

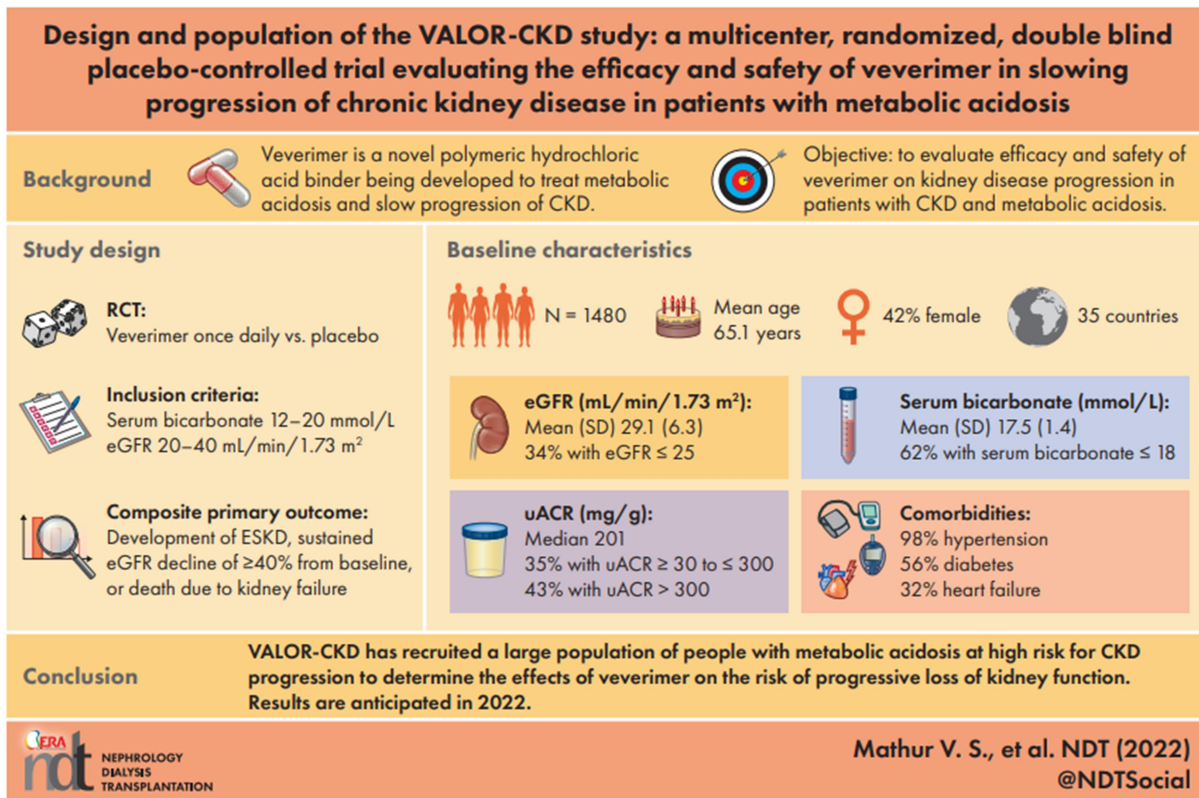
**Design and Population of the VALOR-CKD Study: A Multicenter, Randomized, Double-Blind Placebo-Controlled Trial Evaluating the Efficacy and Safety of Veverimer in Slowing Progression of Chronic Kidney Disease in Patients with Metabolic Acidosis**

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Running Head: Veverimer and Kidney Outcomes in Patients with CKD

## GRAPHICAL ABSTRACT



## ABSTRACT

**Background.** Whether treating metabolic acidosis slows progression of chronic kidney disease (CKD) has not been established. Veverimer is a novel hydrochloric acid binder that removes acid from the gastrointestinal tract leading to an increase in serum bicarbonate; it is being developed to treat metabolic acidosis with the goal of slowing progression of CKD.

**Methods.** The VALOR-CKD trial is an international, randomized, multicenter, double-blind, placebo-controlled study designed to evaluate the effect of once-daily veverimer on kidney disease progression in patients with metabolic acidosis and CKD. Eligibility criteria include a serum bicarbonate in the range of 12–20 mmol/L and an estimated glomerular filtration rate (eGFR) of 20–40 mL/min/1.73 m<sup>2</sup>. The primary outcome is kidney disease progression defined

as the development of end-stage kidney disease, a sustained decline in eGFR of >40% from baseline, or death due to kidney failure. Key secondary endpoints include effects on physical function.

**Results.** Between December 2018 and December 2021, 1,480 participants were randomized.

The mean age at baseline was 65.1 years and 42% of the patients were female. The mean baseline eGFR was 29.1 mL/min/1.73 m<sup>2</sup> and mean serum bicarbonate was 17.5 mmol/L. The median urine albumin-to-creatinine ratio at screening was 201 mg/g and the median 5-year predicted risk of kidney failure was 24%. Diabetes and hypertension were present in 56% and 98% of participants, respectively.

**Conclusions.** VALOR-CKD has recruited a large population of people with metabolic acidosis at high risk for CKD progression to determine the effects of veverimer on the risk of progressive loss of kidney function.

**Keywords:** chronic kidney disease, CKD progression, metabolic acidosis, serum bicarbonate, veverimer

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## KEY LEARNING POINTS

### What is already known about this subject?

- Acid retention, caused by reduced kidney function, results in metabolic acidosis, a condition associated with increased risk of progression of chronic kidney disease (CKD) and increased mortality.
- In a previously published 12-month, randomized, blinded, placebo-controlled trial, treatment with veverimer, a once-daily, non-absorbed drug that binds and removes hydrochloric acid from the gastrointestinal lumen, resulted in sustained increases in serum bicarbonate and improved physical function compared to placebo.

