The soluble guanylate cyclase activator runcaciguat significantly improves albuminuria in patients with chronic kidney disease: a randomized placebo-controlled clinical trial

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Running head: sGC activator runcaciguat improves albuminuria in CKD

ABSTRACT

Background and hypothesis. In chronic kidney disease (CKD) the nitric oxide (NO)−soluble guanylate cyclase (sGC)−cyclic guanosine monophosphate (cGMP) pathway is impaired. Runcaciguat, an sGC activator, activates heme-free sGC, restoring cGMP production. This phase 2a trial studied the efficacy, safety, and tolerability of runcaciguat in CKD patients with or without sodium-glucose co-transporter-2 inhibitor (SGLT2i).

Methods. Patients with CKD and established atherosclerotic cardiovascular disease or heart failure, plus type 2 diabetes (T2D) and/or hypertension, were enrolled. All were receiving stable maximum tolerated renin−angiotensin system inhibitors with or without SGLT2i. They were randomized 3:1 to runcaciguat once daily, titrated weekly (30–120 mg if tolerated), or placebo for 8 weeks. The primary efficacy endpoint was urine albumin-to-creatinine ratio (UACR) (average of post-randomization Days 22, 29, and 57 vs baseline). CONCORD was separately powered for CKD and T2D with stable SGLT2i comedication, CKD and T2D without SGLT2i, and non-diabetic CKD.

Results. Of 243 patients randomized, 229 were included in the full analysis set (FAS) and 170 in the per-protocol set (PPS). In the PPS, UACR decreased by −45.2% versus placebo with runcaciguat in patients with CKD without SGLT2i ($P < .001$) and by −48.1% versus placebo in patients with CKD taking SGLT2i ($P = .02$) In the FAS, the relative reductions were −46.9% ($P < .001$) and −44.8% ($P = .01$), respectively. No significant difference was observed between patients with or without SGLT2i. In non-diabetic CKD, UACR was reduced versus baseline with runcaciguat, but the change was not statistically significant ($P = .10$). Serious treatment-emergent adverse events were reported in 7% of patients receiving runcaciguat and 8% receiving placebo.

Conclusion. Runcaciguat improved albuminuria in patients with CKD, irrespective of concomitant SGLT2i. Runcaciguat was well tolerated. sGC activation may represent a novel kidney-protective treatment in CKD patients (funded by Bayer AG; ClinicalTrials.gov number, NCT04507061).

KEY LEARNING POINTS

What was known:

- Despite guideline-directed therapies, patients with chronic kidney disease (CKD) remain at risk of disease progression, which may result in kidney replacement therapy; there is therefore an urgent need for novel kidney-protective treatments.
- Impairment of the nitric oxide (NO)–soluble guanylate cyclase (sGC)–cyclic guanosine monophosphate (cGMP) pathway by oxidative stress contributes to CKD progression; restoration of NO−sGC−cGMP signaling by activation of sGC is therefore a potential mechanism to prevent or delay progression.
- This placebo-controlled, phase 2a trial was performed to determine whether runcaciguat, an sGC activator, could improve albuminuria, a widely accepted surrogate for renoprotection, in patients with CKD receiving maximum tolerated renin–angiotensin system (RAS) inhibitors with or without sodium-glucose co-transporter-2 inhibitors (SGLT2is).

This study adds:

- In the per-protocol set, the primary endpoint—urine albumin-to-creatinine ratio (UACR)—was reduced by −45.2% versus placebo in patients without SGLT2i ($P < .001$) and by −48.1% versus placebo with runcaciguat in patients taking SGLT2i ($P = .02$).
- In non-diabetic CKD, UACR was reduced versus baseline with runcaciguat, but the change did not differ significantly between runcaciguat and placebo.
- Runcaciguat was well tolerated with a similar incidence of serious adverse effects in the runcaciguat and placebo groups (7% and 8%, respectively).

Potential impact:

- Runcaciguat may represent a novel kidney-protective treatment in patients with diabetic or non-diabetic CKD, on top of RAS inhibitors and SGLT2is
- Further investigations of runcaciguat in patients with CKD are warranted.

Keywords: albuminuria, chronic kidney disease, sodium-glucose co-transporter-2 inhibitors, soluble guanylate cyclase activator, type 2 diabetes

INTRODUCTION

Approximately 2.4% of worldwide mortality is related to chronic kidney disease (CKD) [1]. By 2040, CKD is expected to be the fifth leading cause of life years lost worldwide [2]. Despite guideline-recommended interventions such as renin–angiotensin system (RAS) inhibition and sodium-glucose co-transporter-2 inhibitors (SGLT2is) [3, 4], patients with CKD remain at risk of disease progression, which may result in kidney replacement therapy [1, 5]. There is, therefore, an unmet need to develop novel kidney-protective treatments.

The nitric oxide (NO)–soluble guanylate cyclase (sGC)–cyclic guanosine monophosphate (cGMP) pathway regulates cardiovascular (CV) and renal function [6-10]. sGC is a heterodimeric heme-containing protein that binds NO and therefore plays a key role in this signaling pathway. The binding of endogenous NO to sGC leads to its activation and subsequent conversion of guanosine triphosphate to cGMP, which is an important second messenger signaling molecule and also involved in physiologic regulation of renal blood flow [8, 10]. Also, cGMP could have an antifibrotic effect as enhanced cGMP signaling inhibits extracellular matrix formation, collagen and fibronectin production, and fibroblast-to-myoblast differentiation [11]. Stimulation of sGC reduces inflammation through a vasodilator-stimulated phosphoprotein−nuclear factor KB−NLRP3 pathway [12]. CKD and frequent comorbidities of CKD, such as diabetes, are associated with increased oxidative stress and thus decreased NO bioavailability [6, 8, 13]. Oxidative stress could lead to sGC oxidation and consequent heme loss of the sGC, which impairs NO binding to the sGC and disrupts NO signaling [13, 14]. Therefore, the kidney-protective effects of cGMP are blocked, contributing to CKD progression and acceleration of CV disease in patients with CKD [6, 8, 13].

sGC activators comprise a class of drugs that potently and selectively activate sGC under oxidative stress, independently of endogenous NO [6, 8, 15]. Therefore, sGC activators may restore cGMP signaling under oxidative stress, prevent CKD progression, and offer potential as disease-

modifying treatments. This hypothesis is supported by studies in animal models of CKD, where sGC activators such as cinaciguat [7], runcaciguat [10, 13, 16], and avenciguat [17] reduced proteinuria, morphologic kidney damage, and renal injury biomarkers, regardless of CKD etiologies in diabetic and non-diabetic models. Avenciguat has recently been reported to reduce urine albumin-to-creatinine ratio (UACR) in patients with CKD [18].

The objective of the current phase 2a trial was to investigate the safety and tolerability of runcaciguat and to determine whether it would reduce albuminuria in patients with CKD and established CV disease or chronic heart failure (HF), either without type 2 diabetes (T2D) or with T2D and with or without SGLT2i use.

MATERIALS AND METHODS

Trial design and oversight

CONCORD (Fig. 1) was a multicenter, double-blind, randomized, placebo-controlled, individual-titration, phase 2a trial conducted at 82 study centers in 13 countries worldwide. The study was performed in accordance with the Declaration of Helsinki and the International Council for Harmonisation guidelines, and was approved by relevant regulatory authorities and ethics committees. All patients provided written informed consent to participate in the study. CONCORD was registered with ClinicalTrials.gov (NCT04507061).

