

# Design of the COmbination effect of FInerenone and EmpaglifloziN in participants with chronic kidney disease and type 2 diabetes using a UACR Endpoint study (CONFIDENCE)

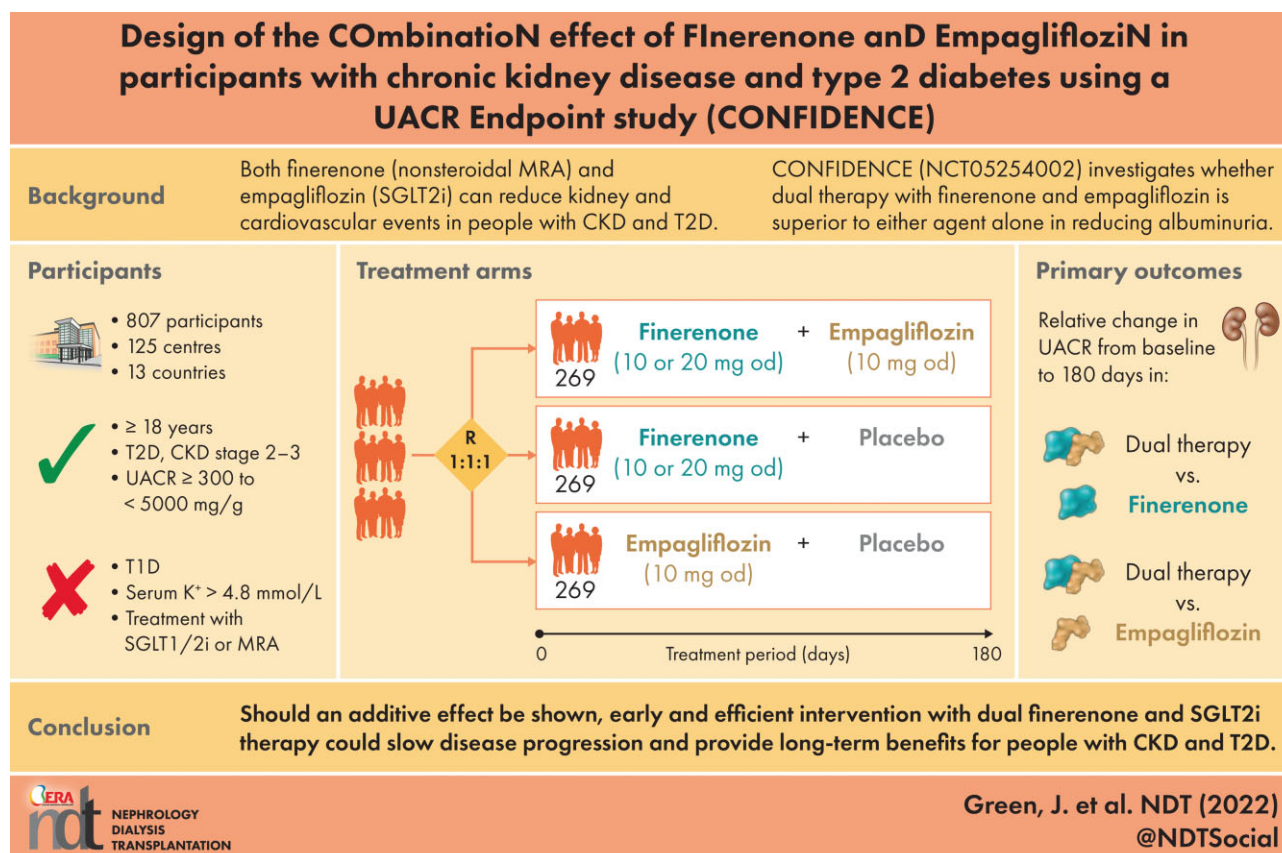
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## GRAPHICAL ABSTRACT



## KEY LEARNING POINTS

### What is already known about this subject?

- Despite approved interventions, people with type 2 diabetes (T2D) with chronic kidney disease (CKD) have an increased risk of kidney failure, cardiovascular (CV) morbidity and all-cause mortality.
- A need exists to slow or attenuate the progression of CKD and reduce CV morbidity and mortality in people with T2D.
- Finerenone, a selective nonsteroidal mineralocorticoid receptor antagonist, and sodium–glucose cotransporter 2 inhibitors (SGLT2is) each reduce adverse kidney and cardiovascular outcomes in people with CKD and T2D.