### What this study adds?

- VALOR-CKD is a randomized, double-blind, placebo-controlled trial designed to assess the effect of veverimer on kidney disease progression in patients with CKD and metabolic acidosis. Kidney disease progression is defined as the development of end-stage kidney disease, a sustained decline in estimated glomerular filtration rate (eGFR) of >40% from baseline, or death due to kidney failure.
- The VALOR-CKD population comprises patients with metabolic acidosis (mean serum bicarbonate 17.5 mmol/L) and CKD (mean eGFR 29.1 mL/min/1.73 m<sup>2</sup>) and includes a high proportion of participants who have not been well represented in previous kidney outcome trials: 57% have nondiabetic kidney disease, 31% have microalbuminuria, 27% have no albuminuria, and 32% have a history of heart failure.

- The VALOR-CKD study seeks to determine the efficacy and safety of veverimer in slowing CKD progression in patients with CKD and metabolic acidosis.

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

- There are no approved treatments for metabolic acidosis in patients with CKD.
- VALOR-CKD will provide data from a large interventional study of metabolic acidosis in patients with CKD (of any etiology) to assess whether treating metabolic acidosis with a once-daily, non-absorbed drug slows progression of CKD.
- This study has the potential to change the treatment paradigm for management of patients with CKD and metabolic acidosis.

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## INTRODUCTION

Chronic kidney disease (CKD) is an irreversible condition that leads to substantial morbidity, mortality and healthcare costs, particularly at later stages (Grade 3 to 5, i.e., estimated glomerular filtration rate [eGFR]  $<60$  mL/min/1.73 m<sup>2</sup>) [1]. In these people, CKD is associated with development of physical and cognitive symptoms, biochemical complications, and difficult-to-control blood pressure, volume overload, and anemia. Efforts to slow CKD progression and delay the need for dialysis are important, as the risk of kidney failure requiring dialysis, cardiovascular events and early death are greatly increased in these high-risk individuals [2].

There remains an unmet need for treatments that address the substantial burden of CKD, particularly those that affect different pathophysiologic mechanisms of kidney injury. A major mechanism of action of existing treatments for CKD progression, renin-angiotensin-aldosterone system inhibitors (RAASi) and sodium-glucose cotransporter-2 (SGLT2) inhibitors, is believed to be their effect on hyperfiltration [3-7]. Various clinical factors, including hyperkalemia, hypotension, acute effects on serum creatinine, low levels of eGFR and/or declining eGFR can limit the use of these medications [8, 9]. Thus, medications that target additional mechanisms or pathways of kidney injury are needed for all patients with CKD, including those in clinical situations that prevent initiation or continued use of RAASi and SGLT2 inhibitors.

Metabolic acidosis is a common complication of moderate to advanced CKD that is also separately associated with progression to kidney failure, cardiovascular events, and all-cause mortality, as well as adverse physical function outcomes [10, 11]. In several kidney physiology studies, the presence of metabolic acidosis in CKD accelerated fibrosis in the remaining kidney

[12], impaired skeletal muscle function [13], and led to poor growth in children [14] and bone demineralization [15]. Previous studies examining the impact of oral alkali intervention for the treatment of metabolic acidosis have found conflicting results. While single-center, unblinded, randomized trials have shown large treatment effects of oral alkali in slowing CKD progression [16, 17], the only multicenter, double-blind, placebo-controlled study (BiCARB Trial), which was at lower risk of bias, showed no benefit in slowing CKD progression or on physical function [18].

Veverimer is a novel polymeric hydrochloric acid binder under development for the treatment of metabolic acidosis and slowing progression of CKD [19]. Unlike sodium bicarbonate or potassium citrate, which are used to neutralize retained acid in patients with metabolic acidosis, veverimer binds and removes HCl from the gastrointestinal tract without introducing a retained counterion [19]. In previous clinical studies, treatment with veverimer increased serum bicarbonate levels with an onset of action of 1 day [20] and a sustained treatment effect up to 1 year [21, 22]. Importantly, treatment was associated with improved patient-reported and objectively measured physical function in a Phase 3 study of 196 individuals with 1 year of follow-up [22].

Establishing the efficacy and safety of veverimer on clinical outcomes in a large multicenter, randomized, double-blinded, placebo-controlled trial is important, as metabolic acidosis in CKD is undertreated [22-24]. In this article, we describe the design and baseline characteristics of the VALOR-CKD study and place it in context of other trials of treatments for metabolic acidosis and treatments that slow CKD progression.

## MATERIALS AND METHODS

### Study Design

The VALOR-CKD (TRCA-303) study (NCT03710291) is a randomized, double-blind, placebo-controlled, parallel-group, multicenter clinical trial. A single-blind active-treatment period of 4-8 weeks (Part A) precedes the double-blind, randomized treatment period (Part B) (Figure 1).

### Study Setting

This study is being conducted in 346 sites in 35 countries in North America, South America, Europe, and Asia-Pacific (see **Supplementary Table S1** for full list of countries).

### Eligibility Criteria for Enrollment

The eligibility criteria were designed to enroll patients with CKD of any etiology with a central laboratory eGFR between 20-40 mL/min/1.73 m<sup>2</sup> and metabolic acidosis, defined as a serum bicarbonate between 12-20 mmol/L.

Patients are required to have 3 fasting (for  $\geq 4$  hours) serum bicarbonate (total CO<sub>2</sub>) measurements spaced at least 2 weeks apart and drawn within a 4- to 6-week period. Each bicarbonate measurement for the study was made onsite, with an i-STAT point-of-care device (Abbott Point of Care, Princeton, New Jersey, USA). At screening, the serum bicarbonate must be between 12-20 mmol/L, inclusive, to permit progression to randomisation.