Inclusion and exclusion criteria

CONCORD enrolled male and female patients aged ≥45 years with CKD (estimated glomerular filtration rate [eGFR] 25–60 mL/min/1.73 m^2 and UACR 30–3000 mg/g), with T2D for at least 2 years and/or with hypertension, defined as systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg. Patients were required to have established atherosclerotic CV disease or New York Heart Association (NYHA) class I−II HF. Patients had to be on maximum tolerated angiotensin-converting enzyme inhibitor (ACEi)/angiotensin receptor blocker (ARB)

(Supplementary appendix, page 2) and other antihypertensive treatment (if needed) at stable doses for ≥3 months prior to randomization, plus glucose-lowering medication as required. Patients receiving aldosterone antagonists were excluded. Further, some non-diabetic and non-hypertension-related kidney diseases were excluded (Supplementary appendix, page 2). Other exclusion criteria included NYHA class III–IV HF, uncontrolled hypertension (>160 mmHg SBP or ≥100 mmHg DBP), glycated hemoglobin (HbA1c) >11% at screening, history of stroke, or dialysis for acute kidney failure.

Trial procedures

After a 4-week screening phase, the study was conducted at Visits 1–5 on Days 1, 8±2, 15±2, 22±2, and 29±2, respectively, Visit 6 on Days 36−49, Visit 7 on Day 57±3, and a follow-up visit on Day 87±7. For clarity, this report refers to Day 1, Day 8, and so on. Patients were randomized 3:1 to receive runcaciguat 30 mg once daily (od) or matching placebo on Day 1. Patients were enrolled into three strata: (1) CKD and T2D on stable SGLT2i comedication for ≥3 months; (2) CKD and T2D not on SGLT2i; and (3) non-diabetic CKD. The third stratum enabled non-diabetic hypertensive CKD to be included. The study planned to randomize 180 evaluable patients (60 per stratum). Recruitment into each stratum was closed once sufficient patients had been reached according to sample size calculation.

During the titration phase, runcaciguat was up-titrated by 30 mg at each visit on Days 8, 15, and 22 from 30 mg to 120 mg od or the individually tolerated maximum dose. Patients received 120 mg (or maximum tolerated dose) from Day 22. Sham titration was performed in parallel in the placebo arm. In case of signs and symptoms of non-tolerability or systemic blood pressure lowering below the defined threshold (SBP <90 mmHg), the dose could be down-titrated to the previous tolerated dose once or maintained under the discretion of the investigator (dose was not up-titrated if SBP was ≥90 and <105 mmHg, or was ≥105 mmHg and decreased by >30 mmHg from previous visit). Study intervention was discontinued in the event of SBP <90 mmHg and/or symptoms of hypotension for >24 hours. The titration phase was followed by a 5-week maintenance phase at 120

mg or the maximum individual tolerated dose. Two urine samples were collected during the screening phase. Before Visits 1–4, Visit 5, Visit 7, and the follow-up visit, spot morning void urine samples were collected on three consecutive days, and UACR was measured in each sample. UACR was not assessed on Visit 6. Further efficacy and safety assessments were performed 30 days after the end of treatment or early discontinuation from the study. The methods for safety assessment are described in the Supplementary appendix, pages 2−4.

Outcomes

The primary efficacy endpoint was the mean change in UACR, taking the average of measurements on Days 22, 29, and 57 versus baseline. Exploratory endpoints included the ratio to baseline (average of Days 22, 29, and 57) and the absolute change from baseline of eGFR (calculated by the Chronic Kidney Disease Epidemiology Collaboration formula [19] using isotope dilution mass spectrometry-traceable creatinine). Absolute changes in SBP, heart rate (HR), HbA1c, and serum cystatin C levels (including changes from baseline [average of Days 22, 29, and 57] and ratio to baseline) were also assessed. Safety and tolerability outcomes included the incidence of adverse events (AEs) and early discontinuation from the study.

Statistical analysis

The primary endpoint was analyzed using a Bayesian variance components model (analysis of covariance [ANCOVA]) with non-informative Jeffreys priors on log-transformed scales. The model included treatment group, visit, and the interaction of visit and treatment group (as well as a stratum for analysis with all strata combined) as fixed effects and log-transformed baseline UACR as covariate. Subject was included as random effect. The frequentist estimates derived from this model are presented here with 95% confidence intervals (CIs). The average of Day 22, Day 29, and Day 57 was calculated based on this model using contrast estimation. This method was chosen to reduce the variance of the UACR endpoint, to obtain more reliable estimates at baseline and during treatment.

The safety analysis set (SAS) included all patients who received at least one dose of study drug. The full analysis set (FAS) included all patients in the SAS with valid UACR assessments (≥2 valid UACR values per visit) at baseline and on Day 8 or later, and who fulfilled the inclusion criteria. The FAS was considered close to an intention-to-treat analysis. The per-protocol set (PPS) included all patients in the FAS with treatment compliance of 85–115% of the planned dosing regimen, valid UACR assessments at baseline and on Day 57, and no validity findings that would have interfered with efficacy assessment. The PPS was the main analysis set for all efficacy analyses. Full details of statistical techniques, including the sample size calculations, are described in the Supplementary appendix, pages 4–6.

RESULTS

Patient characteristics and disposition

The trial ran from September 2020 to April 2022. A total of 395 patients from 82 study centers in 13 countries were enrolled into screening and 243 were randomized into the study. Of these, 170 were eligible for the PPS (127 receiving runcaciguat and 43 receiving placebo) and 229 for the FAS (173 receiving runcaciguat and 56 receiving placebo). The PPS contained 58 patients in the diabetic CKD with SGLT2i stratum, 63 in the diabetic CKD without SGLT2i stratum, and 49 in the non-diabetic CKD stratum. Patient disposition is shown in Figs 2 and 3. The representativeness of the patients is presented in Supplementary appendix, Table S1.

Baseline characteristics were generally well balanced between the treatment arms and strata (Table 1), although as expected, patients with diabetic CKD had a higher mean body mass index, weight, and HbA1c than patients with non-diabetic CKD.

In the combined PPS, 101 patients (80%) in the runcaciguat group and 37 (86%) in the placebo group tolerated the highest dose (120 mg).

Runcaciguat dosing (PPS)

All patients received the intended dose (30 mg) on Day 1. Subsequently, the proportion receiving the intended dose declined but remained >75% at Day 29 in each stratum (Supplementary appendix, Table S2). During titration, the dose was reduced (always because of AEs) in up to 6% of patients (Supplementary appendix, Table S3).

Primary efficacy endpoint (PPS)

Runcaciguat reduced albuminuria in all three strata compared with baseline. However, this reduction remained significant after placebo adjustment only in the diabetic strata. In patients with diabetic CKD without SGLT2i, UACR (average across Days 22, 29, and 57) decreased by −41.5% (95% CI, −47.9 to −34.3) with runcaciguat versus an increase of 6.7% (95% CI, −10.5 to 27.2) with placebo (reduction vs placebo −45.2% [95% CI, −32.3 to −55.6%]; $P < .001$) (Fig. 4A). In patients with diabetic CKD receiving SGLT2i, UACR decreased by −45.6% (95% CI, −58.3 to −29.0) with runcaciguat versus an increase of 4.9% (95% CI, −36.0 to 72.2) with placebo (reduction vs placebo −48.1% [95% CI, −8.9 to −70.5%]; $P = .02$) (Fig. 4B). Therefore, the effect of runcaciguat was observed irrespective of SGLT2i comedication ($P = .41$ for interaction). In both diabetic strata, the ratio of UACR to baseline was numerically lower with runcaciguat than with placebo on Days 8, 15, 22, 29, and 57.

In non-diabetic CKD (Fig. 4C), UACR decreased by −45.9% (95% CI, −60.3 to −26.1) from baseline in the runcaciguat arm and returned toward baseline after treatment cessation, but an unexpected reduction was also seen with placebo (−68.8% [95% CI, −82.5 to −44.2]) ($P = .10$ for runcaciguat vs placebo). This reduction was observed throughout treatment and was maintained at the follow-up visit.

In all three strata the reduction in UACR with runcaciguat was observed 1 week after randomization at a dose of 30 mg od. UACR improved further during the 3-week titration phase and then remained stable during the subsequent maintenance phase. At the follow-up visit, 30 days after treatment cessation, UACR levels returned to baseline.

