. [b]The proportion of the effect of finerenone on the primary composite kidney endpoint attributable to UACR change was based on the following equation: 100 % × (1 − [log(HR_1) / log(HR_0)]), if HR ref < HR adj < 1 where HR_0 is the hazard ratio from an unadjusted base cox regression model and HR_1 is the hazard ratio from the same model but adjusted for time-varying log(UACR). If changes in UACR over the study were a perfect surrogate and if the cox regression models properly represent the causal relationships, we would expect the hazard ratio for treatment effect, when adjusted for the time-varying log (UACR) variable, to be unity. Therefore, the closer to unity the adjusted hazard ratio moves, the larger the effect explained by the adjusting variable. The base model is adjusted for KDIGO UACR and eGFR categories [35], region, cardiovascular disease history, study, age, sex, race and baseline systolic blood pressure and HbA_{1c}. CI, confidence interval; eGFR estimated glomerular filtration rate; HR, hazard ratio; KDIGO, Kidney Disease Improving Global Outcomes; UACR, urine albumin/creatinine ratio.

2.2. Statistical considerations

2.2.1. Sample size assumptions

UACR change from baseline will be analysed assuming a lognormal distribution. Change from baseline on the log scale is equal to the ratio to baseline on the normal scale. Assumptions for the UACR ratios to baseline at 6 months are based on the population from the pool of FIDELIO-DKD and FIGARO-DKD, restricted to patients with UACR ≥ 200 mg/g (≥ 22.6 mg/mmol) and eGFR ≥ 25 and < 90 ml/min/1.73 m^2 [19,22].

The difference in log(UACR), or UACR ratio to baseline on the normal scale, over 6 months, for the placebo group is assumed to be 1.00. The treatment ratio (finerenone/placebo), over 6 months, is assumed to be 0.7 (i.e., the relative difference in UACR ratio to baseline between finerenone and placebo is to be 30 %). A sample size of 214 participants (107 per group) will achieve 90 % power at a two–sided significance level of 5 %, rejecting the null hypothesis of a treatment ratio equal to 1, assuming the true treatment ratio of 0.7 and a standard deviation in log–transformed UACR of 0.8. To account for a potential loss of information, the sample size will be increased to ensure the desired power is achieved. Therefore, the required sample size is estimated to be 220 participants (110 per treatment arm).

2.2.2. Statistical analysis: Primary outcome

The full analysis set (all randomised participants) will be used for primary outcomes analyses. A descriptive summary of UACR values over time, including geometric statistics and descriptions of absolute and relative changes from baseline, will be presented by treatment group and visit. The analysis of UACR will be performed on the log-transformed UACR values, followed by a back transformation to the original scale. The log-transformed ratio of UACR at baseline up to Month 6 (Visit 5) will be analysed by a mixed model for repeated measures with the following factors: treatment group, visit, treatment-by-visit interaction, log-transformed baseline value as a covariate and log-transformed baseline value-by-visit interaction to characterise the patients' baseline-specific response over time.

Primary efficacy will be assessed on the geometric mean of the pairwise UACR treatment ratios between the finerenone and placebo groups at Month 3 (Visit 4) and Month 6 (Visit 5), and the corresponding two-sided 95 % confidence intervals and *P* values will be provided. A threshold of $P = 0.05$ will be taken to assess significance. Furthermore, pairwise UACR treatment ratios for the finerenone and placebo groups will be calculated for each visit, and corresponding two-sided 95 % confidence intervals and *P* values will also be computed. In the event of missing values, a multiple imputation method will be employed, so that patients with values from previous time points will still be included in the final analysis.

2.2.3. Safety

Safety data analyses will be performed using a safety analysis set comprising all randomised participants who take one or more dose(s) of a study treatment. Adverse events that started or worsened after the first dose of study intervention up to 3 days after any temporary or permanent interruption of study intervention will be considered as TEAEs. All safety variables will be analysed using descriptive statistics. The number, incidence and incidence rates per 1000 participant-years of TEAEs and TESAEs will be summarised by treatment group and for the overall population using the Medical Dictionary for Regulatory Activities terms grouped by Primary System Organ Class and Preferred Term. TEAEs pertaining to hyperkalaemia will be summarised by treatment group using frequency counts. For the number of participants with these events, the summary will be provided for all events and for all TEAEs.

2.3. Study oversight

The trial will be overseen by a multi-specialty steering committee, comprising 13 academic members, who participated in the design of the trial. They will oversee its conduct, comment on the data analysis and interpret the data. The steering committee will also include representatives of the sponsor (Bayer AG), one member from the Juvenile Diabetes Research Foundation and patient representatives. The sponsor will be responsible for the collection and analysis of data in collaboration with the steering committee. An independent data- and safety–monitoring committee will be reviewing safety data and overall study conduct throughout the trial; its members will be the only persons unblinded to the study data. All authors will have access to the study database at completion of the trial.

