VALOR-CKD: A Multicenter, Randomized, Double-Blind Placebo-Controlled Trial Evaluating Veverimer in Slowing Progression of CKD in Patients with Metabolic Acidosis

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ABSTRACT

Background Metabolic acidosis is common in CKD, but whether its treatment slows CKD progression is unknown. Veverimer, a novel hydrochloric acid binder that removes acid from the gastrointestinal tract, leads to an increase in serum bicarbonate.

Methods In a phase 3, double-blind, placebo-controlled trial, patients with CKD (eGFR of 20–40 ml/min per 1.73 m^2) and metabolic acidosis (serum bicarbonate of 12–20 mEq/L) from 35 countries were randomized to veverimer or placebo. The primary outcome was the composite end point of CKD progression, defined as the development of ESKD (kidney transplantation or maintenance dialysis), a sustained decline in eGFR of ≥40% from baseline, or death due to kidney failure.

Results The mean (±SD) baseline eGFR was 29.2±6.3 ml/min per 1.73 m^2, and serum bicarbonate was 17.5±1.4 mEq/L; this increased to 23.4±2.0 mEq/L after the active treatment run-in. After randomized withdrawal, the mean serum bicarbonate was 22.0±3.0 mEq/L and 20.9±3.3 mEq/L in the veverimer and placebo groups at month 3, and this approximately 1 mEq/L difference remained stable for the first 24 months. A primary end point event occurred in 149/741 and 148/739 patients in the veverimer and placebo groups, respectively (hazard ratio, 0.99; 95% confidence interval, 0.8 to 1.2; $P = 0.90$). Serious and overall adverse event incidence did not differ between the groups.

Conclusions Among patients with CKD and metabolic acidosis, treatment with veverimer did not slow CKD progression. The lower than expected bicarbonate separation may have hindered the ability to test the hypothesis.

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INTRODUCTION

Metabolic acidosis is common in CKD and is also associated with worsening of GFR, bone and muscle loss, and all-cause mortality.[1,2] Treatment of metabolic acidosis in clinical practice is limited by the lack of any US Food and Drug Administration–approved therapies. Oral alkali supplements, including sodium bicarbonate, are infrequently used and can lead to gastrointestinal side effects or edema.[3,4] Fruits and vegetables increase dietary base, but poor long-term adherence to these diets limits their use.[5]

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Veverimer is an oral, nonabsorbed polymer that selectively binds and eliminates hydrochloric acid in the gastrointestinal tract, leading to increased serum bicarbonate.[6,7] In two previous randomized trials, veverimer was shown to increase serum bicarbonate by 3–4 mEq/L compared with placebo at up to 12 months and improve subjective and objective measures of physical function.[8,9] However, the long-term effects of veverimer on slowing CKD progression are unknown.

We designed the Evaluation of Effect of TRC101 on Progression of CKD in Subjects with Metabolic Acidosis (VALOR-CKD) trial to test the hypothesis that treatment with veverimer slows the progression of CKD among patients with CKD and metabolic acidosis.

Significance Statement

Metabolic acidosis is a common complication of CKD and is associated with more rapid decline of kidney function, but well-powered controlled randomized trials testing the effect of treating metabolic acidosis on slowing CKD progression have not been conducted. The VALOR-CKD study randomized 1480 individuals with CKD and metabolic acidosis, across 320 sites to placebo or veverimer (a novel hydrochloric acid binder). The findings did not demonstrate the efficacy of veverimer in slowing CKD progression, but the difference in serum bicarbonate between placebo and drug arms was only approximately 1 mEq/L. Veverimer was safe and well tolerated.

METHODS

Trial Design and Oversight

The VALOR-CKD study was a randomized, double-blind, placebo-controlled, multicenter clinical trial; details regarding the trial design and baseline characteristics of the participants have been published previously,[10] and the protocol is available in the Supplemental Appendix. The trial was sponsored by Tricida, Inc. and conducted at 346 sites in 35 countries from September 2018 through September 2022. An executive steering committee of seven academic members and two representatives from the sponsor were responsible for the design and oversight of the trial and the reporting of the results. The trial protocol was performed in accordance with the principles of the Declaration of Helsinki. The sponsor conducted the analysis, and all authors had access to the data and participated in interpretation of the data. The first draft of the manuscript was prepared by the first and second author and was reviewed and edited by all the authors. All the authors made the decision to submit the manuscript for publication. The sponsor and the authors vouch for the completeness and accuracy of the data and vouch for the fidelity of the trial to the protocol.