Absolute values and changes from baseline in UACR are shown in Supplementary appendix, Tables S4–S6.

eGFR and serum cystatin C (PPS)

In patients with diabetic CKD without SGLT2i, the average eGFR across Days 22, 29, and 57 decreased from baseline by −1.7 mL/min/1.73 m^2 (95% CI, −3.8 to 0.4) with runcaciguat and increased by 2.6 mL/min/1.73 m^2 (95% CI, −0.5 to 5.8) with placebo (placebo-corrected change, −4.4 mL/min/1.73 m^2; *P* = .03). In patients with diabetic CKD receiving SGLT2i, eGFR decreased by −1.8 mL/min/1.73 m^2 (95% CI, −3.8 to 0.3) with runcaciguat and increased by 0.9 mL/min/1.73 m^2 (95% CI, −2.9 to 4.7) with placebo (placebo-corrected change, −2.6 mL/min/1.73 m^2; *P* = .23). In non-diabetic CKD patients, eGFR decreased by −2.1 mL/min/1.73 m^2 (95% CI, −4.3 to 0.2) with runcaciguat and increased by 3.7 mL/min/1.73 m^2 (95% CI, −0.5 to 7.9) with placebo (placebo-corrected change, −5.8 mL/min/1.73 m^2; *P* = .02) (Fig. 5A). The eGFR results across timepoints are shown in Supplementary appendix, Table S7.

SBP (PPS)

In diabetic CKD without SGLT2i, the average SBP across Days 22, 29, and 57 decreased by −4.5 mmHg (95% CI, −7.6 to −1.4) with runcaciguat and increased by 3.8 mmHg (95% CI, −0.9 to 8.5) with placebo (placebo-corrected change, −8.3 mmHg; *P* = .004). In diabetic CKD with SGLT2i, SBP decreased by −3.1 mmHg (95% CI, −6.5 to 0.3) with runcaciguat and by −0.3 mmHg (95% CI, −6.7 to 6.1) with placebo (placebo-corrected change, −2.8 mmHg; *P* = .45). In non-diabetic CKD, SBP decreased by −1.7 mmHg (95% CI, −4.9 to 1.6) with runcaciguat and increased by 0.8 mmHg (95% CI, −5.2 to 6.8) with placebo (placebo-corrected change, −2.4 mmHg; *P* = .48) (Fig. 5B). The reduction in SBP with runcaciguat was not associated with the change in UACR (Spearman's correlation coefficient, 0.23 for combined PPS). SBP results across timepoints are shown in Supplementary appendix, Table S8.

DBP (PPS)

In diabetic CKD without SGLT2i, the average DBP across Days 22, 29, and 57 decreased by −2.8 mmHg (95% CI, −4.4 to −1.2) with runcaciguat and increased by 1.1 mmHg (95% CI, −1.4 to 3.6) with placebo (placebo-corrected change, −3.9 mmHg; *P* = .01). In diabetic CKD with SGLT2i, DBP decreased by −2.8 mmHg (95% CI, −4.8 to −0.9) with runcaciguat and by −0.3 mmHg (95% CI, −4.0 to 3.4) with placebo (placebo-corrected change, −2.5 mmHg; *P* = .23). In non-diabetic CKD, DBP decreased by −1.3 mmHg (95% CI, −3.5 to 0.9) with runcaciguat and by 0.0 mmHg (95% CI, −4.1 to 4.1) with placebo (placebo-corrected change, −1.3 mmHg; *P* = .58) (Fig. 5C). DBP results across timepoints are shown in Supplementary appendix, Table S9.

HR (PPS)

In diabetic CKD without SGLT2i, HR averaged across Days 22, 29, and 57 increased by 2.6 bpm (95% CI, 0.8 to 4.4) from baseline with runcaciguat and by 2.2 bpm (95% CI, −0.5 to 5.0) with placebo (placebo-corrected change, 0.4 bpm; *P* = .81). In diabetic CKD with SGLT2i, HR increased by 5.0 bpm (95% CI, 2.6 to 7.3) with runcaciguat and by 1.5 bpm (95% CI, −2.9 to 5.9) with placebo (placebo-corrected change, 3.5 bpm; *P* = .17). In non-diabetic CKD, HR increased by 1.5 bpm (95% CI, −0.5 to 3.4) with runcaciguat and decreased by −2.3 bpm (95% CI, −5.9 to 1.3) with placebo (placebo-corrected change, 3.7 bpm; *P* = .07) (Fig. 5D). In the combined PPS, the difference between runcaciguat and placebo was statistically significant (*P* = .05). HR results across timepoints are shown in Supplementary appendix, Table S10.

HbA1c (PPS)

In diabetic CKD without SGLT2i, a reduction in mean absolute HbA1c from baseline of −0.34% (95% CI, −0.57 to −0.12) to Day 57 was observed with runcaciguat compared with an increase of 0.27% (95% CI, −0.07 to 0.62) with placebo (placebo-corrected change, −0.62%; *P* = .004). In diabetic CKD with SGLT2i, HbA1c was reduced by −0.28% (95% CI, −0.48 to −0.09) with runcaciguat and by −0.23% (95% CI, −0.61 to 0.14) with placebo (placebo-corrected change, −0.05%; *P* = .81). In non-diabetic CKD, HbA1c was reduced by −0.11% (95% CI, −0.18 to −0.03) with runcaciguat and by −0.09% (95%

CI, −0.24 to 0.06) with placebo (placebo-corrected change, −0.01%; *P* = .87) (Fig. 5E). HbA1c results across timepoints are shown in Supplementary appendix, Table S11.

Other assessments (PPS)

No relevant changes in body weight or body mass index (BMI) were observed with runcaciguat or placebo (data not shown).

Combined PPS

In the combined PPS, the reductions in eGFR with runcaciguat were not associated with changes in UACR (Spearman's correlation coefficient, 0.18) (Supplementary appendix, Figure S1). The reduction in eGFR was accompanied by an increase in serum cystatin C levels after initiation of runcaciguat, which returned to baseline at follow-up (Supplementary appendix, Table S12). The class of albuminuria did not significantly alter the treatment effect of runcaciguat (interaction analysis, *P* = .83). Other results for the combined PPS are summarized in the Supplementary appendix, pages 22−28.

Full analysis set

In all three strata the primary endpoint and the time courses of UACR in the placebo and runcaciguat groups in the FAS were similar to those observed in the PPS. Ratios to baseline of UACR over time by strata (PPS and FAS) are shown in Tables 2−4 and for the combined patient strata in the Supplementary appendix, Tables S13 and S14 (PPS) and S21(FAS). In both diabetic strata, the ratio was numerically lower with runcaciguat than with placebo on Days 8, 15, 22, 29, and 57 in both the PPS and the FAS. The exploratory endpoint results were also generally similar in the PPS and FAS (Supplementary appendix, Tables S16−S22).

Safety outcomes

Most treatment-emergent AEs (TEAEs) were mild or moderate and occurred in 69.0% and 52.5% of patients receiving runcaciguat and placebo, respectively. The difference between runcaciguat and placebo was driven by mild TEAEs, with comparable frequencies of moderate and severe events observed in both treatment groups. Serious AEs occurred in 6.5% and 8.5% of patients receiving

runcaciguat and placebo, respectively. Study drug-related TEAEs occurred in 32.6% and 20.3% of patients receiving runcaciguat and placebo, respectively, with the difference driven by mild TEAEs. The incidence of TEAEs leading to discontinuation of runcaciguat or placebo was 16.3% and 6.8%, respectively (Table 5).

The most common TEAE with runcaciguat was peripheral edema (12.0% vs 3.4% with placebo), occurring at increased frequency at higher doses during the titration phase (1.6% with first occurrence at 30 mg runcaciguat and 4.7% with first occurrence at 120 mg). Peripheral edema with runcaciguat was rated by the investigator as mild and moderate in 17 (9.2%) and 5 (2.7%) patients, respectively. Only 2 patients receiving runcaciguat (1%) withdrew because of edema. Other TEAEs that were more frequent with runcaciguat than placebo included diarrhea, hypotension, anemia, and asthenia. The most common TEAEs in runcaciguat-treated patients were peripheral edema (12%), dizziness (8%), and diarrhea (7%). One death was reported in each arm: both were due to COVID-19 and unrelated to study medication.