Patients with acute metabolic acidosis are excluded, as are patients who have received a kidney transplant and those in whom initiation of renal replacement therapy (RRT) is anticipated within 6 months. To reduce the risk of unstable kidney function at screening, patients with a history of



acute kidney injury, anuria, or dialysis treatment within 3 months prior to screening are excluded. Likewise, patients may not be screened if they have been hospitalized within the 2 months prior to screening, other than for pre-planned diagnostic or minor therapeutic procedures. Additionally, two screening eGFR measurements drawn at least 2 weeks apart must be within 20% of each other. Patients receiving cytotoxic, immunosuppressive, or other immunotherapy (excluding glucocorticoids) within 6 months for a kidney disease are excluded.

Patients are required to be on the maximal labeled or tolerated dose of an angiotensin-converting enzyme (ACE) inhibitor and/or angiotensin receptor blocker (ARB) at a stable dose for at least 4 weeks prior to screening, unless they have nondiabetic kidney disease and the urine albumin-to-creatinine ratio (UACR) is  $<30$  mg/g ( $<3.39$  mg/mmol). The maximum tolerated dose for an individual patient may be less than the maximum labeled dose or may be zero if the medical reason is documented.

Patients on stable routine oral alkali supplements as well as those not on such supplements are eligible. There are no prohibited drugs. Use of SGLT2 inhibitors is allowed with recommendations to initiate treatment at least 4 weeks prior to screening and to maintain a stable dose thereafter.

The permitted age range at screening is between 18 and 85 years. The screening blood pressure and hemoglobin A1c are required to be  $<160/92$  mmHg and  $\leq 11.0\%$  (97 mmol/mol), respectively. Patients with a corrected serum calcium at screening  $<8.0$  mg/dL (2.0 mmol/L) are excluded due to the hypothetical consideration of inducing ionized hypocalcemia with rapid correction of metabolic acidosis (see Supplementary Table S2 for full list of enrollment eligibility criteria).

## **Eligibility Criteria for Randomization**

Following enrollment into Part A of the study and 4-8 weeks of treatment with veverimer, patients with an increase from baseline in serum bicarbonate by  $\geq 4$  mmol/L or a serum bicarbonate  $\geq 22$  mmol/L are permitted to progress to the next stage of the trial. Patients receiving RRT or who have a confirmed  $\geq 40\%$  eGFR decline during this time are excluded (see **Supplementary Table S3** for full list of randomization eligibility criteria).

## **Pre-Qualification and Screening**

An optional Pre-Qualification Period of up to 8 weeks allows sites to conduct laboratory testing to determine if a patient might qualify for the study and to optimize routine medications as needed. The Screening Period consists of 3 visits (Screening 1, Screening 2, and A1 visits) conducted over 4-6 weeks during which the eligibility for enrollment is determined.

## **Run-in Period (Part A)**

Once eligibility is confirmed, patients proceed into Part A of the study during which they receive single-blind treatment with veverimer. During Part A, which consists of up to two visits (A2 and A3 visits) conducted at 4 and 8 weeks, respectively, patients are assessed for eligibility to randomize into Part B of the study. Ineligible patients and those dropping out of Part A for other reasons (e.g., withdrawal of consent, adverse event) undergo a post-treatment follow-up visit approximately 2 weeks after their last dose of study drug and are not followed further (**Figure 1**). Eligible patients are randomized 1:1 to veverimer or matching placebo and continue into Part B of the study.

## **Intervention and Control**

The starting study drug dose is 6 g veverimer once daily (two packets daily) or placebo once daily (two packets daily; microcrystalline cellulose, National Formulary Grade). Both are administered orally as a suspension in water with a meal.

During Part A of the study, if the serum bicarbonate criteria is not met after 4 weeks of treatment, the dose of veverimer is increased by the interactive response technology (IRT) system from 6 g/day to 9 g/day (from 2 to 3 packets/day).

During Part B, starting at the first in-person visit (Month 3), the study drug dose is algorithmically titrated by the IRT system in the range of 0-9 g/day (0-3 packets or equivalent number of placebo packets) in increments of 1 packet/day to a target bicarbonate concentration of 22-29 mmol/L based on the serum bicarbonate measurement at each visit (**Supplementary Figure S1**).

All blood samples for creatinine measurements required by the protocol are submitted to a central laboratory for analysis using a validated, enzymatic creatinine assay.

## **Randomization and Masking**

Central randomization is performed using an IRT system and based on an adaptive minimization randomization technique [25] to maintain treatment group balance across the 5 stratification variables (**Figure 1**).

While both the active and placebo study drug are powders administered as a suspension in water and packaged identically, the appearance of the placebo (microcrystalline cellulose) powder

within the sealed packets is not identical to the appearance of the investigational product (veverimer). Thus, all study drug dispensation, accountability, and assessment of dosing compliance is performed by a designated unblinded site pharmacist/staff and these individuals are not permitted to perform any other study procedures.

### **Post-Randomization Treatment Period (Part B)**

Following randomization, patients attend in-person visits every 3 months and have a telephone contact approximately mid-way between in-person visits (see **Supplementary Materials** for study procedure schedule). Baseline alkali supplements are adjusted algorithmically based on the study drug dose and serum bicarbonate level (see **Supplementary Materials** for details).

### **Management of Comorbid Conditions During the Study**

As no clinically relevant drug-drug interactions have been identified with veverimer [26], dose separation between concomitant medications, including phosphate and potassium binders, and the study drug is not required. Additionally, there are no restrictions on use of concomitant medications based on drug-drug interaction considerations. Addition of new ACE inhibitors and/or ARBs or dose increases of these medications is not allowed during the study unless medically necessary and other options are not clinically appropriate. Dose reduction or discontinuation of these drugs is not allowed except for a medical reason (e.g., hyperkalemia). The protocol-recommended targets for blood pressure and hemoglobin A1c are in accordance with clinical practice guidelines (see **Supplemental Materials** for details).