Participants

Adults with CKD (eGFR, 20–40 ml/min per 1.73 m^2) and metabolic acidosis (serum bicarbonate 12–20 mEq/L) were eligible for participation. The serum bicarbonate inclusion criteria required three values in the target range, performed using an Abbott i-STAT device at the point of care, 2 weeks apart, within a 6 weeks window. All participants were required to be receiving the maximally tolerated dose of an angiotensin-converting enzyme inhibitor and/or angiotensin receptor blocker, unless they had nondiabetic CKD and absence of albuminuria (the urine albumin-creatinine ratio [UACR] is <30 mg/g, with albumin measured in milligrams and creatinine measured in grams). Oral alkali use at a stable dose at baseline was permitted. Full inclusion and exclusion criteria are provided in the Supplemental Appendix. All patients gave their written informed consent before study entry.

Trial Procedures

The trial consisted of an active treatment run-in period, followed by a responder threshold to become eligible for randomization (Supplemental Figure 1). The full design and methods for VALOR-CKD have been previously reported.[10]

After enrollment into part A (run-in period) of the study and 4–8 weeks of treatment with veverimer, patients with an increase from baseline in serum bicarbonate by ≥4 mEq/L or a serum bicarbonate ≥22 mEq/L progressed to the next stage of the trial (randomized treatment [part B]) after randomization to veverimer or placebo. The active treatment run-in period was designed to maximize the separation in serum bicarbonate levels between treatment groups after randomization. Patients receiving RRT or who had a confirmed ≥40% eGFR decline during part A were excluded from part B. All study drug dispensation, accountability, and assessment of dosing and compliance was performed by a designated unblinded site pharmacist or staff, and these individuals were not permitted to perform any other study procedures. Venous TCO_2 values were obtained using the i-STAT device (Abbott Point of Care, Princeton, NJ) at every visit and confirmed to be congruent with calculated HCO_3.

After randomization, patients attended in-person visits every 3 months and had a telephone contact approximately midway between in-person visits (see Supplemental Appendix for study procedure schedule).

The starting study drug dose was 6 g veverimer once daily (two packets daily) or placebo once daily (two packets daily; microcrystalline cellulose, National Formulary Grade). Both were administered orally as a suspension in water with a meal. During part B, starting at the first in-person visit (month 3), the study drug dose was algorithmically titrated by the Interactive Response Technology system in the range of 0–9 g/d (0–3 packets or equivalent number of placebo packets) in increments of one packet per day to a target bicarbonate concentration of 22–29 mmol/L on the basis of the serum bicarbonate measurement at each visit.

Baseline alkali supplements were adjusted by the protocol algorithm on the basis of the study drug dose and serum bicarbonate at each visit. When the study drug dose was maximal during part B, the baseline alkali supplements were algorithmically discontinued or restarted at the original dose on the basis of the serum bicarbonate level. If the bicarbonate was >30 mmol/L at any time, alkali was discontinued. New alkali use or use of doses higher than the baseline dose was permitted, if needed, as rescue treatment for acute on chronic metabolic acidosis and during the period approaching RRT. The protocol allowed for short-term use of sodium bicarbonate or other alkali treatment for up to 30 days (and for a total of up to 90 days per 12-month period with notification to the Medical Monitor) in patients who were assigned to the maximum dose of study drug (three packets per day).

Outcomes

The primary end point of the study, assessed in a time-to-event analysis, was progression of kidney disease, defined by time to first occurrence of any event in the composite end point consisting of a confirmed ≥40% reduction in eGFR, ESKD, or death due to kidney failure. Confirmation of eGFR decline was based on a second eGFR measurement that was ≥28 days following the index decline. The definition of ESKD required continuously prescribed treatment with hemodialysis (≥2 sessions per week) or peritoneal dialysis (≥4 exchanges per week) for ≥28 days.

The secondary outcomes were, in the prespecified hierarchical order, change in Kidney Disease Quality of Life—Physical Function Domain (KDQOL-PFD) score, change in the time to complete the repeated chair stand test, and a number of time to event analyses (a composite of ≥50% decline in eGFR, ESKD, or all-cause death; a composite of the primary end point and cardiovascular death; all-cause mortality; cardiovascular death; doubling of serum creatinine; all-cause hospitalizations; ESKD or renal death; a ≥50% decline in eGFR; and a ≥40% decline in eGFR).

A clinical event committee whose members were unaware of the treatment group assignments independently reviewed and adjudicated all reported eGFR, ESKD, and death outcome events. The committee regularly received laboratory data that identified patients meeting threshold eGFR declines (*i.e.*, potential end points). Additional information, including outcome definitions and a list of exploratory outcomes, is provided in the Supplemental Appendix and the trial protocol.