### What this study adds?

- CONFIDENCE is a randomized, controlled, double-blind, double-dummy, international, multicenter, three-armed, parallel-group, Phase 2 study in 807 adults with CKD and T2D. Participants will be randomized 1:1:1 to 180 days of treatment with finerenone and empagliflozin, finerenone and matching placebo to empagliflozin, or empagliflozin and matching placebo to finerenone.
- Trial evidence consistently demonstrates a close association between lowering of urinary albumin:creatinine ratio (UACR) with CV and kidney outcomes; a greater reduction in UACR is associated with greater CV or kidney benefit. The primary objective of this study is to demonstrate that dual initiation of finerenone and empagliflozin is superior for reducing UACR compared with either empagliflozin or finerenone alone.
- This trial will inform the scientific and clinical communities whether dual therapy with finerenone and empagliflozin is of additive benefit to patients with CKD and T2D.

### What impact this may have on practice or policy?

- If CONFIDENCE demonstrates an additive effect with dual finerenone and SGLT2i therapy and acceptable safety, simultaneous therapy could be utilized to further slow kidney disease progression and provide long-term benefits for people with CKD and T2D.

## ABSTRACT

**Background.** Despite available interventions, people with type 2 diabetes (T2D) remain at risk of chronic kidney disease (CKD). Finerenone, a potent and selective nonsteroidal mineralocorticoid receptor antagonist, and sodium–glucose cotransporter 2 inhibitors (SGLT2is) can reduce both kidney and cardiovascular risks in people with CKD and T2D. Here we outline the design of a study to investigate whether dual therapy with finerenone and an SGLT2i is superior to either agent alone.

**Methods.** CONFIDENCE (NCT05254002) is a randomized, controlled, double-blind, double-dummy, international, multicenter, three-armed, parallel-group, 7.5 - to 8.5-month, Phase 2 study in 807 adults with T2D, stage 2–3 CKD and a urine albumin:creatinine ratio (UACR)  $\geq 300$ – $<5000$  mg/g. The primary objective is to demonstrate that 6 months of dual therapy comprising finerenone and the SGLT2i empagliflozin is superior for reducing albuminuria versus either agent alone. Interventions will be once-daily finerenone 10 mg or 20 mg (target dose) plus empagliflozin 10 mg, or empagliflozin 10 mg alone, or finerenone 10 mg or 20 mg (target dose) alone.

**Results.** The primary outcome is a relative change from baseline in UACR among the three groups. Secondary outcomes will further characterize efficacy and safety, including changes in estimated glomerular filtration rate and incident hyperkalemia.

**Conclusions.** CONFIDENCE is evaluating the safety, tolerability and efficacy of dual use of finerenone and an SGLT2i in adults with CKD and T2D. Should an additive effect be shown, early and efficient intervention with dual finerenone and