DISCUSSION

We had hypothesized that runcaciguat would reduce albuminuria in patients with CKD. This phase 2a trial confirmed that runcaciguat significantly reduced UACR from baseline compared with placebo in patients with T2D and CKD with CV comorbidity, on top of RAS inhibition and irrespective of treatment with SGLT2is. Our results are in line with preclinical data that runcaciguat reduces UACR and improves kidney function as well as morphologic, urinary, and plasma markers of kidney damage in ZSF1 rats [16].

Some mechanistic insight into the effects of runcaciguat on UACR may be provided by the slight reduction in eGFR observed with runcaciguat (mean −2.1 to −3.2 mL/min/1.73 m^2 on Day 57 in the FAS; Supplementary appendix, Table S16). This effect was reversible upon cessation of runcaciguat and was accompanied by a temporary and significant increase in serum cystatin C levels after treatment initiation. These data suggest that the effect of runcaciguat on kidney function potentially may be due to a decrease in intraglomerular filtration pressure. In general, pharmacotherapies and

dietary interventions that reduce glomerular hyperfiltration by reducing glomerular pressure, which manifests clinically as an acute and reversible dip in eGFR, are kidney-protective and are associated with long-term kidney function preservation in patients with CKD [20-22]. The reduction in SBP with runcaciguat may have contributed to the improvement in UACR, but this reduction was small and seems unlikely to have been the only mechanism of this effect.

The explanation for the increase in eGFR with placebo is unclear. This finding is entirely explained by the placebo group in the non-diabetic stratum, which appears to respond atypically not only for albuminuria but also for eGFR.

Runcaciguat was well tolerated, with no overall safety concerns. All TEAEs deemed to be related to study treatment by the investigator were mild to moderate in intensity. Of note, the incidence of peripheral edema with runcaciguat was dose-related. Peripheral edema was generally mild and no correlation with an increase in body weight or with worsening of HF events was noted. The mechanism of edema requires more investigation. The incidences of diarrhea, hypotension, anemia, and asthenia were also numerically increased with runcaciguat. Hypotension, dizziness, peripheral edema, and gastrointestinal AEs have also been reported with the sGC stimulators riociguat [23, 24], praliciguat [25, 26], and vericiguat [27], and have been attributed to relaxation of smooth muscle cells in the vasculature and gastrointestinal tract [18, 27, 28].

The reduction in albuminuria seen in the current study is consistent with recently reported pooled results of two phase 2b trials of avenciguat in patients with CKD [18]. At 20 weeks, avenciguat 1, 2, and 3 mg three times daily reduced placebo-corrected UACR by −15.5%, −13.2%, and −21.5%, respectively. Avenciguat was well tolerated in this study and a phase 1b trial [29].

Our results showed reductions in SBP and HbA1c with runcaciguat versus placebo in patients with diabetic CKD without SGLT2i. Preclinical studies with runcaciguat in rats reported reductions in HbA1c, cholesterol, and triglycerides [16], and praliciguat reduced HbA1c, serum cholesterol, and 24-hour SBP in patients with diabetic CKD [25]. The explanation for the reduction in HbA1c with runcaciguat in patients with diabetic CKD without SGLT2i is unclear: no relevant changes in BMI or

body weight were seen. Such a change in HbA1c was not observed in the other two strata; it may therefore be a chance finding. Secondary metabolic effects of runcaciguat, if present, could be explained by its action on the NO–sGC–cGMP pathway. Activation of sGC increases cGMP levels, which can influence vascular tone, insulin signaling, and glucose uptake [30-32]. These changes could potentially affect glycemic control indirectly by altering blood flow to insulin-sensitive tissues or modifying insulin secretion and action, particularly in patients with metabolic dysfunction. Further clinical studies are required to confirm these findings and the underlying mechanisms.

The current study has limitations. Firstly, the short trial duration (57 days) precluded evaluation of the durability of effects. Secondly, the placebo groups were small, especially in the non-diabetic CKD stratum, resulting in wide CIs for comparing runcaciguat with placebo. There were 48 patients excluded from the PPS because of UACR collection failure on Day 57, yet the data were similar for the PPS and FAS. All patients were white; this is a common limitation of phase 1 and 2 studies and reflects the region in which the study was conducted. Of note, an allocation ratio of 3:1 was selected to enable more patients to receive active treatment, to allow better assessment of the AE profile. However, this randomization ratio also led to few patients receiving placebo per stratum. This probably contributed to the inability to show a treatment effect in non-diabetic CKD, which had UACR reductions with runcaciguat numerically similar to the groups with diabetes. However, stratified inclusion reflected the objective of this phase 2a study, which was to show first signals of efficacy in three different populations and guide subsequent trials. The three strata were therefore analyzed independently in accordance with the original analysis plan. Finally, randomization into the non-diabetic CKD stratum was closed early, before the planned number of participants were recruited, as the recruitment was impacted by the onset of the COVID-19 pandemic and the war in Ukraine. This reduced the statistical power for this stratum, but the other two strata were unaffected. Two patients in the placebo arm of the non-diabetic CKD stratum had large decreases in UACR from baseline. The results in these patients and the small sample size of this group may explain the implausible UACR reduction in the placebo arm of this stratum.

In conclusion, the sGC activator runcaciguat significantly improved albuminuria in patients with CKD on top of ACEi/ARB and SGLT2i treatment. Our results suggest an incremental value for drugs targeting the sGC pathway to modify disease progression despite concomitant therapy with other drug classes. Runcaciguat was well tolerated, with no safety concerns. sGC activation may present a novel approach for the management of patients with CKD, warranting further investigations.

DATA AVAILABILITY STATEMENT

Availability of the data underlying this publication will be determined according to Bayer's commitment to the EFPIA/PhRMA "Principles for responsible clinical trial data sharing." This pertains to scope, timepoint, and process of data access.

As such, Bayer commits to sharing upon request from qualified scientific and medical researchers patient-level clinical trial data, study-level clinical trial data, and protocols from clinical trials in patients for medicines and indications approved in the United States and European Union as necessary for conducting legitimate research. This applies to data on new medicines and indications that have been approved by the EU and US regulatory agencies on or after January 01, 2014. Interested researchers can use www.vivli.org to request access to anonymized patient-level data and supporting documents from clinical studies to conduct further research that can help advance medical science or improve patient care. Information on the Bayer criteria for listing studies and other relevant information is provided in the member section of the portal.

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Statistical analysis: SK, FF.

Interpretation of results: All.

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RTG reports receiving grants from AbbVie, AstraZeneca, Bayer AG, the Dutch Kidney Foundation and Heart Foundation, Galapagos, Otsuka, Roche, and Sanofi-Genzyme. **DCW** reports receiving grants for consultancy fees from Bayer AG, Eledon, Galderma, Gilead, GlaxoSmithKline, Janssen, Mundipharma, Tricida, and Vifor; speaker fees from Amgen, Astellas, Mundipharma, and Zydus; honoraria from Astellas and Boehringer Ingelheim; and provides ongoing consultancy for AstraZeneca. He also provided support to the KDIGO Guideline Development. **FMD** reports receiving consultancy fees from Daiichi Sankyo and Mundipharma, and payment or honoraria from ALTER Medica and Daiichi Sankyo. **MS** reports nothing to disclose. **DT, MB, KP**, and **FF** are full-time employees of Bayer AG. **SK** is a full-time employee and stockholder of Bayer AG. **RES** reports receiving grants to his institution from Ablative Solution, Amgen, AstraZeneca, Boehringer Ingelheim, IPPmed, Medtronic, Novartis, Novo Nordisk, and Recor; and speaker and advisor fees from Ablative Solutions, Apontis, AstraZeneca, Bayer AG, Boehringer Ingelheim, Lilly, Medtronic, Merck, Novartis, Novo Nordisk, Recor, and Servier.

