Veverimer versus placebo in patients with metabolic acidosis associated with chronic kidney disease: a multicentre, randomised, double-blind, controlled, phase 3 trial

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Summary

Background Patients with advanced chronic kidney disease lose the capacity to fully excrete endogenous acid, resulting in chronic metabolic acidosis that increases the risk of disease progression and causes muscle catabolism and bone resorption. Veverimer, a non-absorbed, counterion-free, polymeric drug, selectively binds and removes hydrochloric acid from the gastrointestinal lumen, unlike current oral sodium bicarbonate therapy for metabolic acidosis that only neutralises accumulated acid. We assessed the efficacy and safety of veverimer as a treatment for metabolic acidosis in patients with chronic kidney disease.

Methods We did a multicentre, parallel, randomised, double-blind, placebo-controlled study at 37 sites (hospitals and specialty clinics) in Bulgaria, Croatia, Georgia, Hungary, Serbia, Slovenia, Ukraine, and the USA. Eligible participants were patients aged 18–85 years with non-dialysis-dependent chronic kidney disease (estimated glomerular filtration rate of 20–40 mL/min per 1·73 m²) and metabolic acidosis (serum bicarbonate concentration of 12–20 mmol/L). Patients were randomly assigned (4:3) to veverimer 6 g/day or placebo for 12 weeks while they consumed their typical diet. Both drugs were taken as oral suspensions in water with lunch. Randomisation was done by study site personnel with a computer-generated randomisation code with balanced permuted blocks (block size of seven) and stratified by baseline bicarbonate (≤18 mmol/L *vs* >18 mmol/L). Patients and investigators were masked to treatment allocation; however, because the appearance of placebo differed from veverimer, a non-masked site staff member who had no other role in the study dispensed, prepared, and supervised dosing of the study drugs. The composite primary efficacy endpoint was the difference (veverimer–placebo) in the proportion of patients achieving at week 12 either an increase of 4 mmol/L or more from baseline in serum bicarbonate concentration or serum bicarbonate in the normal range of 22–29 mmol/L, assessed in the modified intention-to-treat population (all patients with a baseline and at least one post-baseline serum bicarbonate value). Patients fasted for at least 4 h (consuming only water) before measurements of bicarbonate. Safety was assessed in all patients who received any amount of study drug. This trial is registered with ClinicalTrials.gov, number NCT03317444.

Findings Between Sept 26, 2017, and Feb 9, 2018, we randomly assigned 124 participants to veverimer and 93 to placebo. The composite primary endpoint was met by 71 (59%) of 120 patients in the veverimer group versus 20 (22%) of 89 patients in the placebo group (a difference of 37%, 95% CI 23–49; p<0·0001). The most common body system in which adverse events in the veverimer group occurred was gastrointestinal; of these, non-treatment limiting diarrhoea was the most common event (11 [9%] *vs* three [3%] in the veverimer and placebo groups, respectively). The most common treatment-related adverse events were gastrointestinal (diarrhoea, flatulence, nausea, and constipation) occurring in 16 (13%) patients with veverimer and five (5%) patients with placebo. Two deaths occurred during the study, both in the placebo group (unstable angina and pneumonia).

Interpretation Veverimer effectively and safely corrected metabolic acidosis. Longer-term studies are warranted to assess the effects of veverimer on physical functioning and to assess other deleterious consequences of metabolic acidosis including progression of chronic kidney disease and bone health.

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Introduction

The loss of kidney function reduces the capacity to excrete acid generated from metabolism, resulting in chronic metabolic acidosis. Observational data show that 21% of patients with an estimated glomerular filtration rate (eGFR) of 30–44 mL/min per 1·73 m² and 36% of patients with an eGFR of less than 30 mL/min per 1·73 m² have metabolic acidosis.[1] These prevalence estimates might not fully reflect the proportion of patients with chronic kidney disease who have adverse effects related to acid retention and have been able to maintain serum bicarbonate in the normal range at the expense of bone resorption and increased skeletal muscle catabolism.[2–6] Several observational and several small-scale prospective interventional

Research in context

Evidence before this study

Chronic metabolic acidosis is a common complication of chronic kidney disease that is due to failure to completely excrete metabolically produced acid and is associated with unfavourable outcomes including disturbed protein and bone mineral metabolism. Findings from epidemiological studies and some small-scale prospective interventional trials support that metabolic acidosis also contributes to progressive worsening of chronic kidney disease toward end-stage kidney disease. These data support an additional, and arguably more urgent, need for effective treatment strategies for metabolic acidosis. We reviewed the scientific literature for English-language articles published between January, 1960, and August, 2018, using "metabolic acidosis treatment" as a search phrase, and identified two major treatment strategies: 1) oral sodium-based alkali that enters the systemic circulation to neutralise accumulated acid and 2) reduction of dietary acid intake to a level below that at which the compromised kidney acid excretory capacity is sufficient to excrete more completely the smaller accumulated acid load. Both strategies have challenges that limit their usefulness in at least some patients with chronic kidney disease. Individuals with a very low glomerular filtration rate that limits their capacity to excrete metabolically produced acid also have decreased capacity to excrete the obligate sodium load that accompanies treatment with sodium-based alkali, making them susceptible to exacerbation of hypertension and concomitant oedematous states. Furthermore, low-acid diets are high in base-producing components such as fresh fruits and vegetables and low in processed foods such as meats that are acid-producing, which can be difficult to sustain in individuals with low incomes. A more physiologically and clinically attractive treatment would be an easily administered oral drug that removed acid from the body without entering the systemic circulation.