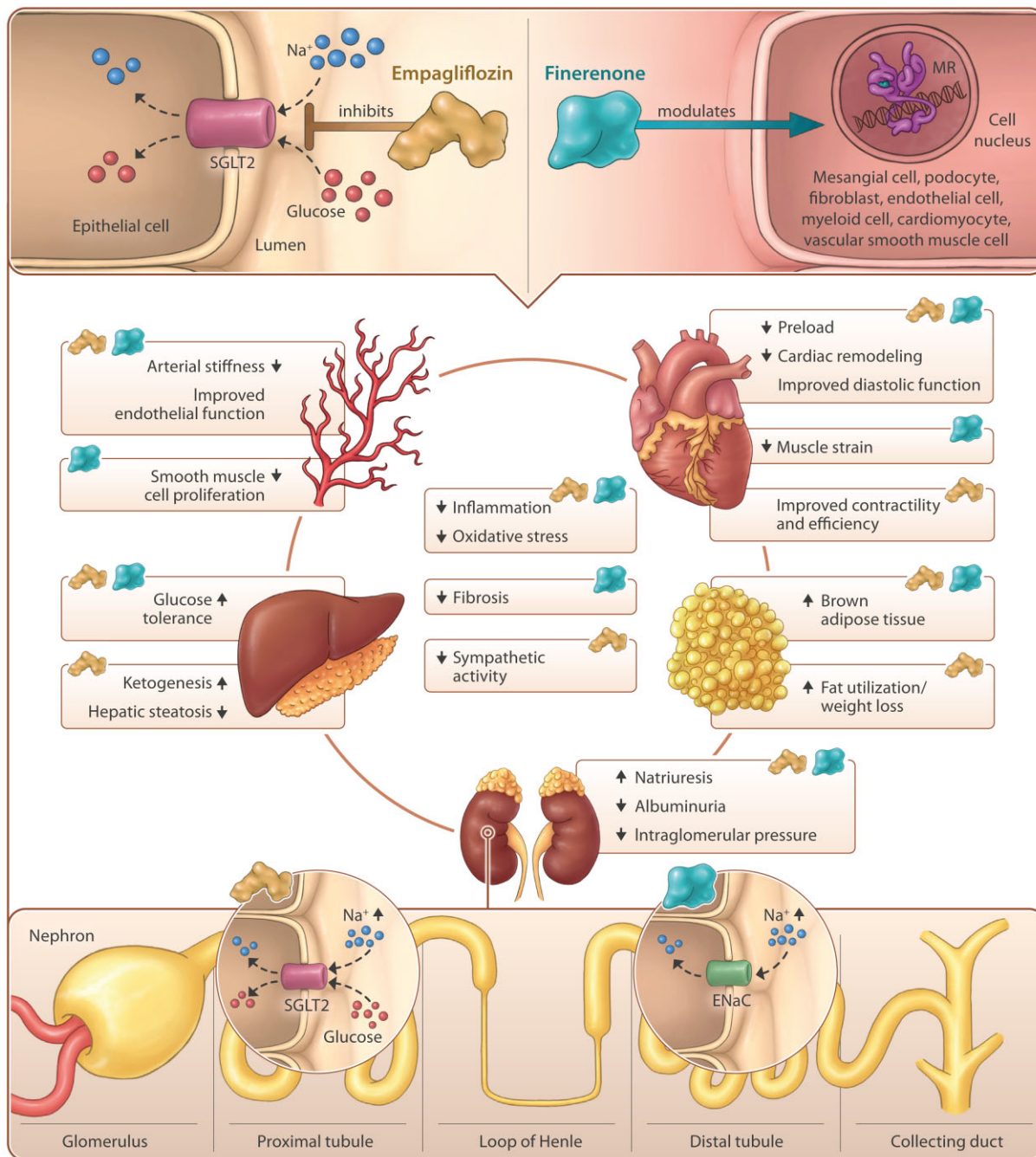
SGLT2i therapy could slow disease progression and provide long-term benefits for people with CKD and T2D.

**Keywords:** chronic kidney disease, diabetes, empagliflozin, finerenone, macroalbuminuria

## INTRODUCTION

Diabetes is the leading cause of chronic kidney disease (CKD) worldwide, with ~30–50% of adults with type 2 diabetes (T2D) also having CKD [1, 2]. CKD is associated with an increased risk of dialysis, cardiovascular (CV) events and all-cause mortality, a risk that increases with decreasing estimated glomerular filtration rate (eGFR) and increasing albuminuria levels [3], the former with a threshold of ~60 mL/min/1.73 m<sup>2</sup> and the latter without a threshold. For the prevention of CV and CKD progression, guidelines recommend lifestyle modifications, such as physical activity, weight loss, smoking cessation and dietary interventions [4–6]. Pharmacological interventions include blood pressure (BP) control, minimizing albuminuria with renin–angiotensin–aldosterone system blockade, glycemic control and lowering of serum lipoproteins [4–6]. Despite these treatment approaches, people with diabetes remain at risk of developing CV events and progression to kidney failure [1]. Therefore, new therapeutic agents to slow the progression of kidney disease and reduce morbidity and mortality in people with T2D are greatly needed.

Sodium–glucose cotransporter 2 inhibitors (SGLT2is) were developed for glycemic control in T2D; however, their most important effects were later found to be a reduction of kidney and CV events in people with CKD, regardless of



**FIGURE 1:** Proposed mechanisms for reducing adverse cardiovascular- and kidney-related outcomes based on preclinical and clinical studies using finerenone and SGLT2 inhibitors.

T2D diagnosis. In two landmark studies, SGLT2is reduced the risk of kidney failure and death from kidney or CV causes compared with placebo in people with CKD [7, 8].

Finerenone is a selective nonsteroidal mineralocorticoid receptor antagonist (MRA) that reduced the primary composite kidney outcome in the Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) study [9]. The drug also reduced the primary composite CV outcome in the Finerenone in Reducing CV Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD) study [10]. Both SGLT2i and finerenone

have been included as recommended treatments for CKD in patients with T2D in recent guidelines [11].