Safety analyses included assessment of adverse events, vital signs, and central laboratory testing.

Statistical Analysis

The statistical analysis plan and power calculations have been published previously,[10] and the complete prespecified statistical analysis plan is provided with the protocol (Supplemental Appendix). In brief, VALOR-CKD was an event-based trial that was designed to terminate when the independent blinded Clinical Events Adjudication Committee had positively adjudicated the requisite number of primary end point events. The study was originally designed to randomize 1600 participants and to continue until 511 of them experienced a primary end point 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. An adaptive randomization minimization technique[11] was used to maintain treatment group balance across the stratification variables. Stratification variables were weighted such that bicarbonate, eGFR, and albuminuria carried a weight of 2 and heart failure and alkali use carried a weight of 1. Active monitoring of the adaptive randomization and stratification was conducted by an independent unblinded statistician during the study.

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 1480 participants and 237 participants had experienced a positively adjudicated primary end point events. At the final data base lock, 298 patients had an event, providing 80% power to detect a hazard ratio of approximately 0.72.

The main efficacy analyses were performed in the intent-to-treat population. The effect of the study intervention on the primary end point was evaluated using a Cox proportional hazard model adjusting for age, sex, history of diabetes, and baseline stratification variables (Supplemental Figure 1). The estimated treatment effect was expressed as the hazard ratio (veverimer/placebo) and its 95% confidence interval. Similar methods were used for time-to-event secondary end points. Rank-based analysis of covariance models, adjusting for age, sex, history of diabetes, and baseline stratification variables (Supplemental Figure 1), was used to assess the treatment effect on physical function, as determined using the KDQOL-PFD and the time to completion of the repeated sit–stand test.

RESULTS

Participants

From September 2018 to September 2022, a total of 5200 patients in 35 countries underwent screening, of whom 2198 were enrolled in part A. Of those, 1480 (67%) patients met the responder run-in criteria and were randomized to veverimer or placebo (Supplemental Figure 1). Randomized participants were exposed to study drug for a median of 775 days.

Baseline characteristics of the randomized population were well balanced between the two groups (Table 1). The mean age was 65 years, 58% were male, and 84% were White. The baseline (SD) eGFR and serum bicarbonate were 29.2±6.3 ml/min per 1.73 m^2 and 17.5±1.4 mEq/L, respectively, and the median (interquartile range) UACR during screening was 201 (794) mg/g and UACR ≤300 mg/g in most (57.4%) patients.

Table 1. Demographic and clinical characteristics of the patients at baseline[a]

Characteristic	Veverimer (*n*=741)	Placebo (*n*=739)
Age, yr	65.0±11.9	65.2±12.3
Female sex, *no.* (%)	308 (41.6)	318 (43.0)
Race, *no.* (%)[b]		
White	620 (83.7)	619 (83.8)
Black	10 (1.3)	10 (1.4)
Asian	59 (8.0)	61 (8.3)
Other	52 (7.0)	49 (6.6)
Weight, kg	79.9±15.8	80.3±15.8
Body mass index[c]	28.5±4.9	28.7±5.0
Current smoker, *no.* (%)	56 (7.6)	65 (8.8)
Hypertension, *no.* (%)	726 (98.0)	724 (98.0)
Diabetes mellitus, *no.* (%)	423 (57.1)	399 (54.0)
Heart failure, *no.* (%)	230 (31.0)	241 (32.6)
BP, mm Hg		
Systolic	133.6±11.5	133.6±12.2
Diastolic	77.5±8.4	77.7±8.0
Screening eGFR[d]		
Mean, ml/min per 1.73 m^2	29.2±6.0	29.0±5.9
Distribution, *no.* (%)		
≤25 ml/min per 1.73 m^2	247 (33.3)	259 (35.0)
>25 ml/min per 1.73 m^2	494 (66.7)	480 (65.0)
Screening urinary ACR, median (IQR)[d,e]	199 (853)	203 (749)
Serum bicarbonate[f]		
Mean, mEq/L	17.4±1.4	17.5±1.3
Distribution, *no.* (%)		
≤18 mEq/L	456 (61.5)	459 (62.1)
>18 mEq/L	285 (38.5)	280 (37.9)
Venous pH (mean)	7.308 (0.003)	7.305 (0.003)
Baseline KDQOL-PFD (median)	65.0	65.0
Baseline repeat sit-to-stand chair test time, s (median)	16.0	16.0
Previous medication, *no.* (%)		
ACE inhibitor or ARB	726 (98.2)	715 (97.0)
Statin	395 (53.5)	399 (54.1)
Loop diuretic	287 (38.8)	286 (38.8)
Oral alkali	83 (11.2)	87 (11.8)
Proton pump inhibitors	65 (8.8)	72 (9.8)
SGLT2 inhibitor	10 (1.4)	9 (1.2)

ACE, angiotensin-converting enzyme; ACR, albumin-creatinine ratio; ARB, angiotensin receptor blocker; IQR, interquartile range; KDQOL-PFD, Kidney Disease Quality of Life—Physical Function Domain; SGLT2, sodium–glucose cotransporter 2.