### **Outcomes and Endpoint Adjudication**

The primary endpoint of the study is progression of kidney disease, defined by time to first occurrence of any event in the composite endpoint consisting of a confirmed  $\geq 40\%$  reduction in

eGFR, end-stage kidney disease (ESKD), or death due to kidney failure (**Figure 2**).

Confirmation of eGFR decline is based on a second eGFR measurement that is  $\geq 28$  days following the index decline. The definition of ESKD requires continuously prescribed treatment with hemodialysis ( $\geq 2$  sessions per week) or peritoneal dialysis ( $\geq 4$  exchanges per week) for  $\geq 28$  days. Death due to kidney failure is defined as death occurring in a patient for whom RRT was determined to be indicated but either not initiated (e.g., because of patient refusal) or withheld (e.g., because it is deemed futile) where death is not caused by a specific non-cardiovascular cause (e.g., progression of cancer, trauma). Thus, death due to kidney failure, is considered an ESKD equivalent (See **Supplementary Table S4** for detailed endpoint definitions).

All the secondary and exploratory endpoints are listed in **Figure 2**.

### **Statistical Power and Other Considerations**

VALOR-CKD is an event-based trial that is designed to terminate when the independent blinded CEAC has positively adjudicated the requisite number of primary endpoint events.

The study was designed to randomize 1,600 participants and to continue until 511 of them experienced a primary endpoint event. This number would provide 87% power at a two-sided p-value of 0.05 to detect a 24% relative risk reduction for the primary outcome. On May 19, 2022, the study sponsor initiated an orderly early termination of the study for administrative reasons related to availability of financial resources; at this time the trial had randomized 1,480 participants and 237 participants had experienced a positively adjudicated primary endpoint events, with event accrual projected to continue into the third quarter of 2022. We then re-calculated the power based on a final number of 250 or 300 events. With 250 primary outcomes,

the trial will have 78% power to detect a hazard ratio (HR) of 0.70, and with 300 primary outcomes, there will be 85% power to detect the same HR.

The main efficacy analyses will be conducted in the intent-to-treat population (all randomized patients). The effect of the study intervention on the primary endpoint will be tested using a Cox proportional hazard model adjusting for age, sex, history of diabetes, and baseline stratification variables. The estimated treatment effect will be expressed as the hazard ratio and its 95% confidence interval (CI). Similar methods will be used for time-to-event secondary endpoints. Physical function endpoints will be analyzed using a rank-based analysis of covariance (ANCOVA) model adjusting for the same covariate variables. Only if the primary efficacy endpoint is found to be statistically significant will the sequential hierarchical testing of the secondary efficacy endpoints be performed. The same one-sided alpha will be used for the primary endpoint and secondary endpoints. Analyses of safety data will be performed in all patients receiving any amount of study drug treatment.

#### **Adaptations due to Coronavirus Disease 2019 (COVID-19) and the 2022 War in Ukraine**

While enrollment was not paused during the COVID-19 pandemic in 2020-2021, individual sites at different points in the pandemic have been rendered unable to screen and enroll new participants. To mitigate disruptions to the study operations due to COVID-19 related restrictions and, subsequently, the 2022 war in Ukraine, the study was adapted to minimize missed data collection and interruptions in study drug dosing (e.g., collecting study data by phone and delivery of study drug to patients' homes [see **Supplementary Materials** for details]).

## **Ethical Approval**

The VALOR-CKD study is being conducted in accordance with United States Food and Drug Administration regulations, the ICH E6 guidelines for Good Clinical Practice, the Declaration of Helsinki, and Institutional Review Board or Independent Ethics Committee requirements. The study is also being conducted in accordance with the European Union Clinical Trials Directive 2001/20/EC (EUCTD) for sites in the European Union (EU). The study protocol was approved by Institutional Review Boards, independent Ethics Committees, and competent authorities according to national and international regulations. All patients gave their written, informed consent before study entry.

## **Study Oversight**

A Steering Committee blinded to study data provides input on important study decisions and will oversee publications and communications of the study results (**Figure 3**). An independent Clinical Endpoint Adjudication Committee (CEAC) blinded to treatment assignment and serum bicarbonate adjudicates potential eGFR decline endpoints, potential ESKD events and causes of death for all post-randomization death events. An independent unblinded Data Monitoring Committee (DMC) reviews safety data approximately every 3 months and makes recommendations as to whether the study should continue as is, be modified to protect subjects' safety, or be terminated. The DMC had no other role in the ongoing study; they did not participate in the development of the study statistical analysis plan.

## RESULTS

A total of 5,246 patients were screened. Of these, 2,198 patients were enrolled into Part A and, of those, 1,480 patients (67%) were randomized (**Figure 4**). The most common reasons for screen failure were ineligibility on the eGFR or serum bicarbonate criteria. The study randomized patients from December 2018 to December 2021. The number randomized was 92.5% of what was originally planned (N = 1,600).

Baseline characteristics of the randomized population are shown in **Table 1**. Nearly 60% of the population was  $\geq 65$  years, 42% were female, those of a race other than White comprised 16% of the population, and 13% were Hispanic or Latino individuals. Common comorbidities included hypertension (98%), hyperlipidemia/dyslipidemia (65%), diabetes (56%), and heart failure (32%). The baseline (standard deviation) eGFR and serum bicarbonate were 29 (6.3) mL/min/1.72 m<sup>2</sup> and 17.5 (1.4) mmol/L, respectively, and the median UACR during screening was 201 mg/g with UACR  $\leq 300$  mg/g in the majority (57.4%) of patients. In 57% of patients, etiology of CKD was attributed to a cause other than diabetes. Alkali supplements were used by 12% of patients at baseline and ACE inhibitors or ARBs by 98%. The median 5-year Kidney Failure Risk Equation (KFRE) [27] risk of ESKD of the study population was 24%.

The post-randomization treatment period and follow-up are ongoing. Top-line efficacy and safety results are expected in October 2022.