Whether dual therapy with finerenone and an SGLT2i could provide further reductions in kidney and CV risk than either alone is an important question. These two drug classes have shared and distinct pathophysiological pathways (Fig. 1). Results from *post hoc* subgroup analyses of clinical studies and a preclinical model of hypertension-induced cardiorenal disease suggest that dual finerenone and SGLT2i therapy may provide additive renoprotective effects [12, 13]. In rats, dual finerenone and empagliflozin therapy resulted



in greater reductions in proteinuria than with either agent alone as monotherapy [12]. A subgroup analysis of the FIDELIO-DKD trial found that improvements in the urinary albumin:creatinine ratio (UACR) were observed regardless of whether participants were being treated with an SGLT2i or not [2]. Similarly, among participants with heart failure and reduced ejection fraction, SGLT2i (dapagliflozin) benefits were unaffected by simultaneous treatment with a steroidal MRA (spironolactone or eplerenone; Supplementary data, Table S1) [14]. Similarly, the renoprotective effects of dapagliflozin in people with CKD were independent of baseline MRA use [15]. Given the *post hoc* nature and limited power of these subgroup analyses, results are only hypothesis generating [13].

The CombinationN effect of Finerenone and Empagliflozin in participants with CKD and type 2 diabetes using a UACR Endpoint (CONFIDENCE) study will investigate whether dual therapy comprising finerenone and the SGLT2i empagliflozin is superior to either drug alone in reducing UACR. CONFIDENCE is, to our knowledge, the first parallel-group, randomized controlled trial to evaluate the safety, tolerability and additive efficacy of dual finerenone and empagliflozin therapy in people with CKD and T2D. This article will outline the study design and analysis plan.

## MATERIALS AND METHODS

### Study design

CONFIDENCE is a randomized, controlled, double-blind, double-dummy, international, multicenter, three-armed, parallel-group, Phase 2 study in people with CKD and T2D. The primary objective will be to demonstrate whether initiation of dual finerenone and empagliflozin therapy is superior in reducing UACR than either empagliflozin or finerenone alone. CONFIDENCE will be conducted at ~125 sites across an anticipated 13 countries. Participant screening began in April 2022 and final participant randomization is targeted for May 2023. It is anticipated that ~1614 participants will be screened to reach the required total of ~807 randomized 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. CONFIDENCE is being conducted in compliance with the principles of the Declaration of Helsinki and in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice. All study participants will provide written informed consent prior to study enrolment. The study is registered with [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (NCT05254002).

**Study participants.** Eligible individuals will be  $\geq 18$  years of age at screening with a diagnosis of T2D [16], a clinical diagnosis of CKD stage 2–3, an eGFR of 30–90 mL/min/1.73 m<sup>2</sup>, a UACR of  $\geq 300$ –<5000 mg/g and on treatment with the clinically maximum tolerated dose of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker. Key eligibility criteria are detailed in Supplementary data, Table S2. A screening visit will occur  $\leq 2$  weeks before randomization.

**Study parts.** CONFIDENCE comprises two consecutive parts (Supplementary data, Table S2). In part A, participants will have an eGFR of 40–90 mL/min/1.73 m<sup>2</sup>. Following administration of their first study drug dose on Day 1, participants will remain at the study site for 4–6 h for BP monitoring and then undergo ambulatory BP monitoring (ABPM) for a duration of 24 h. In part B, inclusion criteria will be expanded to an eGFR of 30–90 mL/min/1.73 m<sup>2</sup>. Participants will not be required to undergo ABPM. A decision to progress from part A to part B, which includes extension of enrolment to participants with an eGFR as low as 30 mL/min/1.73 m<sup>2</sup>, will be made by the sponsor and Steering Committee following an analysis of safety findings for the first 50 participants in part A and unblinded review by the independent Data Monitoring Committee.