[a]Plus–minus values are mean±SD. Percentages may not total 100 because of rounding.

[b]Race was reported by the investigators; the designation "other" includes American Indian or Alaska Native, multiple, and other.

[c]The body mass index is the weight in kilograms divided by the square of the height in meters.

[d]Screening eGFR (or albumin-creatinine ratio) is defined as the mean of eGFR (or albumin-creatinine ratio) values collected at the screening 1 and screening 2 visits.

[e]The albumin-creatinine ratio was calculated with albumin measured in milligrams and creatinine measured in grams.

[f]Baseline bicarbonate is defined as the average of the values of serum bicarbonate collected at the screening 1 visit, screening 2 visit, and part A visit 1 (predose), measured onsite using an i-STAT point-of-care device.

At the trial conclusion and after a median follow-up of 2.2 years, 204 (28%) patients in the veverimer group and 206 (28%) in the placebo group had discontinued the assigned treatment. Of these, 16% in both treatment groups were discontinued (per protocol) due to meeting the death or ESKD end point and 12% were due to nonfatal adverse events (veverimer 2%; placebo 3%), withdrawal of consent (veverimer 7%; placebo 6%), or other reasons. Dialysis/transplant status and vital status was ascertained at the end of the study for 99.5% and 99.7% of patients, respectively, and adherence to trial regimen (80%–120% of planned doses) was 96% in both veverimer and placebo groups (Supplemental Figure 2). Most patients 626/739 (85%) in the veverimer group were on the maximum dose of 9 g/d.

Efficacy Outcomes

The number of events (annualized rate) of the primary composite outcome of kidney failure, a sustained decline of at least 40% in the eGFR from baseline, or renal death was similar in both groups, occurring in 149 patients (9.9%) and 148 patients (9.6%) in the veverimer and placebo groups, respectively (hazard ratio, 0.99; 95% confidence interval, 0.8 to 1.2; $P = 0.90$) (Figure 1A). These findings were consistent across all prespecified subgroups (Figure 2).

Given the lack of efficacy on the primary end point, all analyses examining secondary end points are considered exploratory. There were no significant between group difference in patient-reported physical function, as determined using the KDQOL-PFD (median difference in change from baseline