Added value of this study

This multicentre, parallel, randomised, double-blind, placebo-controlled study assessed the efficacy and safety of veverimer, a non-absorbed, counterion-free, polymeric drug that selectively binds and removes hydrochloric acid from the gastrointestinal lumen, in the treatment of metabolic acidosis in patients with chronic kidney disease. The primary endpoint for improvement of metabolic acidosis was met in significantly more patients assigned to veverimer than those assigned placebo. Additionally, the veverimer-treated patients had improved quality of life related to physical functioning on the Kidney Disease and Quality of Life Short Form-36 Physical Functioning subscale (p=0·0122) compared with placebo-treated patients and there were no significant safety findings. These data show that veverimer effectively treated metabolic acidosis related to chronic kidney disease by the innovative mechanism of acid binding and excretion from the gastrointestinal tract without the medication entering the systemic circulation and does so with a favourable safety profile.

Implications of all the available evidence

These data show that metabolic acidosis in chronic kidney disease can be effectively treated by the more physiologically desirable mechanism of acid removal with veverimer, with a favourable safety profile. This strategy avoids the challenges of the two currently available treatment strategies and holds promise for its use to treat the metabolic acidosis of a wider spectrum of patients with chronic kidney disease.

studies indicate that metabolic acidosis is not only a consequence of chronic kidney disease, but also a modifiable risk factor for the disease's progression.[7–15] A review[16] of the mechanisms by which metabolic acidosis leads to progression of chronic kidney disease discussed how adaptive renal mechanisms intended to facilitate acid removal, such as stimulation of endothelin, angiotensin II, and aldosterone, and the process of ammoniagenesis promote renal inflammation and fibrosis.[16]

In clinical practice, patients with chronic kidney disease can be treated with oral sodium bicarbonate to neutralise retained acid. However, for patients unable to tolerate the additional sodium intake, such as those with advanced chronic kidney disease and hypertension, heart failure, or volume overload, treatment options are scarce, particularly since potassium-containing alkali salts might also be contraindicated in this population. Gastrointestinal intolerability of sodium bicarbonate can also be treatment-limiting for some patients.[17,18] Alternatively, patients can be treated with diets that are high in base-producing components that lower endogenous acid production such as fresh fruits and vegetables and low in processed foods such as meats that are acid-producing. However, compliance with these diets is difficult for patients; in one study, only 14% of patients who were enrolled on a low-protein diet run-in phase were sufficiently compliant to qualify for randomisation.[9]

Veverimer (formerly designated TRC101) is a drug being developed as a first-in-class hydrochloric acid binder for the treatment of metabolic acidosis. It is a non-absorbed polymer composed of low-swelling, spherical beads that selectively bind and remove hydrochloric acid from the gastrointestinal lumen through the faeces. The chemical composition and degree of crosslinking of the veverimer polymer determines its ion-binding properties. Veverimer is a neutral, polymeric base (polyamine) that becomes protonated once ingested, and has high proton binding capacity (>5 mmol/g) across the physiological gastrointestinal pH range (1·5–7). Once protonated, the resulting charged amine groups on the polymer are neutralised with anions in the gastrointestinal lumen. The high degree of crosslinking in the polymer restricts access to the protonated binding sites of veverimer,

allowing preferential binding of chloride, the most abundant and smallest anion in the upper gastrointestinal tract. The chloride selectivity prevents the polymer from removing larger anions (eg, short-chain fatty acids) from the intestine that might be metabolised to base and from subsequent exchange of intestinal chloride with systemic bicarbonate.[19] Mechanistically, removing hydrochloric acid from the gastrointestinal tract through binding to a non-absorbed polymer that is then excreted is more specific than, but similar to, removing gastric acid via nasogastric suction or vomiting, both of which increase serum bicarbonate. Thus, the mechanism of action of veverimer in treating metabolic acidosis is fundamentally different from acid neutralisation by bicarbonate supplementation.

We hypothesised that removal of gastrointestinal acid with veverimer would be a safe and effective treatment for metabolic acidosis associated with chronic kidney disease. Veverimer is not an ion-exchange polymer (ie, it does not contain a counterion); therefore, ions that are potentially deleterious to these patients such as sodium and potassium are not released when acid is bound. In a first-in-human, randomised controlled trial in non-dialysis-dependent patients with chronic kidney disease and metabolic acidosis, done in clinical research units where a standardised low protein diet (around 0·7 g/kg per day) was administered, 2 weeks of veverimer (3, 6, or 9 g/day) significantly increased serum bicarbonate concentrations by 3–4 mmol/L compared with placebo ($p<0·0001$).[20] Although this study provided proof-of-concept for the mechanism of action of veverimer, the slope of the increase in serum bicarbonate did not plateau during the short treatment period of this study. The maximum effect of veverimer on serum bicarbonate, whether the effect would be maintained over a longer treatment duration, and how veverimer would affect serum bicarbonate in situations of variable, and probably higher, outpatient dietary protein intake are unknown. To answer these questions, and to explore the effects of acidosis correction on measures of clinical benefit (eg, patient-reported outcomes and physical function), we undertook a trial in outpatients with chronic kidney disease and metabolic acidosis who were consuming their typical diet over a 12-week treatment period.

Methods

Study design and participants

We did a multicentre, parallel, randomised, double-blind, placebo-controlled study at 37 sites (hospitals and specialty clinics) in eight countries (Bulgaria, Croatia, Georgia, Hungary, Serbia, Slovenia, Ukraine and the USA). The study protocol (appendix) was approved by each site's relevant institutional review board or ethics committee and appropriate competent authorities in accordance with applicable laws and regulations.

Eligible participants were patients with non-dialysis-dependent chronic kidney disease aged 18 to 85 years with a systolic blood pressure of less than 170 mm Hg and glycated haemoglobin A_{1c} of 9% (75 mmol/mol) or less. During the screening period (up to 2 weeks), three qualifying fasting serum bicarbonate values over 14 days were required to establish eligibility; the first two values and the average of all three were required to be within the range 12–20 mmol/L. Two qualifying eGFR values not different by more than 20% and in the range of 20–40 mL/min per 1·73 m² were required during screening.