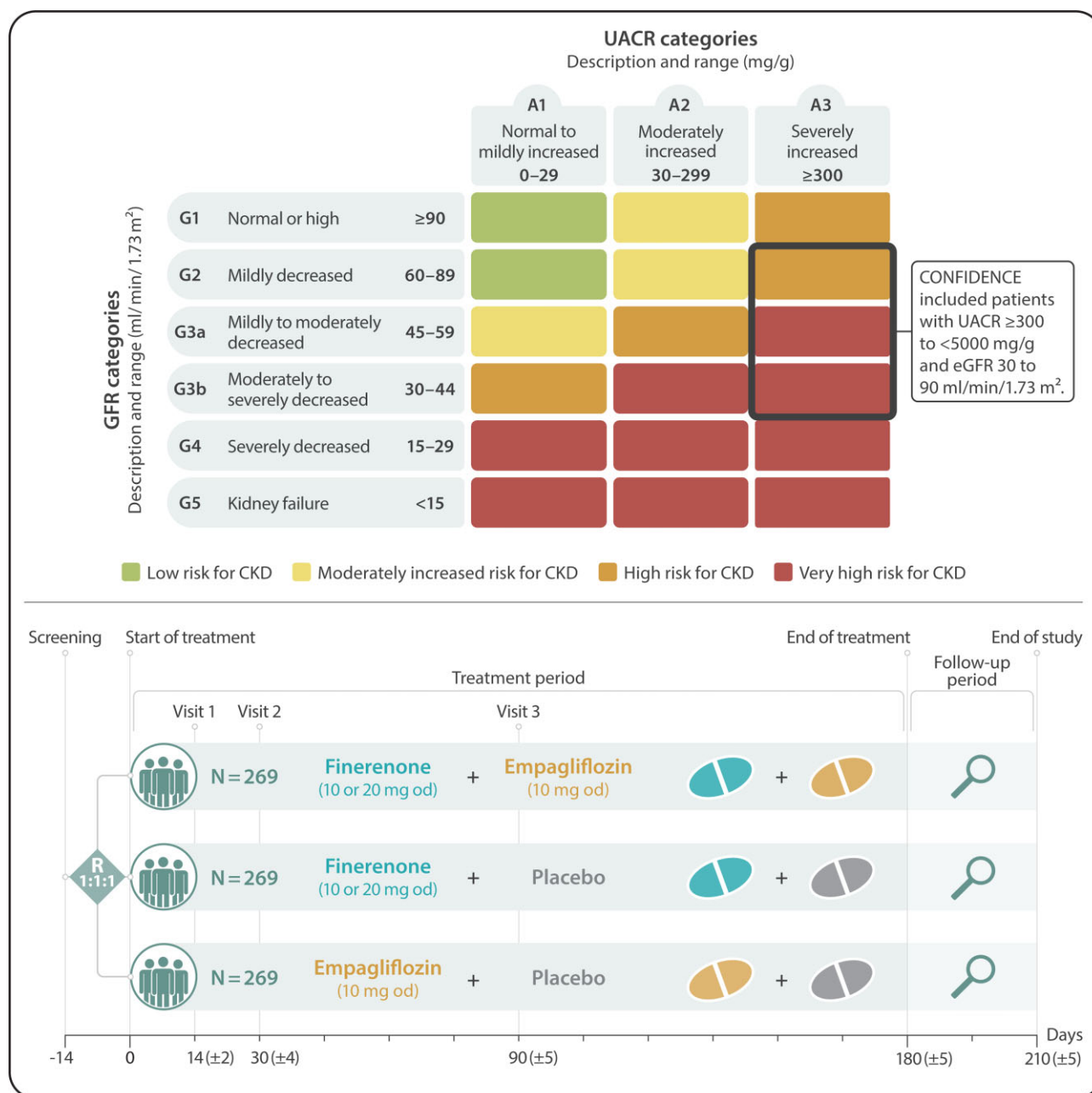
**Randomization and study treatment.** Participants will be randomized 1:1:1 to finerenone [10 or 20 mg once daily (OD)] and empagliflozin (10 mg OD), finerenone (10 or 20 mg OD) and matching placebo to empagliflozin, or empagliflozin (10 mg OD) and matching placebo to finerenone (Fig. 2). Randomization will be stratified by eGFR ( $<60$  mL/min/1.73 m<sup>2</sup>,  $\geq 60$  mL/min/1.73 m<sup>2</sup>) and UACR ( $\leq 850$  mg/g,  $>850$  mg/g) values at screening. There are also caps on the percentage of participants with eGFRs  $\leq 75$  mL/min/1.73 m<sup>2</sup> and  $>75$  mL/min/1.73 m<sup>2</sup> (Supplementary data, Table S2).

Starting on Day 1, finerenone 10 or 20 mg tablets (or matching placebo) will be administered orally with empagliflozin 10 mg (or matching placebo) OD. The starting dose of finerenone will depend on the participant's eGFR level at the screening visit: a lower dose of 10 mg OD if eGFR is  $<60$  mL/min/1.73 m<sup>2</sup> or the higher (target) dose of 20 mg OD if eGFR is  $\geq 60$  mL/min/1.73 m<sup>2</sup>.