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Tables

Table 1: Baseline demographics and disease characteristics.

	Combined PPS		Diabetic CKD without SGLT2i		Diabetic CKD with SGLT2i		Non-diabetic CKD	
	Runcaciguat ***n* = 127**	**Placebo** ***n* = 43**	**Runcaciguat** ***n* = 44**	**Placebo** ***n* = 19**	**Runcaciguat** ***n* = 45**	**Placebo** ***n* = 13**	**Runcaciguat** ***n* = 38**	**Placebo** ***n* = 11**
Age (yr) [mean ± SD]	70.5 ± 7.4	70.0 ± 6.9	72.7 ± 6.2	70.5 ± 6.1	69.2 ± 6.8	69.7 ± 6.5	69.5 ± 8.9	69.5 ± 9.0
Male sex [no. of patients (%)]	102 (80)	34 (79)	35 (80)	16 (84)	37 (82)	11 (85)	30 (79)	7 (64)
White race and ethnicity [no. of patients (%)]	127 (100)	43 (100)	44 (100)	19 (100)	45 (100)	13 (100)	38 (100)	11 (100)
BMI (kg/m^2) [mean ± SD]	30.9 ± 4.3	29.6 ± 4.3	31.5 ± 3.7	30.1 ± 4.6	31.7 ± 4.3	30.4 ± 3.9	29.0 ± 4.6	27.7 ± 4.2
Weight (kg) [mean ± SD]	89.0 ± 15.1	86.1 ± 14.9	91.4 ± 14.3	89.9 ± 16.6	91.4 ± 16.0	87.8 ± 12.6	83.2 ± 13.7	77.4 ± 11.5
Current smoker [no. of patients (%)]	20 (16)	4 (9)	7 (16)	1 (5)	7 (16)	2 (15)	6 (16)	1 (9)
SBP (mmHg) [mean ± SD]	140.3 ± 14.8	137.4 ± 13.3	141.0 ± 14.9	142.1 ± 11.4	140.7 ± 16.9	132.5 ± 15.3	139.1 ± 12.2	135.0 ± 12.0
DBP (mmHg) [mean ± SD]	76.8 ± 10.0	72.5 ± 10.4	73.7 ± 9.1	71.9 ± 9.8	76.8 ± 10.3	71.4 ± 8.4	80.4 ± 9.6	74.9 ± 13.7
Heart rate (bpm) [mean ± SD]	67.9 ± 11.6	66.6 ± 11.2	67.4 ± 12.4	64.8 ± 10.6	68.2 ± 11.7	68.3 ± 13.5	68.0 ± 10.9	67.8 ± 9.8
HbA1c (%) [mean ± SD]	6.9 ± 1.3	7.3 ± 1.5	7.2 ± 1.2	7.9 ± 1.3	7.4 ± 1.3	7.8 ± 1.4	5.9 ± 0.7	5.6 ± 0.5

RAASi use [no. of patients (%)]	126 (99)	42 (98)	44 (100)	18 (95)	44 (98)	13 (100)	38 (100)	11 (100)
eGFR (mL/min/1.73 m^2) [geometric mean (SD)]	42.1 (1.3)	41.0 (1.3)	40.9 (1.3)	38.1 (1.3)	43.4 (1.3)	44.0 (1.3)	42.0 (1.4)	42.7 (1.2)
eGFR (mL/min/1.73 m^2) [no. of patients (%)][a]								
≤30	18 (14)	4 (9)	5 (11)	3 (16)	6 (13)	1 (8)	7 (18)	0
>30–≤45	58 (46)	24 (56)	23 (52)	10 (53)	20 (44)	8 (62)	15 (39)	6 (55)
>45	51 (40)	15 (35)	16 (36)	6 (32)	19 (42)	4 (31)	16 (42)	5 (45)
UACR[b] (mg/g) [geometric mean (SD)]	235.8 (3.0)	179.5 (3.4)	244.5 (3.2)	187.6 (3.3)	229.4 (3.1)	169.0 (3.5)	233.5 (2.7)	178.5 (3.9)
UACR (mg/g) [no. of patients (%)]								
30–≤300	74 (58)	30 (70)	25 (57)	13 (68)	26 (58)	9 (69)	23 (61)	8 (73)
>300	53 (42)	13 (30)	19 (43)	6 (32)	19 (42)	4 (31)	15 (39)	3 (27)

Data are shown for the PPS. Percentages might not add up to 100 because of rounding.

[a]Patients were required to have an eGFR ≥25 mL/min/1.73 m^2 but ≤60 mL/min/1.73 m^2 at screening according to the inclusion criteria.

[b]Weighted geometric mean of five UACR values obtained at screening and baseline.

BMI: body mass index; CKD: chronic kidney disease; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate (CKD-EPI equation); HbA1c: glycated hemoglobin; PPS: per-protocol set; RAASi: renin–angiotensin–aldosterone system inhibitor; SBP: systolic blood pressure; SD: standard deviation; SGLT2i: sodium-glucose co-transporter-2 inhibitor; UACR: urine albumin-to-creatinine ratio.

Table 2: Ratio to baseline for UACR across timepoints: diabetic CKD without SGLT2i.

	PPS		FAS	
	Mean estimate (95% CI)	***P*-value[a]**	**Mean estimate (95% CI)**	***P*-value[a]**
Day 8				
Runcaciguat	0.772 (0.663 to 0.899)	.05	0.726 (0.630 to 0.838)	.01
Placebo	1.013 (0.805 to 1.274)		1.027 (0.810 to 1.302)	
Day 15				
Runcaciguat	0.662 (0.568 to 0.771)	.03	0.638 (0.552 to 0.737)	.01
Placebo	0.895 (0.711 to 1.125)		0.909 (0.717 to 1.152)	
Day 22				
Runcaciguat	0.574 (0.492 to 0.669)	< .001	0.569 (0.491 to 0.659)	< .001
Placebo	0.965 (0.767 to 1.214)		0.993 (0.783 to 1.259)	
Day 29				
Runcaciguat	0.590 (0.508 to 0.686)	< .001	0.590 (0.508 to 0.684)	< .001
Placebo	1.158 (0.921 to 1.457)		1.196 (0.943 to 1.156)	
Day 57				
Runcaciguat	0.591 (0.508 to 0.687)	< .001	0.583 (0.500 to 0.679)	< .001
Placebo	1.086 (0.863 to 1.367)		1.101 (0.865 to 1.402)	
Average of Days 22, 29, and 57				
Runcaciguat	0.585 (0.521 to 0.657)	< .001	0.580 (0.516 to 0.653)	< .001
Placebo	1.067 (0.895 to 1.272)		1.093 (0.902 to 1.326)	
Day 87 (follow-up visit)				
Runcaciguat	0.950 (0.813 to 1.110)	.18	0.958 (0.821 to 1.119)	.18
Placebo	1.148 (0.913 to 1.445)		1.170 (0.916 to 1.494)	

[a]Two-sided *P*-values for the difference between runcaciguat and placebo.

CI: confidence interval; CKD: chronic kidney disease; FAS: full analysis set; PPS: per-protocol set; SGLT2i: sodium-glucose co-transporter-2 inhibitor; UACR: urine albumin-to-creatinine ratio.

Table 3: Ratio to baseline for UACR across timepoints: diabetic CKD with SGLT2i.