Exclusion criteria were: serum bicarbonate concentration low enough to need emergency intervention or assessment for an acute acidotic process, or anuria, dialysis, or acute or chronic worsening renal function (eg, ≥30% decline in eGFR) in the 3 months before the first screening visit; recent history of chronic obstructive pulmonary disease, heart failure with New York Heart Association Class IV symptoms, stroke, transient ischaemic attack, cancer, cardiac event, diabetic gastroparesis, bariatric surgery, bowel obstruction, swallowing disorders, severe gastrointestinal disorders, or hospitalisation other than for pre-planned diagnostic or minor invasive procedures; a heart or kidney transplantation, and planned initiation of renal replacement therapy within 12 weeks; a liver enzyme (alanine aminotransferase, aspartate aminotranferase, or total bilirubin) concentration of more than three times the upper limit of normal; and a serum calcium concentration of 2 mmol/L or less or a serum potassium concentration of less than 3·8 mmol/L or more than 5·9 mmol/L. Concomitant medication requirements for study participation precluded use of any other investigational medication as well as other binder drugs (except for short-term use of potassium binders for treatment of hyperkalaemia) and required stable doses (whenever possible) of the following if they were used: calcium-containing supplements; antacids; histamine H_2-blockers; proton pump inhibitors; oral alkali; diuretics; renin-angiotensin-aldosterone system inhibitors; and non-ophthalmic carbonic anhydrase inhibitors. Dosing of oral concomitant medications and study drug was separated by at least 4 h. Before enrolment, all patients provided written informed consent.

Randomisation and masking

Eligible patients were randomly assigned (4:3) to veverimer 6 g/day or placebo for 12 weeks. Randomisation was done by study site personnel via a centralised interactive response technology system using a computer-generated randomisation code with balanced permuted blocks (block size of seven). The random allocation sequence was verified by an independent statistician. The protocol called for randomisation to be stratified by screening eGFR (<30 *vs* ≥30 mL/min per 1·73 m²) and baseline bicarbonate (≤18 mmol/L *vs* >18 mmol/L). After the study was unmasked, the interactive response technology system was discovered to have only been programmed to stratify by baseline bicarbonate strata. As

See Online for appendix

a result, the actual ratio of veverimer to placebo patients with an eGFR of at least 30 mL/min per 1·73 m² was 1·6:1 and the actual ratio of patients with an eGFR of less than 30 mL/min per 1·73 m² was 1·2:1, instead of the planned ratio of approximately 1·3:1 for each of the two eGFR strata.

Because the appearance and weight of veverimer and placebo were not identical, study drug dispensing, preparation, supervision of the patient's first dose in the clinic, and study drug accountability were done by an unmasked designated site staff member who had no other responsibilities for the study. The study sponsor, statistician, investigators, patients, and all contract research organisation staff (except personnel responsible for monitoring drug dispensing and accountability records) remained masked to treatment assignments throughout the study. Site personnel were trained on masking requirements, and these requirements were detailed in a masking plan.

Procedures

The starting study drug dose was 6 g/day veverimer (two packets per day) or placebo (two packets per day) administered orally as a suspension in water with lunch. The first dose was administered in the clinic on the day of randomisation, after which patients self-administered the study drug for 12 weeks and recorded the dose in a diary, which was reviewed, together with used and unused study drug returned at each visit. Beginning at week 4, the study drug dose was algorithmically titrated by the interactive response technology system in the range from 0–9 g/day (or equivalent number of packets of placebo) to a target bicarbonate concentration of 22–29 mmol/L based on the bicarbonate measurement at each visit. The dose was down-titrated if bicarbonate was in the high to normal range (27–30 mmol/L) and interrupted if it was more than 30 mmol/L (appendix).

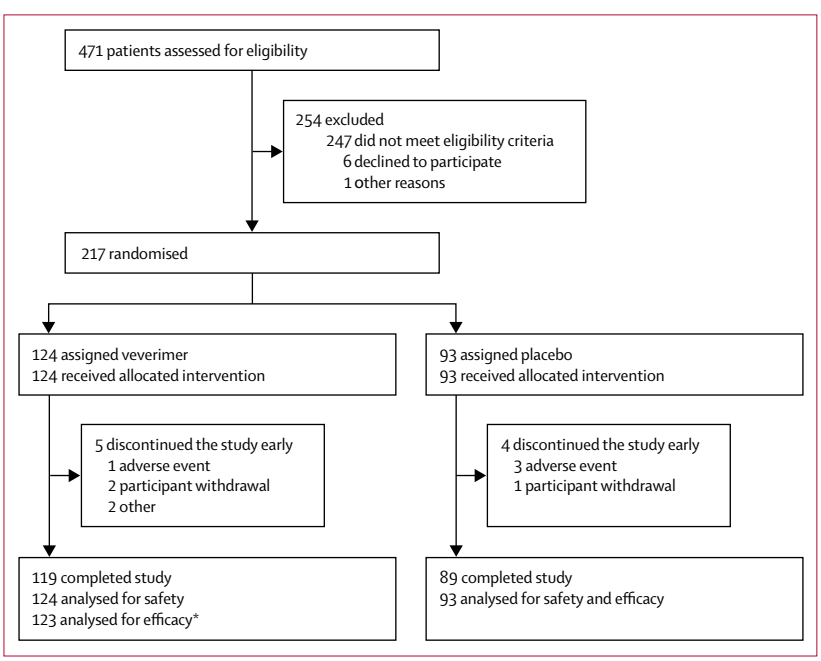

Figure 1: **Trial profile**
Screen failures due to bicarbonate or eGFR ineligibility accounted for most enrolment exclusions. *One excluded from efficacy analysis because of no post-baseline bicarbonate values.