After 30 days for participants starting on finerenone 10 mg, finerenone will be up-titrated to the 20-mg target dose provided the locally determined serum/plasma potassium (K<sup>+</sup>) concentration is  $\leq 4.8$  mmol/L and the eGFR the decrease is  $<30\%$  compared with the value measured at the prior visit. Corresponding sham up-titrations will be performed for placebo. Down-titration from a 20-mg to a 10-mg dose is 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. Protocol-specified reasons for permanent discontinuation of interventions are events of investigator-reported ketoacidosis or Fournier's gangrene, at the specific request of the sponsor and in liaison with the investigator for instances such as noncompliance and safety concerns.

**Study follow-up.** Visits subsequent to randomization will occur on Days 14, 30, 90 and 180. A follow-up/end-of-study visit will be scheduled 30 days after the last dose (Day 210; Fig. 2). The total study duration for each participant will be ~7.5 months or 8.5 months with optional pre-screening.

**Efficacy and safety assessments.** Demographic characteristics and medical history will be recorded at screening. UACR will be evaluated at all scheduled visits using the first morning void (FMV) urine samples collected at the participant's home. For each subsequent visit, two FMV samples will be collected  $\pm 7$  days from the visit date. Prescreening



**FIGURE 2:** Study design. The number of participants will be capped in parts A and B as follows: up to 80% with an eGFR  $\leq 75$  mL/min/1.73 m<sup>2</sup> and up to 20% with an eGFR  $> 75$  mL/min/1.73 m<sup>2</sup>. Up-/down-titration based on eGFR, serum/plasma potassium or potassium, safety and tolerability. R, randomization.

UACR will be assessed at local laboratories and a central laboratory will be used for all other time points. eGFR will be automatically calculated for all scheduled visits by the central laboratory using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation [17], modified as required for Japanese participants [18], and will be used for screening/eligibility and primary data analysis. A new CKD-EPI creatinine- and cystatin C-based equation will also be used to calculate eGFR without modification for the participants' race for a sensitivity analysis (Supplementary Text S1) [19]. Locally measured serum creatinine will be used to calculate eGFR in the electronic case report form using the CKD-EPI

creatinine equation (e.g. for finerenone titration). eGFR will be automatically calculated for all scheduled visits by the central laboratory using the CKD-EPI creatinine equation.

Safety will be assessed at all scheduled visits. K<sup>+</sup> will be monitored for safety assessments at all scheduled visits and determined both centrally and locally. A 12-lead electrocardiogram (ECG) will be performed at screening, baseline and end of treatment. In addition, BP will be assessed at all scheduled visits.

**Primary and other outcomes.** The primary objective of the study is to demonstrate that dual finerenone and empagliflozin therapy is superior in reducing UACR compared

with either empagliflozin or finerenone alone. There will be two primary outcomes to address this objective: the relative change in UACR from baseline to 180 days in the group receiving dual finerenone and empagliflozin therapy versus finerenone alone and the relative change in UACR from baseline to 180 days in the group receiving dual finerenone and empagliflozin therapy versus empagliflozin alone.

The secondary objectives, as detailed in Supplementary data, Table S3, are to further investigate the efficacy of dual therapy versus each treatment alone, including changes in UACR at various time points, and reaching different magnitudes of UACR reduction (30%, 40%, 50%). Secondary outcomes also include safety of dual therapy versus each treatment alone, including assessment of initial and longer-term changes in eGFR, acute kidney injury and specific types of treatment-related adverse events (AEs), such as hyperkalemia (thresholds defined in Supplementary data, Table S3), genital mycotic infections and symptomatic hypotension.

### Statistical considerations

**Sample size assumptions.** Dual therapy will be powered to detect a 20% further reduction in UACR compared with either drug as monotherapy. Past research allows us to assume that the treatment effect of empagliflozin on UACR lowering is ~30% [20] and the treatment effect of finerenone on UACR lowering is ~35% at 180 days [9]. Based on previous study findings, it was calculated that group sample sizes of 226 and 226 (dual therapy versus finerenone alone) and 228 and 228 (dual therapy versus SGLT2i alone) would achieve 80% power to reject the null hypothesis of equal means, with a standard deviation for both groups in log-transformed UACR of 0.77. Assuming dropout and screen failure rates of ~15% and 50%, respectively, group sample sizes of 269, 269 and 269 are anticipated to be sufficient to detect a 20% further reduction in UACR in the dual therapy arm versus empagliflozin or finerenone alone.