## DISCUSSION

With the randomization of 1,480 patients with CKD and metabolic acidosis, VALOR-CKD will provide important evidence on the efficacy and safety of veverimer for the treatment of metabolic acidosis and of preventing progression of CKD in patients with CKD and metabolic acidosis. At completion, the study will also provide important evidence to determine the potential benefit of treating people with CKD-associated metabolic acidosis, and be the first to study CKD progression and kidney failure as primary outcomes for a unique approach to removing acid.

Veverimer is a novel, non-absorbed, polymeric hydrochloric acid binder developed specifically for the treatment of metabolic acidosis and slowing CKD progression. After ingestion, veverimer is protonated, and the positively charged polymer selectively binds the smallest anion in the gastrointestinal tract, chloride, with little or no binding of other anions, such as phosphate, citrate, fatty acids, and bile acids [19]. In previous randomized trials, treatment with veverimer improved serum bicarbonate levels [20, 21], and in a one-year study, improved chair stand time and patient-reported physical function [22]. Although there was preliminary evidence of improvement in a composite of death and CKD progression in the one-year study, the numbers of these outcomes were small and confirmation of clinical benefit in a larger study with longer follow up was required.

Previous studies have also evaluated treatment of metabolic acidosis on prevention of CKD progression using oral sodium bicarbonate. There are important differences in the population, intervention, design and outcomes studied in the VALOR-CKD study when compared to these previous trials. In an unblinded, single-center study, de Brito-Ashurst and colleagues

randomized 134 individuals with CKD and metabolic acidosis in the United Kingdom to oral sodium bicarbonate or standard care and found a greater than 80% risk reduction (RR) in progression to kidney failure (RR 0.13 [0.04, 0.40]; 4 vs 22 events) [16]. Similar findings were observed in other open-label randomized studies, including the UBI study in Italy, where a 60% risk reduction for a CKD progression outcome was observed after 5 years of follow-up [28]. In contrast, the only double-blind, placebo-controlled trial of oral alkali in patients with CKD and metabolic acidosis found no impact of treatment on the rate of deterioration of kidney function [18]. The BiCARB study, which was conducted in 230 participants from 7 centers in the United Kingdom, randomized older adults with CKD and metabolic acidosis to sodium bicarbonate or placebo. Despite a 1.1 mmol/L between group difference in serum bicarbonate levels at 1 year, there was no effect on kidney or physical function outcomes after 2 years of follow up. More than 30% of patients discontinued treatment during the study [18]. Other randomized trials that had lower rates of sodium bicarbonate discontinuation [29, 30] studied patients with normal serum bicarbonate levels and, therefore, may not be directly relevant to the population we studied.

VALOR-CKD will be one of the first and largest randomized trials in the CKD population to evaluate objective (5-repetition chair stand test) and patient-reported (Kidney Disease and Quality of Life Physical Function Domain [KDQOL-PFD]) measures of physical function as key secondary outcomes. Previous studies examining changes in physical function with oral alkali therapy had conflicting results [16, 18, 29]. Furthermore, sustained improvements in physical function or health-related quality of life have not been demonstrated with any treatments for CKD or its complications including anemia management or hyperphosphatemia [31, 32]. Given

the importance of physical function, and the lack of therapies to improve quality of life in patients with CKD, new interventions are urgently needed.

One of the theoretical challenges for this study is the potential use of confounding concomitant treatments over the duration of the study. Recruitment for VALOR-CKD began in 2018, and was complete in 2021, with entry criteria requiring acidotic patients (serum bicarbonate between 12-20 mmol/L) with an eGFR between 20-40 mL/min/1.73 m<sup>2</sup>. In this timeframe, rates of SGLT2 inhibitor use at baseline in the study population was low (1.3% of patients), and non-steroidal mineralocorticoid receptor antagonists (MRA) use was absent. Oral alkali use was allowed in VALOR-CKD but only 12% of patients were on alkali supplements at baseline, a finding consistent with multiple studies in different countries [22-24]. Proton pump inhibitor use is not expected to impact the effect of veverimer on serum bicarbonate levels or its efficacy in slowing CKD progression [19, 26]; these drugs were used by 9% of patients at baseline.

The primary endpoint of the VALOR-CKD study is the time to first occurrence of any event in the composite of a confirmed 40% decline in eGFR, progression to kidney failure requiring dialysis or transplantation or death from kidney failure. This endpoint is similar to other recent randomized trials in kidney disease, including EMPA-KIDNEY [33] and FIDELIO [34]. Other studies have used endpoints requiring a larger decline in eGFR (e.g., 50%; [5]), or a doubling of serum creatinine (equivalent to a 57% decline in eGFR; [35, 36]). However, all of these other interventions had an acute effect on eGFR and were therefore more susceptible to Type 1 error from a more liberal GFR decline endpoint than is VALOR-CKD, which uses a non-absorbed polymer drug [19] with no known acute effects on eGFR [21]. Nonetheless, VALOR-CKD will also assess other kidney endpoints (e.g., 50% decline in eGFR, doubling of serum creatinine),

kidney failure alone, cardiovascular death, and all-cause hospitalization as prespecified secondary outcomes (**Figure 2**).

In conclusion, VALOR-CKD is designed to assess the efficacy and safety of veverimer, a novel once-daily, non-absorbed drug that increases serum bicarbonate by binding and removing acid from the gastrointestinal lumen. The results of the study, which are expected in 2022, have the potential to change the future paradigm for the treatment of metabolic acidosis in patients with CKD.