Screening 1 and screening 2 visits were at least 5 days apart, and screening 1 and baseline visits were no more than 14 days apart. Following randomisation, patients attended scheduled visits at weeks 1, 2, 4, 6, 8, 10, and 12 during which serum bicarbonate was measured using an i-STAT Handheld Blood Analyzer (Abbott Point of Care, Princeton, NJ, USA) and safety assessments were done (appendix). Patients fasted for at least 4 h (consuming only water) before measurements of bicarbonate concentrations to reduce the indirect effect of food-induced secretion of bicarbonate into the bloodstream. Venous blood for bicarbonate measurement was drawn into a 2 mL lithium heparin tube and transferred with a mini-pipette as soon as possible (within 10 min) into an i-STAT G3+ cartridge for assessment of bicarbonate with the iSTAT device. Tubes were capped until blood was transferred into the cartridge, and strict adherence to blood drawing and transfer techniques were required, as described in the study laboratory manual. The i-STAT devices were calibrated before and during the study according to the manufacturer's recommendations. The Kidney Disease and Quality of Life (KDQoL) Short Form (SF)-36, question 3 (physical functioning domain) and standardised repeated chair-stand test were administered at baseline and week 12. The KDQoL physical function domain, which quantifies patients' self-reported degree of limitation in doing daily activities such as climbing stairs and walking (appendix), was forward and backwards translated, linguistically validated, culturally adapted, reviewed by clinicians, and cognitively debriefed (ie, using an interview-based technique to identify and solve any potential issues with translation of the instrument) patients with chronic kidney disease (appendix). Following completion of study treatment at week 12, patients either rolled over into a 40-week extension study or underwent two follow-up visits (at weeks 13 and 14) after the last dose of study drug; the extension study is still ongoing.

Outcomes

The composite primary endpoint was the difference (veverimer–placebo) in the proportion of patients meeting the responder definition; ie, achieving an increase of 4 mmol/L or more from baseline in serum bicarbonate at week 12 or a serum bicarbonate concentration in the normal range (22–29 mmol/L) at week 12. The primary endpoint was based on measurement of bicarbonate at the study sites using the i-STAT point of care device. Because bicarbonate measurement is susceptible to error when samples are not immediately analysed, central laboratory assessment of bicarbonate was not done. The secondary endpoint was the least-squares (LS) mean change from baseline in serum bicarbonate to week 12.

Baseline was defined as the mean of the bicarbonate values at screenings 1 and 2 and day 1 (pre-dose). The protocol pre-specified two exploratory efficacy endpoints: the change from baseline to week 12 in the total score of the KDQoL physical function domain and the duration of the repeated chair-stand test, which measured the time to complete, as rapidly as possible, repeated standing from a chair five times.[21] The range for the minimal clinically important differences reported for the KDQoL subscales is 3–5 points.[22–25] Safety was assessed through adverse events collection, vital signs, 12-lead electrocardiograms (ECGs), laboratory tests (chemistry, lipids, haematology, urinalyses), and physical examination.

	Veverimer (n=124)	Placebo (n=93)
Age (years)	62·9 (12·6)	63·2 (12·1)
Age ≥65 years	65 (52%)	48 (52%)
Sex		
Male	74 (60%)	60 (65%)
Female	50 (40%)	33 (35%)
Race		
White	121 (98%)	89 (96%)
Black or African American	3 (2%)	3 (3%)
Multiple	0	1 (1%)
Region		
Europe	113 (91%)	77 (83%)
USA	11 (9%)	16 (17%)
Body-mass index (kg/m²)	28·8 (4·2)	28·3 (4·1)
Systolic blood pressure (mm Hg)	136·1 (9·1)	136·5 (9·1)
Selected medical history		
Hypertension	120 (97%)	90 (97%)
Diabetes	76 (61%)	65 (70%)
Dyslipidaemia or hyperlipidaemia	73 (59%)	50 (54%)
Left ventricular hypertrophy	58 (47%)	38 (41%)
Congestive heart failure	36 (29%)	31 (33%)
Percutaneous coronary intervention or coronary bypass graft	22 (18%)	18 (19%)
Myocardial infarction	18 (15%)	13 (14%)
Stroke	9 (7%)	11 (12%)
Peripheral vascular disease	5 (4%)	9 (10%)
Atrial fibrillation or atrial flutter	7 (6%)	6 (6%)
Peripheral vascular disease intervention or surgical arterial bypass	1 (1%)	3 (3%)
Transient ischaemic attack	1 (1%)	0
Cause of chronic kidney disease		
Diabetes and hypertension	41 (33%)	28 (30%)
Hypertension	37 (30%)	29 (31%)
Diabetes	17 (14%)	19 (20%)
Glomerulonephritis	8 (6%)	8 (9%)
Interstitial nephritis	7 (6%)	3 (3%)
Cystic renal disease	5 (4%)	4 (4%)
Other	9 (7%)	2 (2%)
(Table 1 continues in next column)		
(Continued from previous column)		
Medication use		
Sodium bicarbonate	12 (10%)	7 (8%)
ACE inhibitors or ARBs	83 (67%)	76 (82%)
Diuretics	74 (60%)	59 (63%)
Loop	46 (37%)	43 (46%)
Thiazide	40 (32%)	28 (30%)
Loop plus thiazide	13 (10%)	12 (13%)
Calcium-channel blockers	69 (56%)	56 (60%)
Anti-diabetic drugs	66 (53%)	52 (56%)
β blockers	57 (46%)	49 (53%)
Lipid-modifying agents	55 (44%)	49 (53%)
Anti-thrombotic agents	47 (38%)	45 (48%)
Drugs for acid-related disorders	12 (10%)	6 (6%)
Calcium carbonate	1 (1%)	0
Laboratory values		
Serum bicarbonate (mmol/L)	17·3 (1·4)	17·3 (1·5)
>18 mmol/L	43 (35%)	32 (34%)
≤18 mmol/L	81 (65%)	61 (66%)
Venous blood pH	7·30 (0·08)	7·30 (0·08)
Venous blood base excess (mmol/L)	−9·2 (2·2)	−9·1 (2·2)
Estimated GFR (mL/min per 1·73 m²)	29·2 (6·3)	27·8 (5·4)
Blood urea nitrogen (mmol/L)	13·8 (4·9)	13·6 (4·8)
Serum creatinine (μmol/L)	194·9 (52·5)	205·3 (55·3)
Serum sodium (mmol/L)	139·8 (2·6)	139·3 (2·9)
Serum potassium (mmol/L)	4·9 (0·6)	4·9 (0·6)
Serum chloride (mmol/L)	107·0 (3·7)	107·3 (4·7)
Serum calcium (mmol/L)	2·32 (0·14)	2·27 (0·13)
Serum phosphate (mmol/L)	1·21 (0·20)	1·23 (0·20)
Serum magnesium (mmol/L)	0·87 (0·11)	0·86 (0·10)
Haemoglobin (g/L)	124·6 (18·3)	125·5 (17·7)
Urine albumin-to-creatinine ratio (mg/mmol)*	24·8 (17·4–35·4)	36·7 (24·7–54·3)
Physical functioning		
KDQOL SF-36 physical function domain total score†	53·3 (23·6)	54·1 (27·1)
Repeated chair stand (s)‡	17·3 (11·6)	15·5 (8·8)