**Statistical analysis: primary outcomes.** The full analysis set (FAS; all randomized participants with no Good Clinical Practice violations) will be used for primary outcomes analyses. To determine whether dual finerenone and empagliflozin therapy is superior to either agent alone in reducing UACR, a repeated measures mixed model will be utilized, with factors for treatment group, visit, treatment  $\times$  visit interaction, factors for the two stratification levels (UACR category and eGFR category), log-transformed baseline UACR value as a covariate nested within the UACR category and log-transformed baseline UACR value  $\times$  visit interaction. Pairwise ratios between the finerenone plus empagliflozin versus the finerenone alone and empagliflozin alone treatment groups will be calculated and corresponding two-sided 95% confidence intervals (CIs) will be computed. A two-sided two-sample *t*-test of equal variance at an overall two-sided significance level of  $\alpha = 0.05$  (0.025 for the initial hypothesis) will be used. 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 analysis. The Bonferroni–Holm method will be applied to adjust for the multiple testing

of two hypotheses. UACR will be analyzed assuming a log-normal distribution. Assumptions for the UACRs to baseline after 6 months are based on the data from the FIDELIO-DKD study for finerenone and the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) for SGLT2i [9, 20]. Further details on sensitivity and secondary efficacy outcomes are presented in Supplementary Text S2.

**Safety.** Safety data analyses will be performed using a safety analysis set comprising all randomized participants who take one or more doses of a study treatment.

### Study oversight

The trial is being overseen by a multispecialty steering committee comprising nine academic members who participated in the design of the trial, will oversee its conduct and will comment on the data analysis, as well as nonvoting representatives of the sponsor (Bayer AG). The sponsor is responsible for the collection and analysis of data in conjunction with the authors. The CONFIDENCE study is funded by Bayer AG. 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.

## DISCUSSION

CONFIDENCE is, to our knowledge, the first phase 2, head-to-head study comparing the efficacy and safety of dual treatment comprising an SGLT2i and a nonsteroidal MRA to either agent alone in people with CKD and T2D. CONFIDENCE will assess the clinical benefits of dual finerenone and SGLT2i therapy on kidney outcomes in people with CKD and T2D using the change in UACR as the primary outcome and as an indicator for progression of CKD.

Secondary analyses of prior trials suggest that such dual therapy will be associated with a positive benefit–risk profile [14, 15]. In the Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure (DAPA-HF) study, the incidences of volume depletion and kidney dysfunction were similar with and without background use of an MRA in the dapagliflozin-treated group, although individuals taking an MRA had a slightly higher baseline eGFR than those not taking an MRA. In addition, the incidence of moderate or severe hyperkalemia in people treated with dapagliflozin was low and similar with and without MRA use (1.3% and 1.9%, respectively). Furthermore, the rate of serious hyperkalemia in participants receiving an MRA was lower with dapagliflozin than with placebo [14]. Similarly, in the Dapagliflozin and Prevention of Adverse Outcomes in CKD (DAPA-CKD) trial, a lower incidence of hyperkalemia with dapagliflozin versus placebo was observed, regardless of MRA use at baseline [15]. In a small, randomized crossover clinical trial (Rotation for Optimal Targeting of Albuminuria and Treatment Evaluation-3), the combination of an MRA with an SGLT2i in patients with CKD resulted in a meaningful and additive reduction in UACR from baseline (53%) that represented a greater change than afforded by

either agent ( $P < .05$ ) [21]. Furthermore, the combination was also associated with significantly fewer hyperkalemia-related AEs than an MRA alone (4.3% versus 17.4%;  $P < .01$ ) [21]. In addition, a recent meta-analysis demonstrated that the relative effect of SGLT2is versus placebo on reduced serious hyperkalemia ( $K^+ \geq 6.0$  mmol/L) was consistent regardless of the use of an MRA at baseline [22].

A *post hoc* analysis of the FIDELIO-DKD trial has also found similar benefits in UACR reduction with finerenone; UACR reduction with finerenone versus placebo was 31% in participants treated without an SGLT2i and 25% with an SGLT2i [2]. In this same *post hoc* analysis, participants treated with finerenone and an SGLT2i had fewer hyperkalemia-related AEs than those receiving finerenone without an SGLT2i (8.1% versus 18.7%); however, that analysis was confounded by a higher eGFR and lower UACR in the subgroup of participants receiving an SGLT2i as compared with those without [2].