3. Discussion

Despite guideline-recommended treatments, CKD-related mortality and morbidity remain high in people with type 1 diabetes [23,24]. Since the introduction of ACEis, ARBs and strict blood glucose control in the standard of care of individuals with type 1 diabetes, no new treatment modalities for the management of CKD in people with type 1 diabetes have been identified [7]. Therefore, treatments that can slow CKD progression are an unmet need in people with type 1 diabetes. The FINE-

ONE trial is designed to expand the kidney protective indication of finerenone to adults with type 1 diabetes and CKD.

The current treatment for type 1 diabetes and CKD is based on evidence obtained from clinical trials conducted in the late 1980s and early 1990s. Compared with conventional glycaemic control, intensive glycaemic control reduced the risk of microvascular complications in the DCCT trial with fewer cases of kidney failure in the DCCT-EDIC trial (long-term follow-up data from the DCCT trial) [25,26]. Lewis, et al. (1993) demonstrated that the risk of kidney failure was also reduced with active treatment compared with placebo in a kidney outcomes trial of captopril [20]. These landmark trials improved the pharmacotherapy and prognosis for many people with type 1 diabetes and CKD. Since the early 1990s, unfortunately few efforts have been undertaken to further improve the treatment of CKD associated with type 1 diabetes, despite

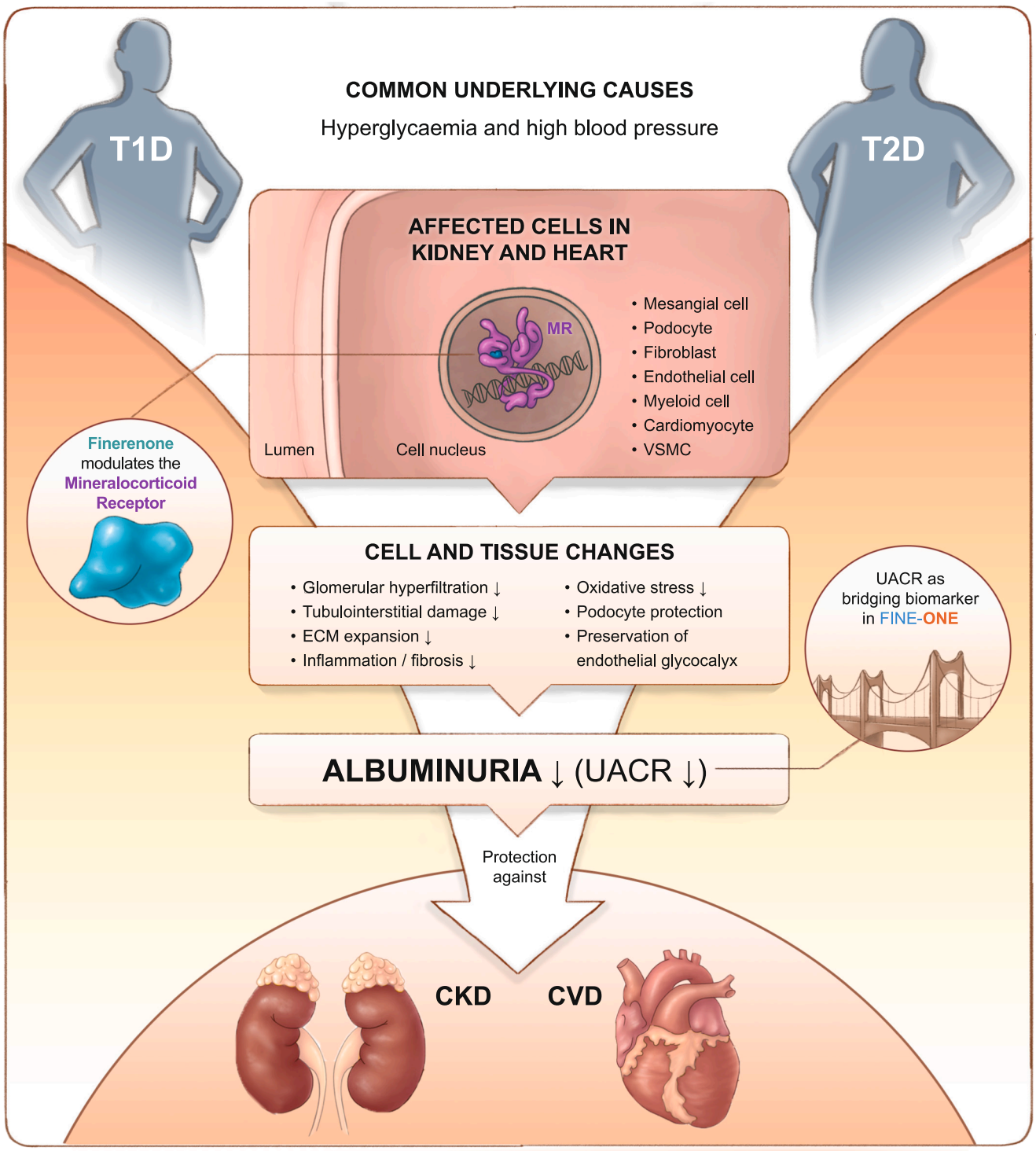


Fig. 4. Albuminuria has a similar role in the pathophysiology of CKD in type 1 and type 2 diabetes. CKD, chronic kidney disease; CVD, cardiovascular disease; ECM, extracellular matrix; MR, mineralocorticoid receptor; T1D, type 1 diabetes; T2D, type 2 diabetes; UACR, urine albumin/creatinine ratio; VSMC, vascular smooth muscle cell. Adapted from Green, et al (2022) [36] under the terms of the Creative Commons Attribution-Non Commercial License (https://creativecommons.org/licenses/by-nc/4.0/).

multiple studies demonstrating that these individuals continue to experience a high risk of adverse kidney and cardiovascular outcomes. Although new therapies for people with type 2 diabetes have emerged, the benefits and risks of these therapies for adults with type 1 diabetes remains undefined because they were excluded from previous trials. The FINE-ONE study aims to expand the current indication for kidney protection with finerenone from type 2 diabetes to type 1 diabetes. If successful, it would be the first drug in 30 years with a registration for kidney protection in type 1 diabetes on top of standard of care.