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## CONFLICT OF INTEREST STATEMENT

V.S.M., D.A.B., L.I., E.L., V.P., M.W., D.E.W., D.C.W. and N.T. were paid consultants to Tricida, Inc. (South San Francisco, CA) in connection with the development of this manuscript. V.S.M., D.A.B., L.I., G.K., V.P., D.E.W., D.C.W. and N.T. are Steering Committee members of VALOR-CKD study. V.S.M., D.A.B., D.E.W. and N.T. report consultancy, personal fees, and equity ownership from Tricida, Inc., related to the submitted work. L.I., E.L., V.P., M.W. and D.C.W. report consultancy and personal fees from Tricida, Inc., related to the submitted work. G.K., D.P. and Y.S. are employees of Tricida, Inc. and own stock or stock options in Tricida, Inc. V.S.M., G.K., D.P. and Y.S. are listed on patents related to work for Tricida, Inc. V.S.M., D.A.B., D.E.W. and N.T. are members of advisory boards at Tricida, Inc. G.K. is a member of the Board of Directors for Tricida, Inc. V.M. reports additional consulting fees from Tricida, Inc., Equillium, Myovant, Rigel, Corvidia, Acuta, Frazier, Intarcia, PTC Bio and Sanifit, all outside the submitted work. D.A.B. reports additional consulting fees from Amgen, Sanofi/Genzyme, Fresenius/Relypsa/Vifor, personal fees as a medical advisory board member from Sanifit, speaker fees from Sanofi/Genzyme and stock ownership in Amgen and past stock ownership in Relypsa, all outside this work. L.I. reports additional consulting fee from Health Logics outside the submitted work. D.C.W. reports additional consulting fees from Bayer, Boehringer Ingelheim, GlaxoSmithKline, Gilead, Janssen, Mundipharma, Merck Sharp and Dohme, and Zydus, all outside the submitted work. N.T. reports additional consulting fees and research funding from Bayer, Boehringer Ingelheim, Otsuka, Janssen and Astra Zeneca. N.T.

holds stock or stock options in Pulsedata, Klinrisk, Quanta and Renibus. .All authors take full responsibility for the content of the manuscript and had full access to the data described in the manuscript, ensuring the integrity of the data and the accuracy of the data analysis.

### **AUTHORS' CONTRIBUTIONS**

All authors were involved in the development of the study protocol and statistical analysis plan.

V.S.M. G.K., D.P., and Y.S. were responsible for management of the study, and E.L. and M.W. were responsible for the statistical analyses. All authors contributed to the interpretation of the results and preparation of this manuscript.

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### **DATA AVAILABILITY STATEMENT**

The data underlying this research will be made available upon reasonable request to the corresponding author.

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**Table 1: Baseline Demographic and Clinical Characteristics of the Randomized Participants.**

Characteristics	Randomized Participants (N = 1,480)
<b>Demographics</b>	
Age (year), mean (SD)	65.1 (12.1)
≥65 years, (%)	58.8
≥75 years, (%)	22.2
Sex, (%)	
Male	57.7
Female	42.3
Race, (%)	
White	83.7
Asian	8.1
American Indian or Alaska Native	6.6
Black or African American	1.4
Other	<0.2
Ethnicity, (%)	
Not Hispanic or Latino	86.6
Hispanic or Latino	13.4
Geographic region, (%)	

Europe	74.7
North America	12.3
South America	4.5
Rest of World	8.5
<b>Selected Medical History, (%)</b>	
Hypertension	98.0
Hyperlipidemia or Dyslipidemia	65.4
Diabetes Mellitus	55.5
Heart Failure	32.2
Anemia	37.4
Coronary artery disease	33.0
Left ventricular hypertrophy	29.2
Percutaneous coronary intervention or coronary artery bypass grafting	17.2
Myocardial infarction	14.1
Peripheral vascular disease	9.1
Atrial fibrillation or atrial flutter	9.6
Stroke	6.8
Hyperparathyroidism	7.0
Vitamin D deficiency	5.9
<b>Smoking History</b>	
Current	8.2
Former	28.4

<b>Primary Cause of Chronic Kidney Disease, (%)</b>	
Diabetes	18.0
Diabetes and hypertension	25.3
Hypertension	33.9
Glomerulonephritis	5.7
Polycystic kidney disease	3.5
Interstitial nephritis	2.0
Urologic	2.0
Other congenital / hereditary	0.5
Other cystic renal disease	0.3
Other	5.2
Unknown	3.2
<b>Vital Signs</b>	
Systolic blood pressure (mmHg), mean (SD) <sup>1</sup>	133.6 (11.9)
<140 mmHg, (%)	70.4
140 – <160 mmHg, (%)	28.6
≥160 mmHg, (%)	0.9
Diastolic blood pressure (mmHg), mean (SD) <sup>1</sup>	77.6 (8.2)
Body mass index (kg/m <sup>2</sup> ), mean (SD)	28.6 (5.0)
<b>Laboratory Values</b>	
Baseline serum bicarbonate (mmol/L), mean (SD) <sup>2</sup>	17.5 (1.4)
≤18 mmol/L, (%)	61.8
>18 mmol/L, (%)	38.2

Baseline eGFR (mL/min/1.73 m <sup>2</sup> ), mean (SD) <sup>4</sup>	29.1 (6.3)
Screening eGFR (mL/min/1.73 m <sup>2</sup> ), mean (SD) <sup>5</sup>	29.1 (6.0)
≤25 mL/min/1.73 m <sup>2</sup> , (%)	34.2
>25 mL/min/1.73 m <sup>2</sup> , (%)	65.8
Screening UACR (mg/g), median <sup>6</sup>	201
<30 mg/g, (%)	22.8
≥30 – ≤300 mg/g, (%)	34.6
>300 mg/g, (%)	42.6
<b>Prior (Baseline) Medications, (%)</b>	
ACE inhibitors or ARBs	98.0
Oral alkali supplements <sup>7</sup>	11.6
Insulin	23.9
Sodium-glucose cotransporter-2 inhibitors	1.3
Glucagon-like peptide-1 analogues	0.9
Statins	53.9
Loop diuretics	38.9
Proton pump inhibitors	9.4
Potassium or phosphate binders	5.0
<b>Kidney Failure Risk, (Median %)</b>	
2-year risk of ESKD (KFRE)	8
5-year risk of ESKD (KFRE)	24

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease;

KFRE, Kidney Failure Risk Equation; SD, standard deviation; UACR, urine albumin-to-creatinine ratio

<sup>1</sup> Baseline blood pressure is the mean of all values collected during Screening and Part A Visit 1 (pre-dose).