	PPS		FAS	
	Mean estimate (95% CI)	***P*-value[a]**	**Mean estimate (95% CI)**	***P*-value[a]**
Day 8				
Runcaciguat	0.593 (0.435 to 0.809)	.20	0.650 (0.509 to 0.828)	.13
Placebo	0.914 (0.512 to 1.633)		0.959 (0.613 to 1.501)	
Day 15				
Runcaciguat	0.599 (0.439 to 0.818)	.007	0.628 (0.491 to 0.804)	.002
Placebo	1.484 (0.831 to 2.649)		1.425 (0.896 to 2.266)	
Day 22				
Runcaciguat	0.527 (0.386 to 0.721)	.008	0.580 (0.453 to 0.744)	.003
Placebo	1.298 (0.727 to 2.318)		1.305 (0.820 to 2.075)	
Day 29				
Runcaciguat	0.503 (0.368 to 0.688)	.02	0.533 (0.413 to 0.689)	.006
Placebo	1.113 (0.623 to 1.987)		1.130 (0.710 to 1.797)	
Day 57				
Runcaciguat	0.608 (0.445 to 0.829)	.41	0.643 (0.494 to 0.837)	.43
Placebo	0.800 (0.448 to 1.428)		0.804 (0.492 to 1.315)	
Average of Days 22, 29, and 57				
Runcaciguat	0.544 (0.417 to 0.710)	.02	0.584 (0.472 to 0.722)	.01
Placebo	1.049 (0.640 to 1.722)		1.058 (0.715 to 1.566)	
Day 87 (follow-up visit)				
Runcaciguat	0.730 (0.535 to 0.996)	.10	0.788 (0.606 to 1.024)	.08
Placebo	1.279 (0.708 to 2.310)		1.276 (0.797 to 2.043)	

[a]Two-sided *P*-values for the difference between runcaciguat and placebo.

CI: confidence interval; CKD: chronic kidney disease; FAS: full analysis set; PPS: per-protocol set; SGLT2i: sodium-glucose co-transporter-2 inhibitor; UACR: urine albumin-to-creatinine ratio.

Table 4: Ratio to baseline for UACR across timepoints: non-diabetic CKD.

	PPS		FAS	
	Mean estimate (95% CI)	***P*-value[a]**	**Mean estimate (95% CI)**	***P*-value[a]**
Day 8				
Runcaciguat	0.846 (0.580 to 1.233)	.21	0.774 (0.573 to 1.044)	.52
Placebo	0.509 (0.252 to 1.029)		0.633 (0.367 to 1.092)	
Day 15				
Runcaciguat	0.568 (0.389 to 0.828)	.07	0.524 (0.386 to 0.712)	.42
Placebo	0.272 (0.135 to 0.550)		0.403 (0.230 to 0.704)	
Day 22				
Runcaciguat	0.568 (0.390 to 0.829)	.96	0.576 (0.423 to 0.786)	.56
Placebo	0.557 (0.276 to 1.126)		0.703 (0.391 to 1.262)	
Day 29				
Runcaciguat	0.502 (0.344 to 0.732)	.03	0.536 (0.392 to 0.733)	.14
Placebo	0.207 (0.102 to 0.418)		0.327 (0.185 to 0.580)	
Day 57				
Runcaciguat	0.556 (0.381 to 0.811)	.07	0.547 (0.393 to 0.760)	.25
Placebo	0.264 (0.131 to 0.533)		0.366 (0.201 to 0.668)	
Average of Days 22, 29, and 57				
Runcaciguat	0.541 (0.397 to 0.739)	.10	0.553 (0.428 to 0.714)	.39
Placebo	0.312 (0.175 to 0.558)		0.438 (0.274 to 0.701)	
Day 87 (follow-up visit)				
Runcaciguat	0.882 (0.597 to 1.303)	< .001	0.853 (0.608 to 1.195)	.001
Placebo	0.204 (0.101 to 0.412)		0.267 (0.144 to 0.496)	

[a]Two-sided *P*-values for the difference between runcaciguat and placebo.

CI: confidence interval; CKD: chronic kidney disease; FAS: full analysis set; PPS: per-protocol set; UACR: urine albumin-to-creatinine ratio.

Table 5: Safety outcomes (SAS).

	Combined SAS		Diabetic CKD without SGLT2i		Diabetic CKD with SGLT2i		Non-diabetic CKD	
	Runcaciguat	**Placebo**	**Runcaciguat**	**Placebo**	**Runcaciguat**	**Placebo**	**Runcaciguat**	**Placebo**
	***n* = 184**	***n* = 59**	***n* = 66**	***n* = 23**	***n* = 65**	***n* = 19**	***n* = 53**	***n* = 17**
TEAEs [no. of patients (%)]								
Any AE	127 (69)	31 (53)	51 (77)	14 (61)	44 (68)	11 (58)	32 (60)	6 (35)
Any study drug-related AE	60 (33)	12 (20)	27 (41)	6 (26)	23 (35)	4 (21)	10 (19)	2 (12)
Any SAE	12 (7)	5 (8)	5 (8)	1 (4)	6 (9)	2 (11)	1 (2)	2 (12)
Any SAE with outcome death	1 (<1)	1 (2)	1 (2)	0	0	0	0	1 (6)
Maximum intensity for any TEAE [no. of patients (%)]								
Mild	65 (35)	12 (20)	27 (41)	7 (30)	23 (35)	4 (21)	15 (28)	1 (6)
Moderate	51 (28)	16 (27)	19 (29)	7 (30)	18 (28)	6 (32)	14 (26)	3 (18)
Severe	11 (6)	3 (5)	5 (8)	0	3 (5)	1 (5)	3 (6)	2 (12)
TEAE leading to discontinuing study drug [no. of patients (%)]	30 (16)	4 (7)	11 (17)	0	12 (18)	3 (16)	7 (13)	1 (6)
COVID-19	6 (3)	1 (2)	3 (5)	0	2 (3)	0	1 (2)	1 (6)
Diarrhea	3 (2)	0	1 (2)	0	2 (3)	0	0	0
eGFR decreased	3 (2)	0	1 (2)	0	1 (2)	0	1 (2)	0
Peripheral edema	2 (1)	0	2 (3)	0	0	0	0	0
Dizziness	2 (1)	0	0	0	2 (3)	0	0	0

Acute kidney injury	2 (1)	0	0	0	2 (3)	0	0	0
Hypotension	2 (1)	0	0	0	1 (2)	0	1 (2)	0
Mood altered	0	1 (2)	0	0	0	1 (5)	0	0
BP decreased	0	1 (2)	0	0	0	1 (5)	0	0
Pyrexia	0	1 (2)	0	0	0	1 (5)	0	0
Most common TEAEs [no. of patients (%)]								
Peripheral edema	22 (12)	2 (3)	11 (17)	2 (9)	6 (9)	0	5 (9)	0
Dizziness	15 (8)	4 (7)	8 (12)	2 (9)	3 (5)	1 (5)	4 (8)	1 (6)
Diarrhea	13 (7)	2 (3)	5 (8)	0	5 (8)	2 (11)	3 (6)	0
Fatigue	11 (6)	3 (5)	6 (9)	1 (4)	2 (3)	1 (5)	3 (6)	1 (6)
Headache	11 (6)	2 (3)	4 (6)	2 (9)	4 (6)	0	3 (6)	0
Hypotension	8 (4)	0	2 (3)	0	5 (8)	0	1 (2)	0
Nausea	7 (4)	5 (8)	2 (3)	1 (4)	2 (3)	3 (16)	3 (6)	1 (6)
Anemia	6 (3)	0	3 (5)	0	1 (2)	0	2 (4)	0
Asthenia	6 (3)	0	2 (3)	0	2 (3)	0	2 (4)	0
Vomiting	4 (2)	3 (5)	0	1 (4)	2 (3)	2 (11)	2 (4)	0
Muscle spasms	2 (1)	3 (5)	1 (2)	1 (4)	1 (2)	0	0	2 (12)

TEAEs of interest with an incidence of >3.0% in the combined runcaciguat and/or placebo arm are shown. TEAEs leading to discontinuation of study drug with incidence of >1.0% in the combined runcaciguat arm and/or placebo arm are shown.

AE: adverse event; BP: blood pressure; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; SAE: serious adverse event; SAS: safety analysis set; SGLT2i: sodium-glucose co-transporter-2 inhibitor; TEAE: treatment-emergent adverse event.