The primary outcome of the FINE-ONE trial is the percentage change from baseline in albuminuria (UACR). Albuminuria is a strong risk marker of kidney and cardiovascular disease progression in multiple populations, including people with type 1 diabetes and CKD [27–29]. The development of moderately or severely increased albuminuria (previously known as micro- or macroalbuminuria) are hallmarks of the progression of CKD, as demonstrated by observational studies, which showed that the risk of kidney and cardiovascular outcomes was substantially increased in people with type 1 diabetes who developed moderate or severely increased albuminuria [28,30,31]. Similar to observations in people with type 2 diabetes, the early reduction in albuminuria upon initiation of kidney protective treatment is associated with a slower rate of CKD progression. Specifically, data from the aforementioned trial of captopril [20] show that the early reduction in albuminuria with captopril is associated with a reduction in risk of kidney outcomes, supporting the notion that reducing albuminuria by other treatments may also improve long-term kidney outcomes in type 1 diabetes. Based on these and other data, regulatory authority feedback has been received that albuminuria can be used as a BB for evidence translation for CKD progression from type 2 to type 1 diabetes [21], as it meets the necessary requirements: (1) a small target population with no or few proven effective interventions, (2) the role of albuminuria in the pathophysiology of CKD is largely similar in type 1 and type 2 diabetes (Fig. 4), (3) *meta*-regression of clinical trials demonstrates that treatment effects on albuminuria are strongly associated with treatment effects on kidney failure and (4) the reduction in albuminuria in the FIDELIO-DKD and FIGARO-DKD trials explained 87 % of the effect of finerenone in reducing the risk of the composite kidney outcome (Fig. 3). Therefore, the FINE-ONE trial uses albuminuria as the primary outcome to expand the indication of finerenone for slowing the progression of CKD from type 2 to type 1 diabetes. Owing to the strong association between albuminuria and adverse long–term kidney outcomes in both type 1 and type 2 diabetes, it is assumed that long–term treatment with finerenone will reduce the risk of kidney failure in type 1 diabetes in a similar way to that demonstrated in type 2 diabetes [32–34].

The FINE-ONE trial is part of a series of randomised controlled clinical trials to assess the kidney protective effects of finerenone. The FIND-CKD trial will determine the kidney protective effects of finerenone in 1574 adults with CKD of non-diabetic aetiology (NCT05047263), while the FIONA trial (NCT05196035) and the associated open-label extension trial (NCT05457283) are designed to assess the efficacy and safety of finerenone in approximately 219 children with CKD with or without diabetes. FINE-ONE will thus aim to expand the indication for kidney protection with finerenone from type 2 to type 1 diabetes, while FIND-CKD and FIONA aim to determine the potential expanded role of finerenone for the treatment of CKD of diabetic and non-diabetic aetiologies across all ages.