<sup>2</sup> Baseline serum bicarbonate is the average of the serum bicarbonate collected at the Screening 1 Visit, Screening 2 Visit, and Part A Visit 1 (pre-dose).

<sup>3</sup> Baseline serum anion gap is defined as (baseline serum sodium - (baseline serum chloride + baseline serum bicarbonate) where baseline serum sodium and baseline serum chloride are both the last non-missing values on or prior to the first study drug dosing in Part A.

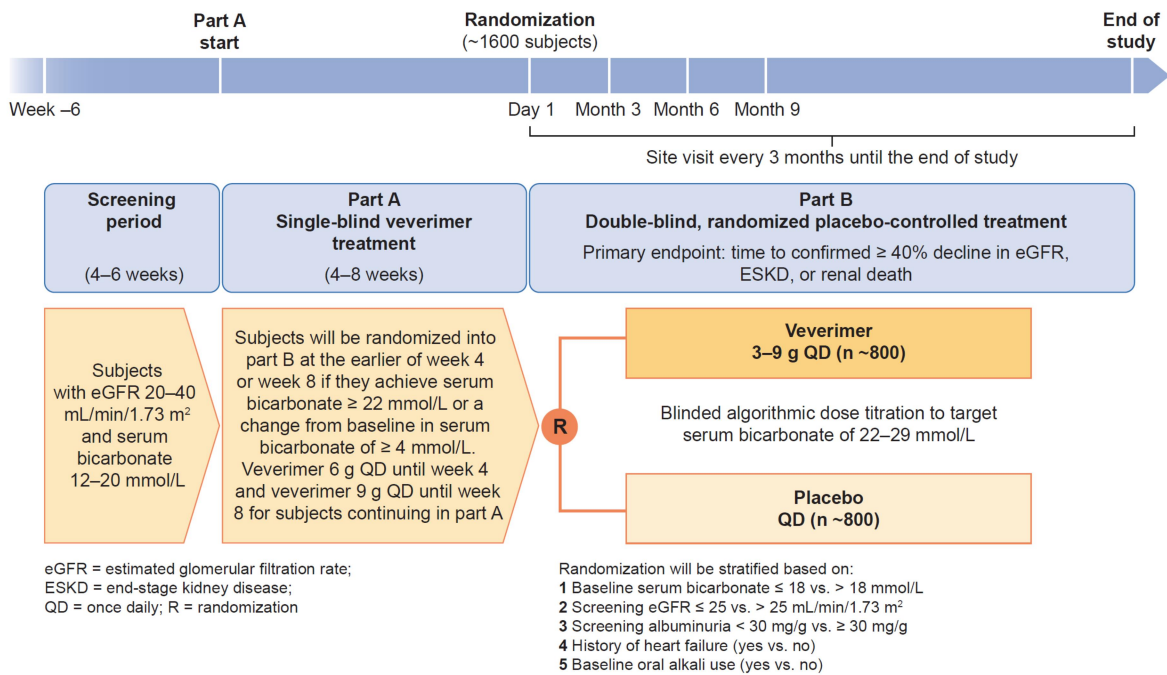
<sup>4</sup> Baseline eGFR includes all eGFR values collected during Screening and Part A of the study.

<sup>5</sup> Screening eGFR includes eGFR values collected at the Screening 1 and Screening 2 Visits.

<sup>6</sup> Screening UACR includes all UACR values collected during Screening.

<sup>7</sup> The majority of patients on oral alkali supplements were taking sodium bicarbonate

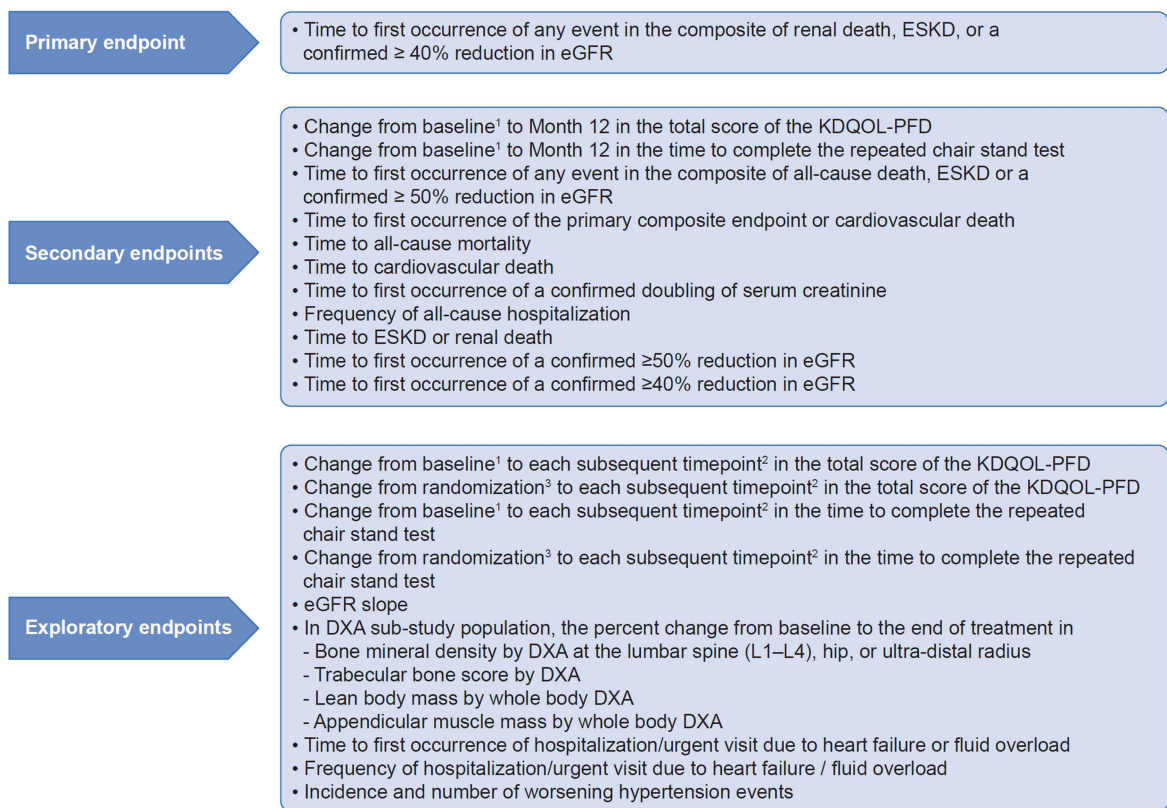
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**Figure 1: VALOR-CKD Design Schematic**