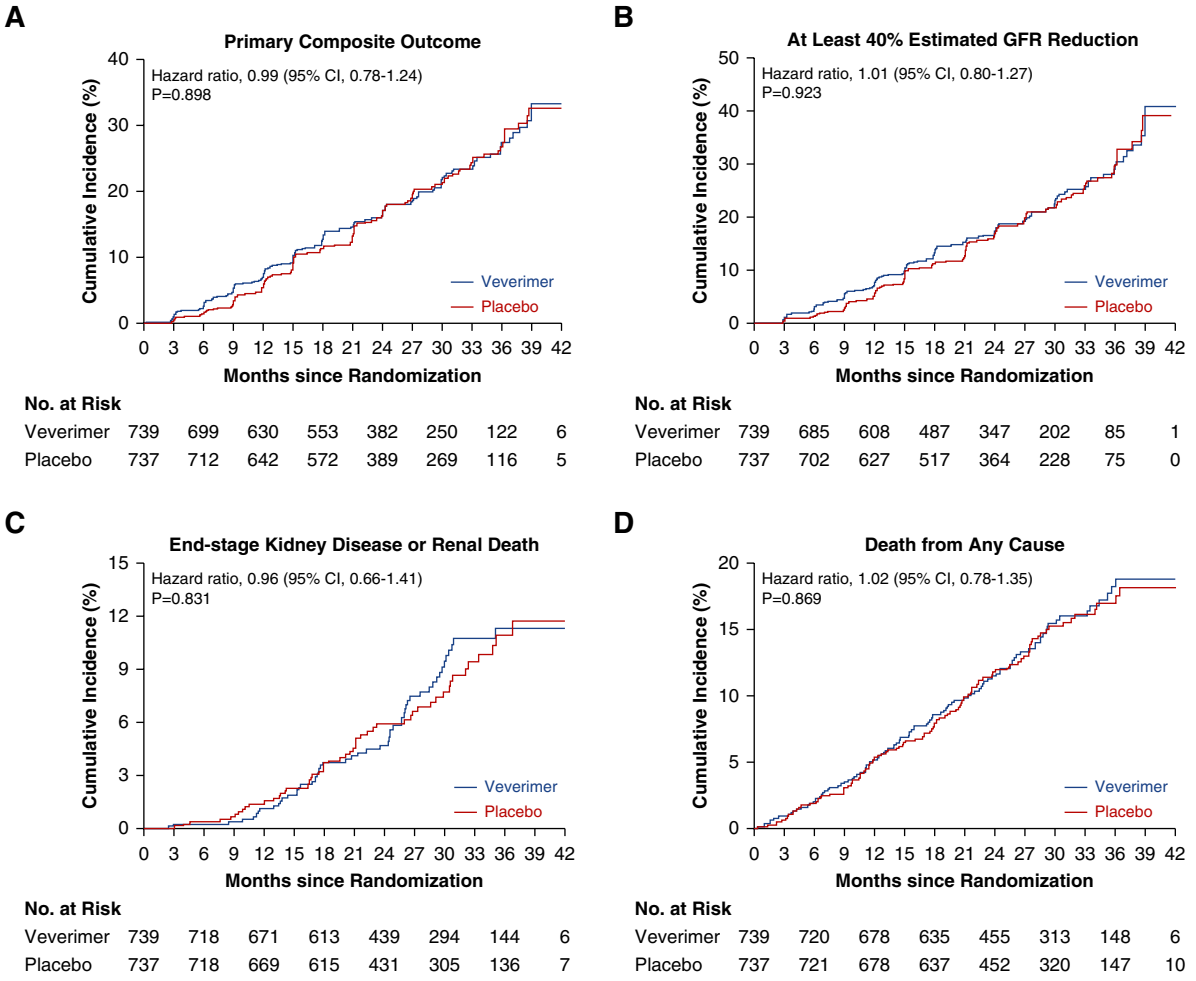


Figure 1. Primary and secondary outcomes. The primary outcome was a composite of a sustained decline in the eGFR of at least 40%, ESKD, or renal death (A). The secondary outcomes of a sustained decline in the eGFR of at least 40% (B), ESKD or renal death (C), and death from any cause (D) were estimated using a Cox proportional hazard model adjusting for age, sex, history of diabetes, and baseline stratification variables. Included in these analyses are all the participants who had undergone randomization and received at least one dose of veverimer or placebo, except for those who double randomized. CI, confidence interval. Figure 1 can be viewed in color online at www.jasn.org.

between veverimer and placebo was 0; $P = 0.87$) or the time to completion of the five times repeated sit–stand test (median difference in change from baseline between veverimer and placebo was −0.1; $P = 0.20$). There were no significant differences in the time to ≥40% decline in eGFR (Figure 1B), ESKD or renal death (Figure 1C), all-cause death (Figure 1D), cardiovascular death or hospitalizations (Supplemental Table 2), or any of the alternative CKD progression end points (≥50% decline in eGFR or composites that included ≥50% decline in eGFR).

The least squares mean (±SEM) eGFR slopes from randomization to the last assessment (before RRT initiation, if this occurred) in the veverimer and placebo groups were −1.67±0.17 and −1.67±0.17, respectively, resulting in no difference between groups. There was no evidence of an acute effect on eGFR from veverimer. The change in the eGFR during the active run-in period was 0.0±0.15 ml/min per 1.73 m^2 and 0.1 ml/min per 1.73 m^2 among patients subsequently randomized to veverimer and placebo, respectively.

Effects of Veverimer on Serum Bicarbonate

In patients who completed the run-in, the baseline serum bicarbonate level of 17.5±1.3 mEq/L rose to 23.4±2.0 mEq/L at the end of the active treatment run-in period. After randomized withdrawal, patients who remained on veverimer had a mean serum bicarbonate level of 22.0±3.0 mEq/L at month 3, whereas those on placebo remained at 20.9±3.3 mEq/L, a difference of 1.1 mEq/L ($P < 0.001$) (Figure 3). This difference in serum bicarbonate levels of approximately 1 mEq/L remained constant through the majority of follow-up (2 years) (Figure 3). Oral alkali use at