Data are mean (SD), n (%), or geometric mean (95% CI). ACE=angiotensin converting enzyme. ARB=angiotensin II receptor blockers. GFR=glomerular filtration rate. KDQOL SF-36=Kidney Disease and Quality of Life, Short Form-36. *Values are from a spot urine collection. †Veverimer n=123; placebo n=93. ‡Veverimer n=111; placebo n=79.

Table 1: **Baseline characteristics of all enrolled participants**

Statistical analysis

On the basis of data from a previous study,[20] we assumed that the primary endpoint responder definition would be met by 50–55% of veverimer-treated patients and by 10% of placebo-treated patients. Therefore, a sample size

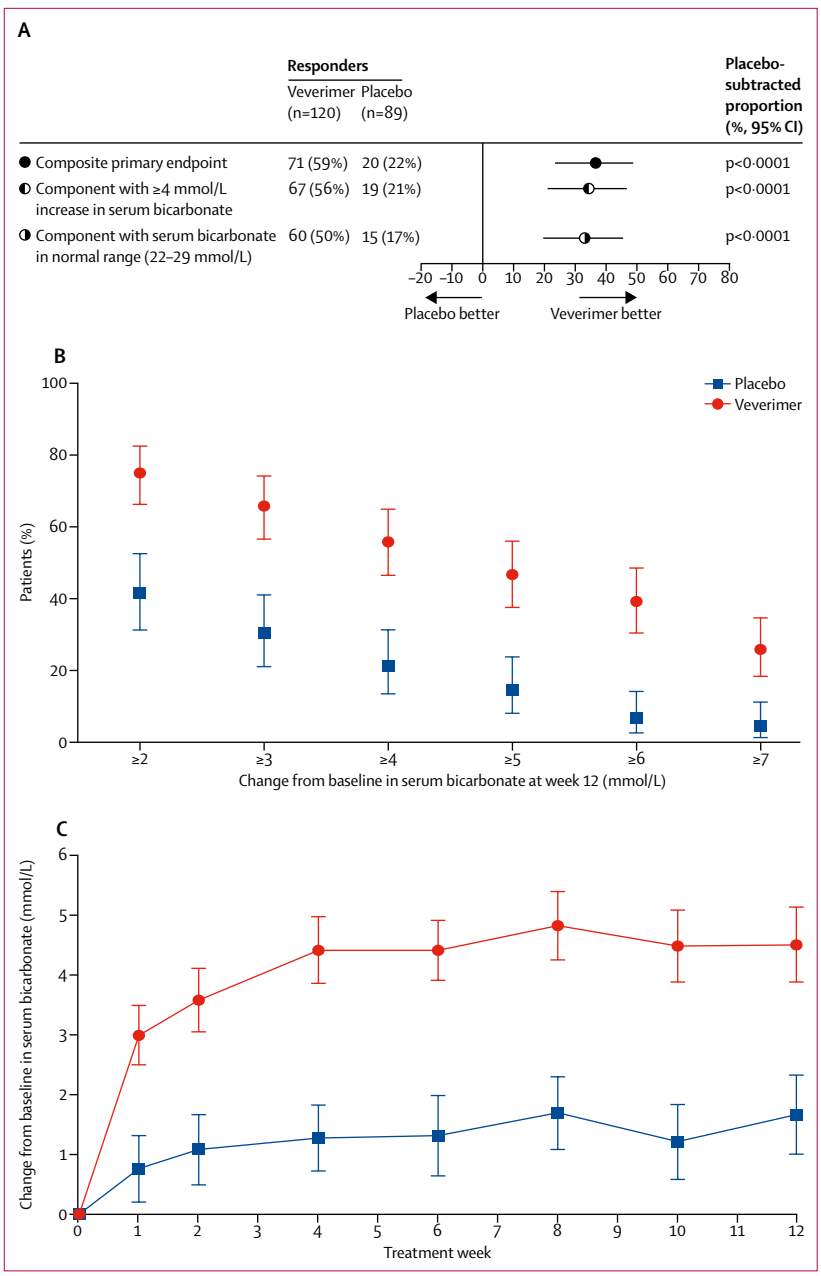

Figure 2: **Change in serum bicarbonate**
In panel A, the top line shows the composite primary endpoint at treatment week 12. The two lower lines depict each component of the primary endpoint. p values are for the difference in proportions between the veverimer and placebo groups. Panel B shows the percentage (95% CI) of patients in the treatment groups whose serum bicarbonate concentrations increased from baseline to week 12 by pre-specified thresholds. Achieving a ≥4 mmol/L increase was a component of the primary endpoint. The baseline bicarbonate concentration (treatment week 0; ie, the mean of the screening 1, screening 2, and baseline day 1 values) was 17·3 mmol/L in both treatment groups (panel C). Values depicted are the least-squares mean (95% CI) changes from baseline in serum bicarbonate (mmol/L).

of 120 patients in the veverimer group and 90 patients in the placebo group would provide 99% power with a 0·05 two-sided significance level using Fisher's exact test. We analysed the primary, secondary, and exploratory endpoints according to the prespecified statistical analysis plan. The individual primary endpoint component analyses were pre-specified but not adjusted for multiple comparisons.