FIGURE LEGENDS

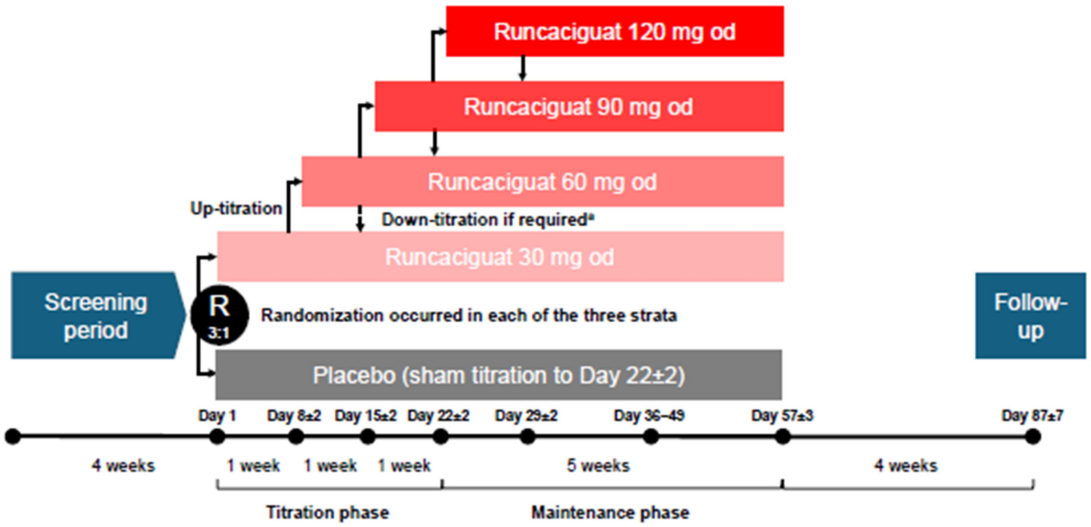

Figure 1: CONCORD study design. [a]Down-titration could be performed once because of tolerability issues or due to safety concerns. This dose was then maintained until the end of treatment. od: once daily; R: randomization.

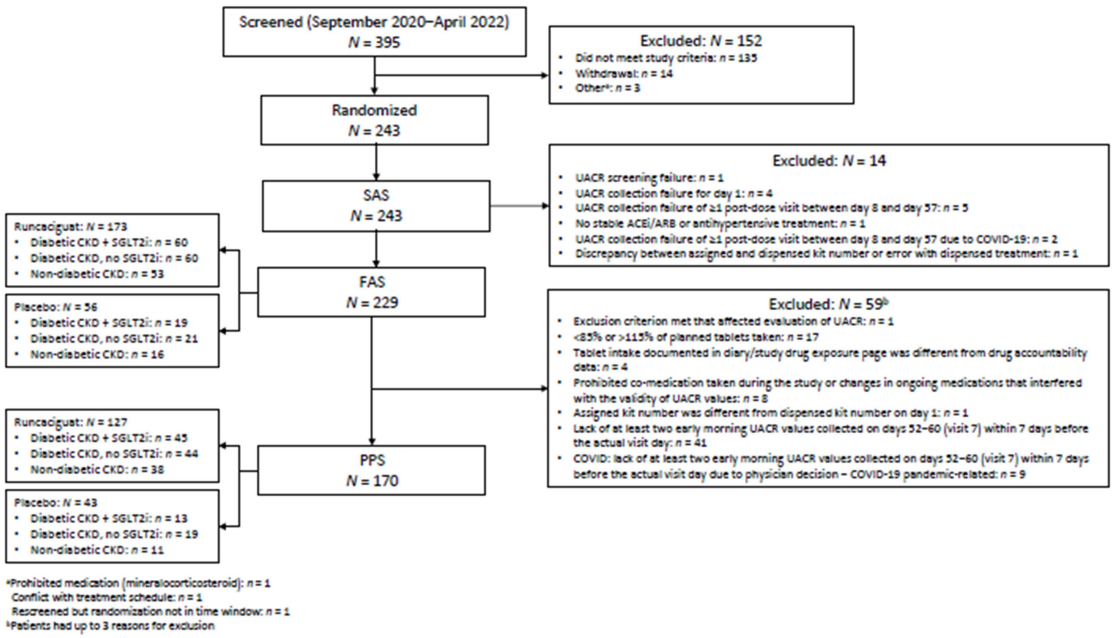

Figure 2: CONSORT flow diagram. If a subject had more than one validity finding that excluded them from an analysis set, all the findings are displayed. [a]Prohibited medication (mineralocorticosteroid): *n* = 1; conflict with treatment schedule: *n* = 1; rescreened but randomization not in time window: *n* = 1. [b]Patients had up to three reasons for exclusion. ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; CKD: chronic kidney disease; FAS: full analysis set; PPS: per-protocol set; SAS: safety analysis set; SGLT2i: sodium-glucose co-transporter-2 inhibitor; UACR: urine albumin-to-creatinine ratio.

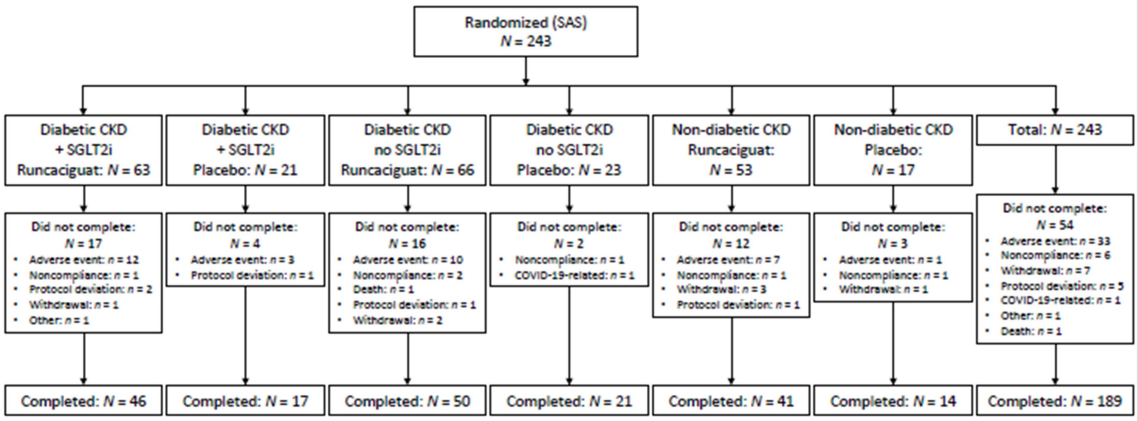

Figure 3: Patient disposition.