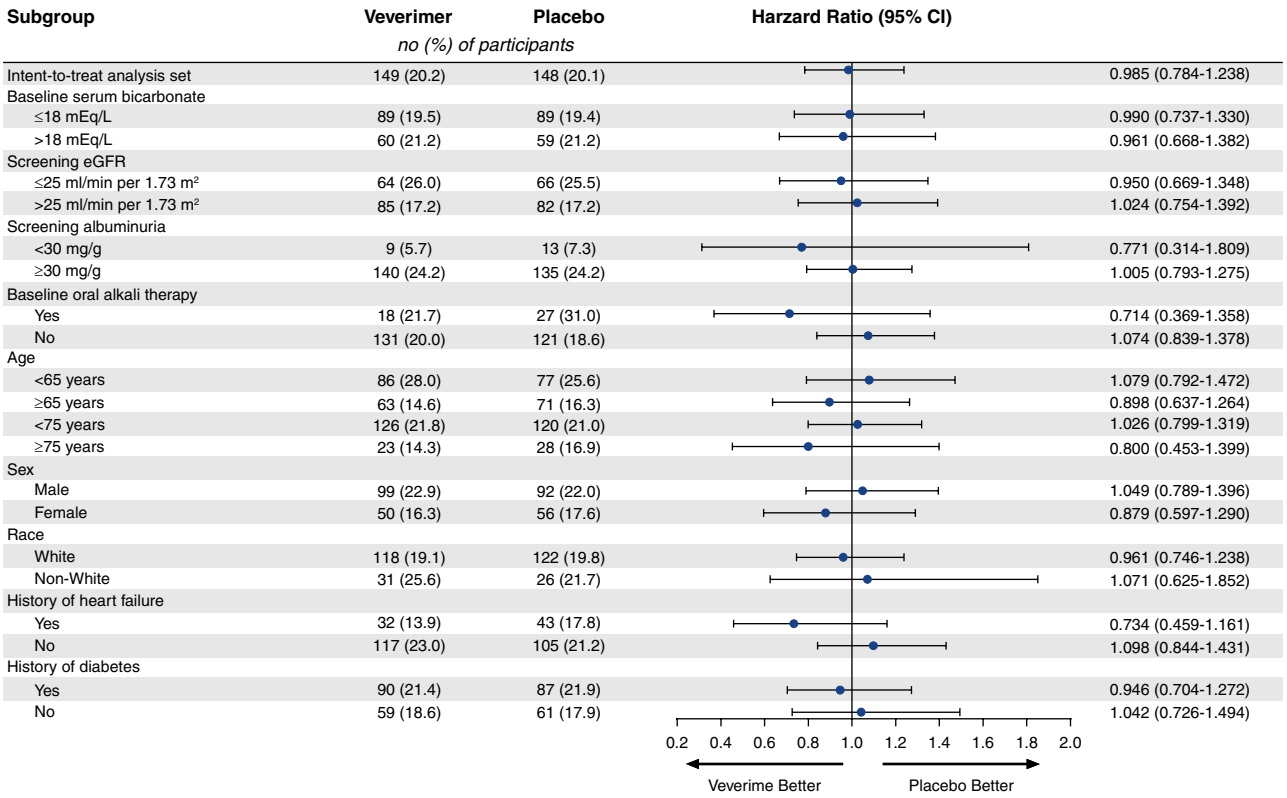


Figure 2. Primary outcome according to prespecified subgroups at baseline. Forest plots of the hazard ratios for the primary outcome (a composite of a sustained decline in the eGFR of ≥40%, ESKD, or renal death) according to prespecified baseline subgroups. Hazard ratios and CIs were calculated with a Cox proportional hazards model for each subgroup, adjusting for age, sex, history of diabetes, and baseline stratification variables. All interaction *P* values were >0.10. Figure 2 can be viewed in color online at www.jasn.org.

baseline was 11.2% in the veverimer group and 11.8% in the placebo group. During follow-up, among patients not on alkali at baseline, 4.2% of the patients in the veverimer group and 6.4% in the placebo group received oral alkali supplementation.