A modified intention-to-treat analysis set, defined as all randomly assigned patients who had a baseline and at least one post-baseline serum bicarbonate value, was used for assessment of efficacy, based on planned treatment assignment. The main analyses (ie, analyses other than sensitivity analyses) did not impute missing data, which in both the placebo and veverimer groups were assumed to be missing at random. Pre-specified per-protocol and sensitivity analyses were done for the primary and secondary efficacy endpoints (appendix). The sensitivity analyses used a multiple imputation method[26] under a missing-not-at-random assumption. The missing data from participants in both treatment groups who discontinued early were constructed from the observed data in the placebo group (appendix).

To control family-wise error rate, hypothesis testing for the primary and secondary endpoints was pre-specified to be done sequentially. Only when the primary endpoint was statistically significant could the analysis for the secondary endpoint be done; ie, the between-group comparison of the mean change in serum bicarbonate from baseline to week 12 using a longitudinal mixed model for repeated measures (MMRM) with baseline bicarbonate and baseline eGFR as continuous covariates and treatment, timepoint, and treatment by timepoint interactions as fixed effects. Statistical significance was defined as a two-sided p value of less than 0·05.

The safety analysis set was defined as all patients who received any amount of study drug (veverimer or placebo) and was used for assessment of safety based on the actual treatment received. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA version 20.0), and safety parameters were summarised descriptively.

The exploratory efficacy endpoints, the total score of the KDQoL SF-36 question 3 (physical function domain) and the repeated chair stand test duration, were analysed with ANCOVA models. The KDQoL SF question 3 individual item scores were transformed by recoding scores of 1, 2, and 3 to 0, 50, and 100, respectively. The total score was the average of the recoded individual scores. The ANCOVA models comprised the change from baseline total score or repeated chair stand test duration as the dependent variable, treatment group as a fixed effect, and baseline value, baseline eGFR, and baseline serum bicarbonate as continuous covariates.

Pre-specified subgroup analyses based on screening eGFR, baseline bicarbonate, geography, demographic factors, and alkali use, and threshold analyses describing the proportion of patients achieving certain pre-specified bicarbonate concentrations at week 12 were analysed using a two-side exact (Clopper-Pearson) 95% CI.

We tested the normality assumptions for the MMRM and ANCOVA models. Because of non-normal distributions, we did a post-hoc data analysis on the rank of

change from baseline in serum bicarbonate. This rank-based model was free from assumptions of normal distribution, constant variance, and linearity. We did similar rank-based analyses of the two quantitative exploratory endpoints.

The protocol was amended three times (on June 5, Aug 3, and Nov 27, 2017); however, no patients were enrolled under the original protocol or amendment 1. The only change made to the protocol between amendments 2 and 3 was an increase in the upper age limit from 80 to 85 years. All analyses and summaries were produced using SAS version 9.4. An unmasked, independent data monitoring committee undertook scheduled reviews of the safety data during the study. This study is registered at ClinicalTrials.gov (number NCT03317444).

Role of the funding source

The funder of the study had a role in study design, data collection, data analysis, data interpretation, and writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Sept 26, 2017, and Feb 9, 2018, we randomly assigned 124 participants to veverimer and 93 to placebo (figure 1). All randomly assigned patients were included in analyses of safety; one patient in the veverimer group was excluded from the efficacy analyses because he did not have any post-baseline bicarbonate values. Missingness for the primary outcome variables and other key covariates was uncommon (<5% at any timepoint; appendix).

The groups were well balanced with respect to demographic characteristics, baseline blood pressure, common comorbidities, causes of chronic kidney disease, common concomitant medication use, renal function, baseline eGFR, and electrolytes (table 1). During the study, a loop diuretic was added in two (2%) patients in the veverimer group and in three (3%) patients in the placebo group. A thiazide diuretic was added in two (2%) patients in the veverimer group and in one (1%) patient in the placebo group. No patient had both a loop and thiazide diuretic added, and no patient had a diuretic dose change during the 12-week study period. The mean baseline serum bicarbonate did not differ between the groups (table 1). Patients receiving veverimer took a mean daily dose of 6·1 g (SD 1·3) during the first 4 weeks, 7·7 g (1·9) during the subsequent 4 weeks, and 7·8 g (2·1) during the last 4 weeks of the treatment period. The mean number of total packets consumed in the veverimer and placebo groups was 190 (SD 47) and 211 (SD 36), respectively.

Imputation was not done for the primary endpoint. Of participants with data for week 12, 71 (59%) of 120 veverimer-treated patients and 20 (22%) of 89 placebo-treated patients met the primary endpoint responder definition (p<0·0001 for the comparison), with a treatment difference (veverimer–placebo) of 37% (95% CI 23–49). A similar placebo-subtracted treatment difference occurred for each of the two components of the primary endpoint (figure 2). Compared with the placebo group, a higher percentage of patients in the veverimer group had increases in serum bicarbonate at all pre-defined thresholds (≥2 through ≥7 mmol/L; figure 2).

The serum bicarbonate curves for the veverimer and placebo groups separated over time starting at treatment week 1 and maintained separation through the end of treatment (figure 2). At week 12, the mean change from baseline in the veverimer and placebo groups was 4·5 mmol/L (95% CI 3·9–5·1) and 1·7 mmol/L (1·0–2·3), respectively (p<0·0001). The LS-mean change from baseline to week 12, the secondary endpoint, was 4·4 mmol/L (SEM 3·5) in the veverimer group and 1·8 mmol/L (3·1) in the placebo group (p<0·0001). Other than in subgroups with fewer than eight patients, the lower-bound of the 95% CI for the treatment difference exceeded 0 within all pre-specified subgroups, including age, sex, geographical region, baseline bicarbonate, screening eGFR, and baseline alkali use (figure 3). Results from post-hoc analyses using a rank-based model were consistent with those from the pre-specified MMRM model (p<0·0001 for treatment effect).