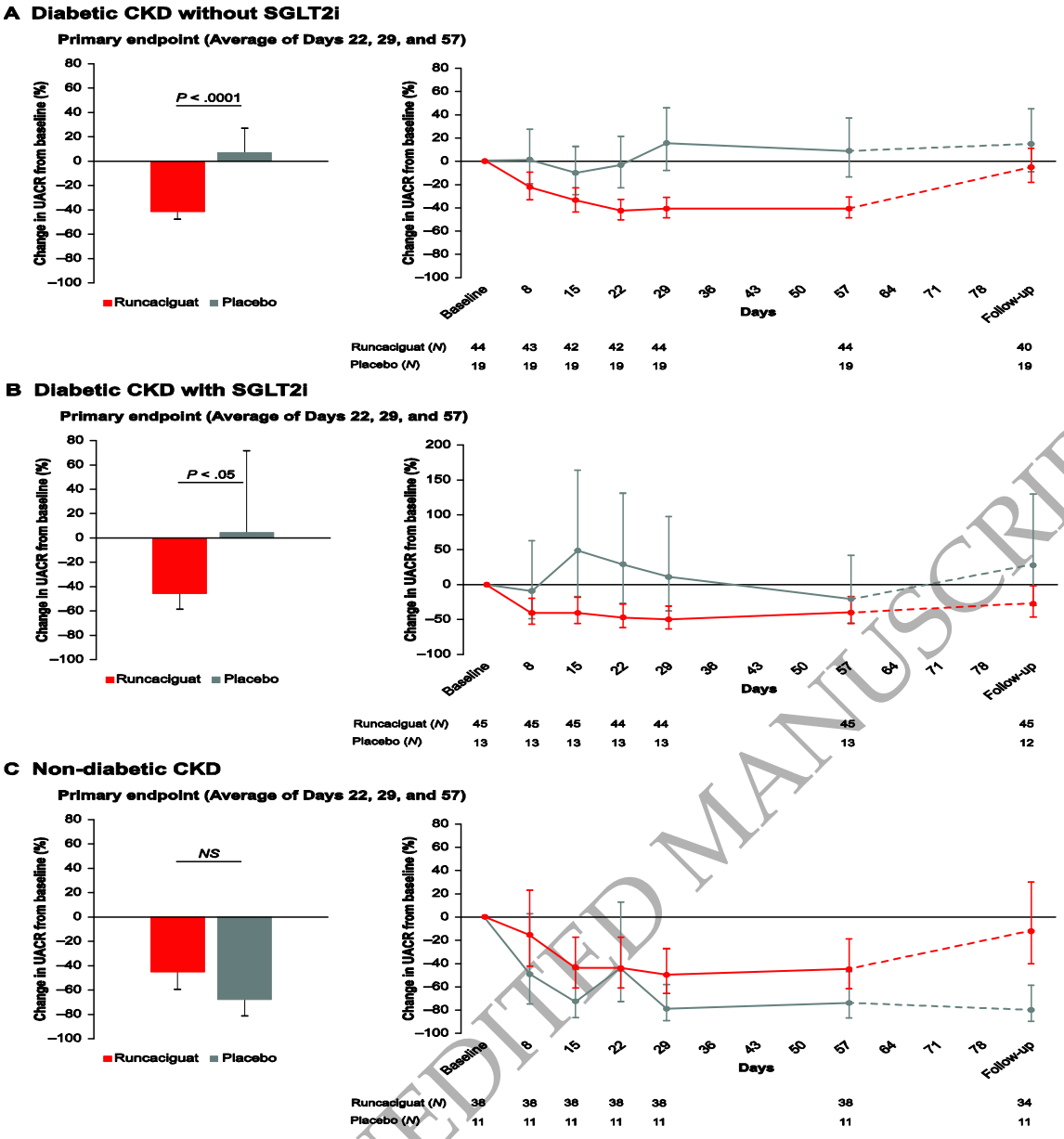

Figure 4: Mean change in UACR over time (95% CI, ANCOVA) (PPS). Estimated mean percent change from baseline and 95% CI (ANCOVA) for (**A**) patients with diabetic CKD not on SGLT2i, (**B**) patients with diabetic CKD on SGLT2i, and (**C**) patients with non-diabetic CKD. Placebo upper limit for the diabetic CKD with SGLT2i stratum was 2.649 (165%) on Day 15, 2.318 (132%) on Day 22, 1.987 (98.7%) on Day 29, and 2.310 (131%) on Day 87 (follow-up). ANCOVA: analysis of covariance; CI: confidence interval; CKD: chronic kidney disease; NS: not significant; PPS: per-protocol set; SGLT2i: sodium-glucose co-transporter-2 inhibitor; UACR: urine albumin-to-creatinine ratio.

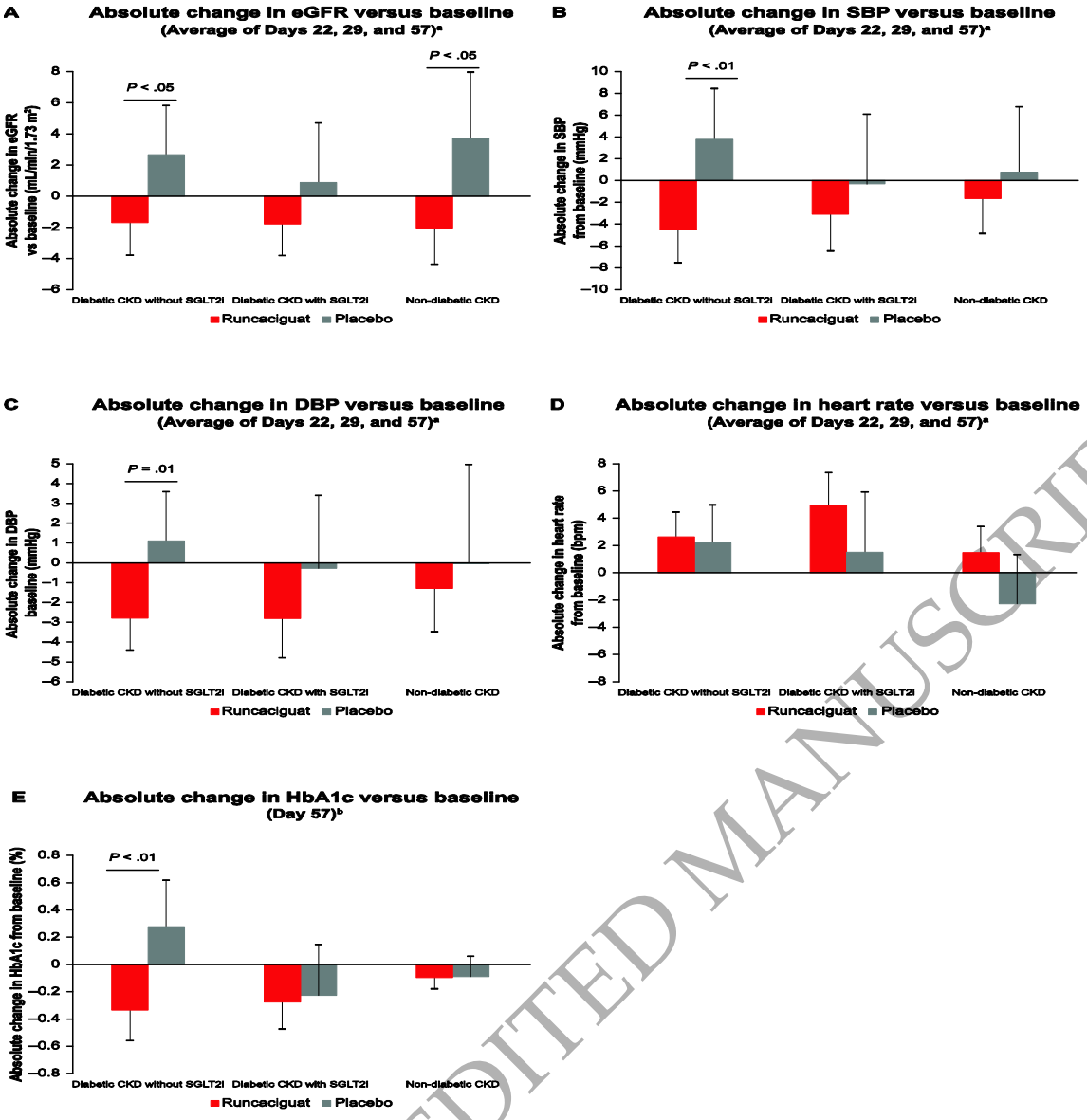

Figure 5: Absolute change in (**A**) eGFR versus baseline[a], (**B**) SBP versus baseline[a], (**C**) DBP versus baseline[a], (**D**) heart rate versus baseline[a], and (**E**) HbA1c versus baseline[b]. [a]Estimated mean absolute change from baseline and 95% CI (ANCOVA) of the PPS for the average across Days 22, 29, and 57. [b]Estimated mean absolute change from baseline and 95% CI (ANCOVA) of the PPS for Day 57.

ANCOVA: analysis of covariance; CI: confidence interval; CKD: chronic kidney disease; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; eGFR: estimated glomerular filtration rate (CKD-EPI equation); HbA1c: glycated hemoglobin; PPS: per-protocol set; SBP: systolic blood pressure; SGLT2i: sodium-glucose co-transporter-2 inhibitor.