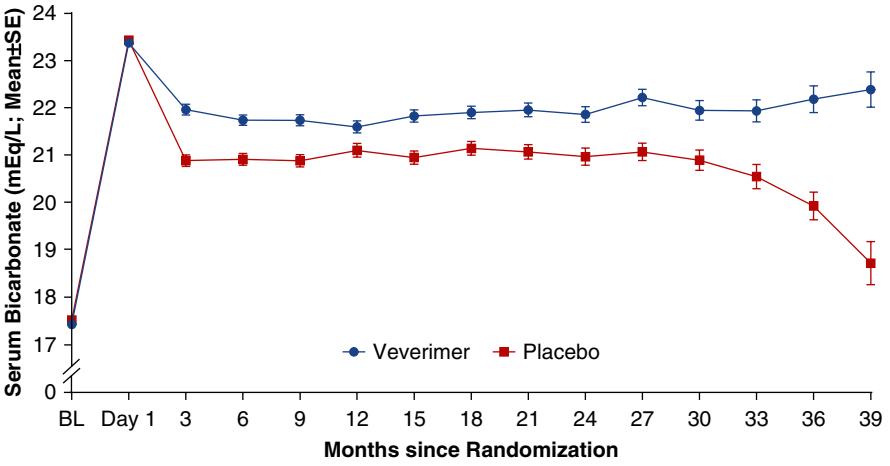
Safety Outcomes and Adverse Events

The incidence of adverse events and serious adverse events was similar overall in the veverimer and placebo groups (Table 2 and Supplemental Table 1). There were no apparent effects of veverimer on UACR or BP (Supplemental Figures 3 and 4 and Supplemental Table 3). Gastrointestinal adverse events were reported in 12.6% and 12.2%, respectively, in the veverimer and placebo groups. Analyses of laboratory parameters, including electrolytes, hematology, liver tests, lipids, glucose, parathyroid hormone, and hemoglobin A1c, revealed no notable differences between groups.

DISCUSSION

In this multicenter, randomized, double-blind, placebo-controlled trial in non–dialysis-dependent patients with CKD and metabolic acidosis, treatment with veverimer did not slow the progression of CKD. No benefit of treatment was observed on the physical function outcomes or any cardiovascular or kidney outcomes. Safety data from this study revealed that the overall safety profile of veverimer was similar to placebo with no increase in the frequency of serious adverse events, adverse events leading to treatment discontinuation, and all-cause or cardiovascular death compared with placebo over an up to approximately 3.25 years of follow-up. The trial was terminated early due to an administrative stop, but it is unlikely that a longer duration of follow-up would have changed the primary or secondary findings.

The VALOR-CKD trial was designed to enroll adults with moderate or severe chronic metabolic acidosis, with 3 individual serum bicarbonate values between 12 and 20 mEq/L, performed 2 weeks apart. Epidemiologic data show incremental increased risk for adverse kidney outcomes associated with each 1 mEq/L change in serum bicarbonate.[12] On the basis of the hypothesis that effects of veverimer on CKD progression would be secondary to its effects on treating metabolic acidosis, we included an active run-in period with requirement for a response (≥4 mEq/L or achieved normal serum bicarbonate) on which randomization was contingent. On the basis of the previous studies with veverimer,[7–9] we expected the placebo group to return



No. of Participants															
Veverimer	739	739	709	688	650	598	595	561	475	387	348	261	188	123	67
Placebo	737	736	712	682	662	602	595	574	471	390	352	284	197	120	64

Figure 3. Change in serum bicarbonate. Mean serum bicarbonate during the study. The I bars indicate SEM. BL denotes baseline. Day 1 is the day of randomized withdrawal to veverimer or placebo, following an active treatment run-in period. Figure 3 can be viewed in color online at www.jasn.org.

to a serum bicarbonate level of 17–18 mEq/L postrandomization withdrawal and for the active treatment to maintain serum bicarbonate levels in t/he 21–22 mEq/L range for the duration of the trial, thus leading to a separation of approximately 3–5 mEq/L. This degree of serum bicarbonate separation did not occur. Despite a mean screening period serum bicarbonate level of 17.4 mEq/L, the postrandomization withdrawal serum bicarbonate in the placebo group was approximately 21 mEq/L through the first 30 months of the study. A possible cause for this observation is that the true baseline was the higher value and that the serum bicarbonate values during the 4–6 week of screening reflected a transient period of acute on chronic metabolic acidosis (*e.g.*, due to diet, AKI, volume expansion) in a significant number of the patients. Given that in the many countries' serum bicarbonate is not routinely measured, investigators may not have been aware that these values did not reflect the patient's typical values.