The safety profile of finerenone was comprehensively characterised in over 6500 people with type 2 diabetes and CKD out of 13,000 people in the combined FIDELITY analysis – a pooled analysis from the phase III studies FIDELIO-DKD and FIGARO-DKD [16,17,19]. In this analysis, finerenone did not alter HbA_{1c} compared with placebo [19]. The FIDELITY investigators reported that the incidence of hyperkalaemia was elevated in participants receiving finerenone compared with placebo, but the proportion of serious hyperkalaemia-related adverse events was low [19]. Discontinuations of study intervention or hospitalisation due to hyperkalaemia were low in the finerenone groups [19]. No deaths due to hyperkalaemia were reported [19]. Proven effective measures for the management of hyperkalaemia in participants with type 2 diabetes in the FIDELIO–DKD and FIGARO–DKD trials have been implemented in FINE-ONE. Only patients with a serum potassium level of $\leq$ 4.8 mmol/l and eGFR of $\geq$ 25–90 ml/min/1.73 m^2 at screening will be included in the study. Furthermore, guidance on up and downtitration of study intervention based on serum potassium and eGFR have been implemented according to the characterised benefit-to-risk profile of finerenone in the FIDELIO-DKD and FIGARO-DKD studies.

The strength of the FINE-ONE trial is that it uses, for the first time, UACR as a bridging biomarker to translate efficacy evidence of finerenone from people with type 2 diabetes and CKD to those with type 1 diabetes and CKD. If successful, a separate kidney outcome trial is not required which will shorten the time to introduction of finerenone in clinical practice. A limitation is that, as with any clinical trial, the results are only applicable to patients who share the characteristics of the enrolled population which limits the generalizability.

In conclusion, based on the large evidence base of finerenone to slow the progression of CKD in people with type 2 diabetes as well as earlier studies demonstrating that RAS inhibition reduces albuminuria and slows CKD in people with type 1 diabetes, the FINE-ONE trial is designed to determine the role of finerenone for kidney protection in people with type 1 diabetes and CKD. FINE-ONE, with its use of UACR as a BB, may establish a new precedent for future clinical trials in people with type 1 diabetes and CKD for whom new therapies are highly needed.

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Author contributions

All authors substantially contributed to the conception, design or planning of the study. HJLH wrote the first draft of the manuscript. JBM and RL substantially contributed to the drafting of the manuscript. All authors substantially contributed to critically reviewing or reviewing the manuscript for important intellectual content.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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HJLH is a consultant for AstraZeneca, Bayer, Boehringer Ingelheim, Chinook, CSL Behring, Dimerix, Eli Lilly, Gilead, Janssen, Merck, Mitsubishi Tanabe, Novartis, Novo Nordisk and Travere. He received research support from AstraZeneca, Boehringer Ingelheim, Janssen and Novo Nordisk.

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HMC reports trial advisory board fees from Bayer, Novo Nordisk, Regeneron, Sanofi and Eli Lilly; grant funding from AstraZeneca and Novo Nordisk; lecture fees from Medscape and owns shares in Bayer and Roche.

LJ reports receiving consulting or lecture fees from Eli Lilly, Novo Nordisk, Merck, Bayer, Sanofi-Aventis, Roche, MSD, Medtronic, AstraZeneca, Boehringer Ingelheim and Abbott.

CM serves or has served on the advisory panel for ActoBio Therapeutics, AstraZeneca, Avotres, Boehringer Ingelheim, Eli Lilly, Imcyse, Insulet, Mannkind, Medtronic, Merck Sharp and Dohme Ltd., Novartis, Novo Nordisk, Pfizer, Roche, Sanofi, Vertex and Zealand Pharma. Financial compensation for these activities has been received by KU Leuven; KU Leuven has received research support for CM from ActoBio Therapeutics, Imcyse, Medtronic, Novo Nordisk and Sanofi; CM serves or has served on the speaker's bureau for AstraZeneca, Boehringer Ingelheim, Eli Lilly, Novo Nordisk, Sanofi and Novartis. Financial compensation for these activities has been received by KU Leuven.

P-HG reports receiving lecture honoraria from Astellas, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Medscape, MSD, Mundipharma, Novo Nordisk, PeerVoice, Sanofi and SCIARC; and being an advisory board member of Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Elo Water, Medscape, MSD, Mundipharma, Nestlé, Novo Nordisk, PeerVoice, Sanofi and SCIARC.

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SER participated in at least one advisory board for AstraZeneca, Bayer and Traverse. Joslin Diabetes Center receives research support from AstraZeneca and Bayer.

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RL is an employee of Bayer AG, Germany.

CS is an employee of Bayer PLC, UK.

RE is an employee of Bayer AB, Sweden.

MFS is an employee of Bayer AG, Germany. MFS is also a shareholder in AstraZeneca, Bayer AG, Eli Lilly and Novo Nordisk.

PK is an employee of Bayer AG, Germany. PK is s a co-inventor of finerenone and holds US and European patents relating to finerenone (US8436180B2 and EP2132206B1).

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Appendix A. Supplementary material

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