At the end of 12 weeks of treatment, physical functioning, as measured by the KDQoL physical function domain increased significantly in the veverimer group

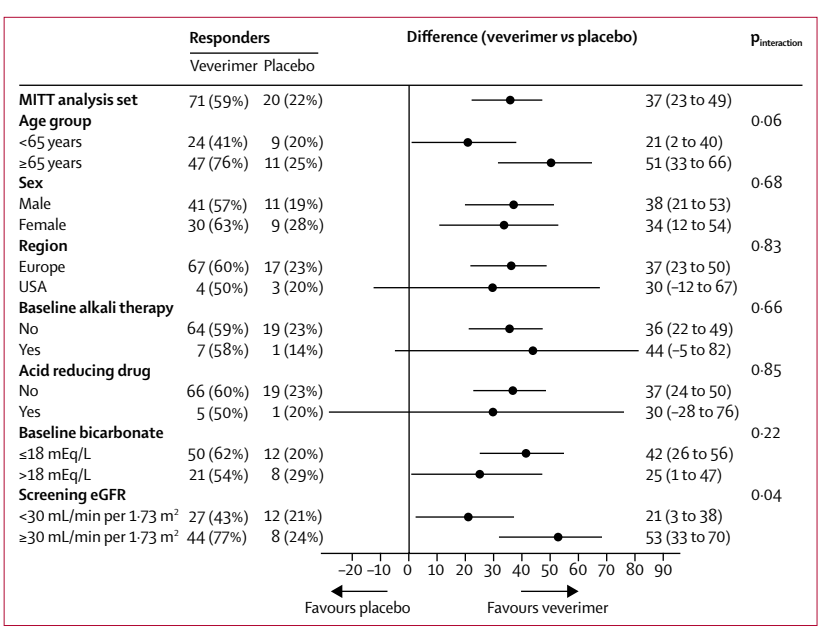

Figure 3: **Subgroup analyses—primary endpoint responders**

Data for differences are percentage of responders (95% CI). Other than in subgroups with fewer than eight patients, the lower bound of the 95% CI for the treatment difference exceeded 0 within all pre-specified subgroups, including age, sex, geographical region, baseline alkali use, baseline bicarbonate and screening estimated glomerular filtration rate (eGFR). p values for the interaction between treatment and each subgroup were obtained from logistic regression models, for which treatment, subgroup, and interaction of treatment with subgroup were included as predictors. However, these values should be interpreted with caution given the post-hoc nature of the analysis and multiple comparisons. MITT=modified intention to treat.

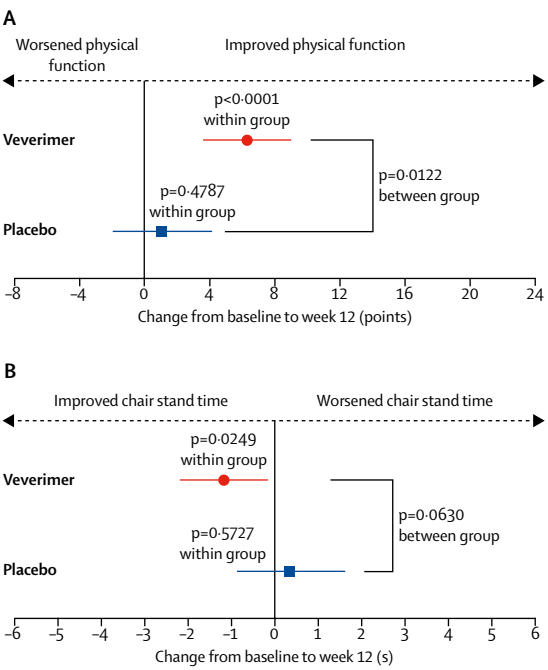

Figure 4: **Change in physical functioning**
Patients reported how limited they were on the ten items of the physical functioning domain of the Kidney Disease and Quality of Life short-form 36 (KDQOL SF-36) at baseline and at treatment week 12 (panel A; appendix). Data are least-squares mean and 95% CI of the change from baseline to week 12 in total score for each group. Panel B shows the least-squares mean and 95% CI of the change from baseline to week 12 in the time taken to do the repeated chair stand test. Not all patients were able to do the test. Data are presented for patients who did the test at both baseline and week 12. (Veverimer n=109; placebo n=76).

	Veverimer (n=124)	Placebo (n=93)
Any	67 (54%)	43 (46%)
Gastrointestinal disorders	21 (17%)	8 (9%)
Diarrhoea	11 (9%)	3 (3%)
Metabolism and nutrition disorders	16 (13%)	8 (9%)
Hyperkalaemia	13 (10%)	6 (6%)
Nervous system disorders	8 (6%)	6 (6%)
Headache	7 (6%)	4 (4%)

Data are the number of patients with adverse events occurring on or after the date of the first dose of veverimer or placebo.

Table 2: **Common adverse events (incidence ≥5%)**

compared with placebo (p=0·012; figure 4). The LS-mean change within the veverimer group (6·3 [95% CI 3·7–8·9]) and the placebo-subtracted treatment effect (5·2 [1·1–9·2]) both exceeded the minimal clinically important difference in KDQoL subscales as reported in scientific literature.[22–25] Physical function, as measured by the repeated chair stand test, numerically improved within the veverimer group (p=0·025) and numerically worsened in the placebo group (p=0·57): the LS mean chair stand time decreased by 1·17 s (95% CI 0·2–2·2) in the veverimer group and increased by 0·35 s (–0·9 to 1·6) in the placebo group (figure 4). The between-group difference was not statistically significant (p=0·063).