Variability in the measurement of serum bicarbonate (*e.g.*, related to volume status, respiratory status, and eGFR) may also have contributed to an inaccurate ascertainment of a stable baseline. Alternative explanations such as a long-term improvement in the kidney's ability to excrete acid with 4–8 weeks of veverimer treatment during the run-in period are unlikely, given that veverimer is not absorbed and the short offset of effect observed in earlier studies.[13–15] Similarly, a long-term change in diet due to dietary counseling in the placebo group is also an unlikely explanation given that dietary counseling alone, without the provision of food, has been shown to be ineffective for the treatment of metabolic acidosis.[16] As with earlier trials, the mean achieved serum bicarbonate in the veverimer group was approximately

Table 2. Summary of safety events in part B

Event Category	Veverimer (*n*=739)	Placebo (*n*=737)
Any adverse event, *no.* (%)[a]	461 (62.4)	452 (61.3)
Any serious adverse event, *no.* (%)	197 (26.7)	205 (27.8)
Any study drug-related adverse event, *no.* (%)	34 (4.6)	32 (4.3)
Any COVID-19–related adverse event, *no.* (%)	60 (8.1)	74 (10.0)
Drug interruption due to adverse event, *no.* (%)	49 (6.6)	44 (6.0)
Drug discontinuation due to adverse event, *no.* (%)	85 (11.5)	81 (11.0)
Most common adverse events (≥5% in veverimer group), *no.* (%)		
Hypertension	65 (8.8)	71 (9.6)
Hyperkalemia	55 (7.4)	43 (5.8)
COVID-19	39 (5.3)	54 (7.3)
Headache	39 (5.3)	37 (5.0)
Anemia	38 (5.1)	36 (4.9)

COVID-19, coronavirus disease 2019.
[a]Participants with multiple events were counted only once at the highest severity in each category.

22 mEq/L, but the placebo subtracted treatment effect in earlier trials of 3–5 mEq/L was not achieved in this trial due to a larger than expected sustained increase in the serum bicarbonate levels in the placebo group.[9] The lack of a washout period between the active run-in period and randomized phase of the study was a potential limitation of the study design as this might have identified patients whose bicarbonate failed to return to their screening baseline.

Our negative findings on the effect of long-term treatment of metabolic acidosis and the lack of improvement in GFR or serum bicarbonate levels are consistent with other multicenter, double-blind, placebo-controlled trials of oral alkali therapy.[17,18] Although single-center or unblinded studies of oral alkali therapy have yielded positive results,[19–21] studies that included blinding and a placebo control are consistently negative for the CKD progression end point and have failed to achieve a sustained increase in serum bicarbonate levels of >2 mEq/L for more than 1 year.[17,18] It is important to note that the negative studies have largely been conducted in patients with normal serum bicarbonate or mild metabolic acidosis. We believe that future trials of therapies targeting metabolic acidosis to slow CKD progression may require a longer run-in period to establish chronicity and severity of disease and target a separation of 3–4 mEq/L between the active and control groups.

Treatment with veverimer was similar in its safety and tolerability to placebo in this diverse older patient population with more than 2 years of follow-up. These safety findings, coupled with previous studies of veverimer demonstrating no evidence of drug–drug interactions,[22] and the lack of systemic absorption[6] suggest that the drug would be safe to test in other populations where oral alkali therapy is currently used. These indications may include pediatric and adult populations with renal tubular acidosis where raising serum bicarbonate levels is the primary goal of therapy or in patients with kidney stones where alkalinization of the urine may be beneficial to prevent stone formation. A proportion of patients with these conditions have an intolerance or inadequate response to oral alkali and may benefit from a safe and well-tolerated treatment option.

In conclusion, among patients with CKD and metabolic acidosis, treatment with veverimer did not reduce the risk of CKD progression. The effect of veverimer on serum bicarbonate levels, compared with placebo, was less than expected and may have limited our ability to detect a change in clinical outcomes.

DISCLOSURES

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DATA SHARING STATEMENT

Data cannot be shared. Data now belongs to Renibus Inc. who acquired this molecule in bankruptcy proceedings. The authors have access to the data but do not have authority to share.

SUPPLEMENTAL MATERIAL

This article contains the following supplemental material online at http://links.lww.com/JSN/E572.

Members of the VALOR-CKD Steering Committee
VALOR-CKD Investigators
Members of the VALOR-CKD Independent Data Monitoring Committee
Members of the VALOR-CKD Clinical Endpoint Adjudication Committee
Supplemental Methods
Inclusion Criteria for Enrollment
Exclusion Criteria for Enrollment
Inclusion Criteria for Randomization
Exclusion Criteria for Randomization
Supplemental Figure 1. Study design.
Supplemental Figure 2. Study participant disposition.
Supplemental Figure 3. Box and whisker plot systolic BP by the treatment group over time (randomized safety analysis set).
Supplemental Figure 4. Box and whisker plot diastolic BP by treatment group over time (randomized safety analysis set).
Supplemental Table 1. All adverse events by preferred term.
Supplemental Table 2. Incidence of death in part B by cause as determined by the CEAC (intent-to-treat analysis set).
Supplemental Table 3. Change from baseline to end of treatment in spot urine albumin-creatinine ratio.

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