The potential for an additive effect of finerenone and SGLT2is on kidney and CV outcomes in T2D is supported by their complementary mechanisms of action (Fig. 1). For example, CKD progression is driven by metabolic and hemodynamic factors, inflammation and fibrosis. The mechanisms by which SGLT2is reduce adverse kidney and CV events independently of diabetes status are not fully understood but may be associated with hemodynamic effects. Glucose-induced diuresis and natriuresis are thought to be involved and result in decreased intraglomerular hypertension and albuminuria via tubular-glomerular feedback [23]. Recent studies have also demonstrated reductions in oxidative stress and inflammation, as well as improved endothelial function and energy utilization [24–28]. Via different mechanisms from SGLT2i, finerenone and other nonsteroidal MRAs have also been shown to reduce oxidative stress and inflammation and improve endothelial function but have the distinct benefit of reducing fibrotic mediators of kidney and CV disease [29–35]. Thus the overlapping and distinct pathophysiological benefits of finerenone and SGLT2i are the basis for further exploration of potential combined benefits in reducing clinical events.

A joint National Kidney Foundation, US Food and Drug Administration and European Medicines Agency workshop has proposed that an early change in albuminuria (i.e. UACR) may be a suitable surrogate for CKD progression in clinical trials [36]. UACR is predictive of long-term outcomes in people with T2D and a change in albuminuria may therefore have utility as a surrogate for CKD progression. For example, in a meta-analysis including >500 000 individuals with diabetes from 28 observational study cohorts, a change in UACR was shown to be associated with a risk of progressing to end-stage kidney disease across the studies included [37]. Similarly, meta-analysis of 41 clinical trials with data for >20 000 participants with diabetes found a clear association between a change in albuminuria and a composite kidney endpoint, with a 30% decrease in albuminuria associated with a 27% reduction in hazard of a composite kidney outcome including end-stage kidney disease [38]. Finally, from a clinical perspective, the current American Diabetes Association Standards of Medical Care in Diabetes recommend a reduction in urinary albumin as a treatment target for CKD in diabetes [11].

As shown in Supplementary data, Table S4, selection of UACR, a surrogate marker for kidney damage [11], as the primary efficacy outcome for CONFIDENCE enables a feasible study of shorter duration and inclusion of fewer participants than if outcomes such as eGFR slope or kidney failure were utilized. An event-driven study would require significantly more participants or a longer duration to accrue the required number of events to detect the assumed hazard ratio of 0.8. A study utilizing a composite kidney outcome comprising kidney failure, change in eGFR  $\geq 40\%$  and death from kidney causes would require randomization of  $\sim 41$  000 patients with a 5-year recruitment period and 3-year follow-up for each participant. Similarly, a CONFIDENCE-style study using eGFR slope as an outcome would require a study duration much longer than the 6 months needed for CONFIDENCE.

As finerenone and empagliflozin are both associated with an initial decrease in BP and eGFR on commencement of treatment [39–42], participants in part A of the CONFIDENCE study will therefore be equipped with an ABPM device before the first intake of study drug to monitor for the occurrence of symptomatic hypotension. Importantly, changes in BP over time and initial eGFR changes have been hypothesized to influence treatment effects of finerenone and SGLT2is. However, investigation of the change in systolic BP (SBP) with finerenone treatment found no strong indications of an interaction between treatment and SBP and only a small proportion of the effects of finerenone on cardiorenal outcomes during treatment could be attributed to BP changes [42]. Similarly, as found in the EMPA-REG OUTCOME trial, an initial decrease in eGFR of  $\geq 10\%$  with empagliflozin treatment occurred in 28% of participants compared with 13% with placebo but did not have a clinically relevant impact on CV or kidney outcomes [41]. However, analysis from DAPA-HF found that patients randomized to dapagliflozin with an early decline in eGFR had improved cardiorenal outcomes (including the primary composite cardiovascular outcome). In contrast, those randomized to placebo with an early decline in eGFR had worse cardiorenal outcomes [43].

In summary, CONFIDENCE is the first randomized controlled trial to evaluate the additive efficacy, safety and tolerability of dual therapy comprising finerenone and an SGLT2i in people with CKD and T2D. Should an additive effect on UACR be established by the CONFIDENCE study, it will suggest that early intervention with both finerenone and SGLT2i therapy slows kidney disease progression and thus may provide long-term reductions in morbidity and mortality for people with CKD and T2D.

## SUPPLEMENTARY DATA

Supplementary data are available at [ndt](#) online.

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## CONFLICT OF INTEREST STATEMENT

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## AUTHORS' CONTRIBUTIONS

All authors substantially contributed to the conception, design and planning of the study. J.G., A.K.M., A.G. and R.A. substantially contributed to the drafting of the manuscript. All authors substantially contributed to critically reviewing or revising the manuscript for important intellectual content.

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