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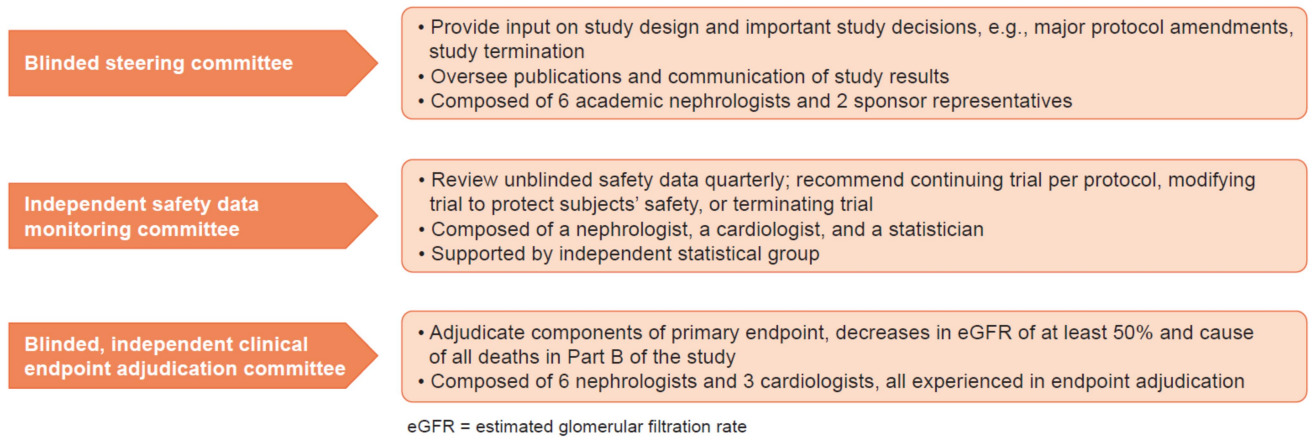


DXA = dual energy x-ray absorptiometry; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; KDQOL-PFD = kidney disease quality of life – physical function domain

<sup>1</sup>A1 visit, predose; <sup>2</sup>Other than month 12; <sup>3</sup>Day 1 visit

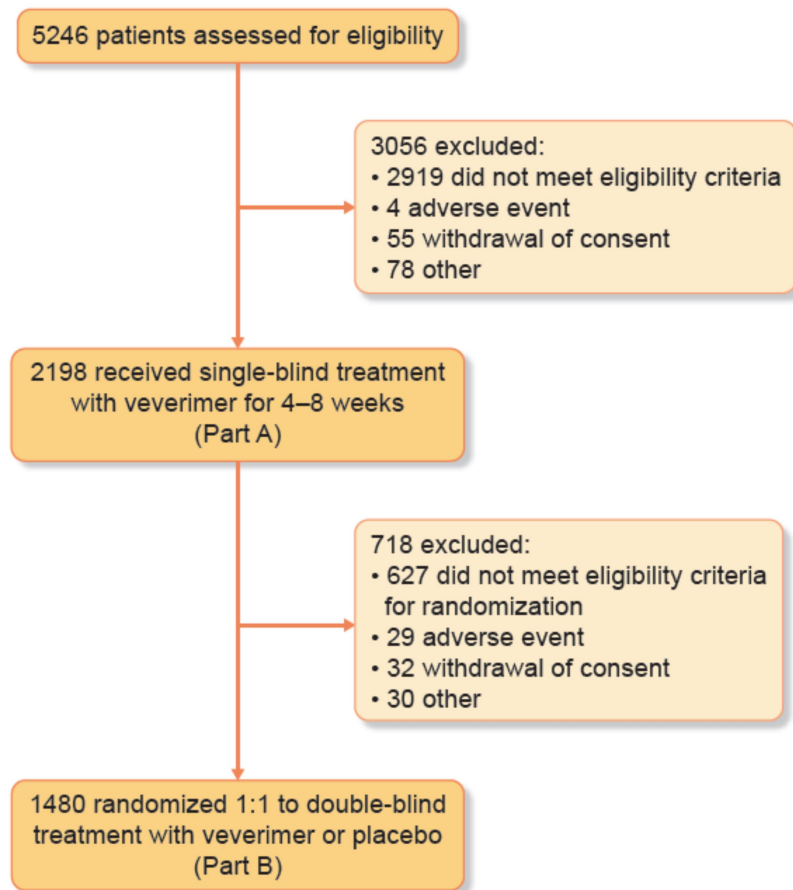
**Figure 2: VALOR-CKD Study Endpoints**

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**Figure 3: VALOR-CKD Committee Structure**

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**Figure 4: VALOR-CKD CONSORT Diagram**