Post-hoc rank-based analyses of physical function showed consistent results for patient-reported physical function (p=0·012) and a stronger association for the between-group difference in the time to complete the repeated chair stand test (p=0·0027), both favouring veverimer.

Veverimer was well tolerated when administered once daily for 12 weeks. Dosing compliance (defined as ≥80% of doses administered) was more than 98% (122/124 patients in the veverimer group; 92/93 patients in the placebo group). Two deaths occurred during the study, both in the placebo group, from unstable angina and pneumonia. The incidence of serious adverse events was low and balanced between the two groups and none were considered related to study drug by the site investigators or occurred in more than one patient. The types of serious adverse events reflected the common comorbidities in the study population (eg, unstable angina, congestive heart failure, diabetic hyperglycaemic coma, and asthenia) and intercurrent events not uncommon in patients with chronic kidney disease (eg, pneumonia, mechanical fall, and acute kidney injury).

Acute kidney injury was reported in two patients, one in the placebo group and one in the veverimer group, occurring between study days 73 and 78 in the setting of a hospitalisation for acute left ventricular dysfunction and requiring dialysis in one patient, and between study days 70 and 72 in the setting of a lobar pneumonia and diabetic hyperglycaemic coma in the other patient.

The most common body system in which adverse events in the veverimer group occurred was gastrointestinal (table 2); of these, non-treatment limiting diarrhoea was the most common event (11 [9%] *vs* three [3%] in the veverimer and placebo groups, respectively). The most common treatment-related adverse events were also in the gastrointestinal system, occurring in 16 patients (13%) in the veverimer group and five patients (5%) in the placebo group; most of these were mild or moderate. The treatment-related gastrointestinal adverse events occurring in more than one patient included diarrhoea (14 [6%]), flatulence (three [1%]), nausea (two [1%]), and constipation (two [1%]). No diarrhoea event was severe or necessitated discontinuation of study drug. The only other treatment-related adverse event that occurred in more than one patient was paraesthesia (in one patient [1%] in each group). There were no apparent effects of veverimer on vital signs, ECG intervals, kidney function, haematology measures, liver function tests, lipids, or urinalyses (appendix). A high serum bicarbonate concentration (>30 mmol/L) occurred transiently in two patients but normalised following interruption of study drug per the protocol titration algorithm. There were no apparent effects on serum electrolytes that would indicate off-target effects of veverimer (appendix). The incidence of serum

potassium of 5·0 or 6·0 mmol/L or more (appendix), and mean serum potassium over time (appendix), were similar in both groups.

Discussion

In non-dialysis-dependent patients with chronic kidney disease and chronic metabolic acidosis, 12 weeks of treatment with veverimer significantly increased serum bicarbonate, with 50% of patients achieving normalisation, 56% achieving an increase of 4 mmol/L or more, and 59% achieving the composite primary endpoint of an increase of 4 mmol/L or more from baseline in serum bicarbonate at week 12 or a serum bicarbonate concentration in the normal range (22–29 mmol/L) at week 12. The effect of veverimer on serum bicarbonate was both rapid and sustained over 12 weeks in these outpatients whose dietary protein intake was not governed by the study protocol.

Accumulation of metabolically produced acid stimulates increases kidney production of endothelin, angiotensin II, and aldosterone—substances that provide the short-term benefit of enhancing renal tubule acid excretion but are detrimental in the long term by promoting inflammation and fibrosis in the kidney interstitium that contributes to a progressive decline of kidney function. Similarly, in response to acid retention the kidney increases ammonia production per functioning nephron to facilitate acid excretion; however, the increased ammonia concentration promotes inflammation and activation of complement that also contributes to kidney fibrosis.

Metabolic acidosis in patients with chronic kidney disease has traditionally been treated with sodium-based alkali supplements (sodium bicarbonate and sodium citrate) that enter the systemic circulation and neutralise accumulated acid. Potassium-based alkali therapies (eg, potassium bicarbonate) are rarely used in patients with chronic kidney disease because of the risk of life-threatening hyperkalaemia. Alternative treatments for metabolic acidosis include vegetarian diets, but these limit patient choice and have low long-term adherence.[17] An alternative treatment would remove, rather than neutralise, acid, without administering a sodium or potassium load. Removal of acid by binding to a non-absorbed polymer that is then excreted is a potential new mechanism for treating metabolic acidosis in patients with chronic kidney disease.

Our study showed that veverimer, a non-absorbed, counterion-free, polymeric drug that selectively binds and removes hydrochloric acid from the gastrointestinal tract, thus increasing systemic bicarbonate concentration, is effective in treating metabolic acidosis. Our findings are consistent with and extend previous work[20] by showing that the effect of veverimer on serum bicarbonate reaches a plateau after 4 to 8 weeks of treatment and the effect is sustained over 12 weeks in an outpatient population with chronic kidney disease eating a free-choice diet.

Previous studies with sodium-based alkali treatment, including our own,[7,10,11,14] enrolled patients with milder acidosis (mean serum bicarbonate 19–23 mmol/L) and excluded patients with cardiovascular disease, diabetes, nephrotic syndrome, oedema, or congestive heart failure to reduce the risk of sodium administration in these vulnerable patients. Although a study[27] from 1975 is often cited as evidence that the risks of sodium bicarbonate due to sodium retention (eg, increased blood pressure and fluid retention) are less than those of a similar amount of sodium chloride, in a subsequent study[28] the same investigators showed that this is only true under conditions of severe dietary sodium chloride restriction (approximately 10 milliequivalents/L per day). In the absence of severe sodium chloride restriction, equivalent amounts of sodium administered with either bicarbonate or chloride resulted in similar increases in blood pressure and bodyweight.[29]

By contrast with previous studies, our study population had more severe acidosis (mean bicarbonate 17·3 mmol/L) and no exclusions for oedematous states or the common comorbidities associated with chronic kidney disease noted above. We did not exclude patients receiving oral alkali treatment. Despite recommendations from chronic kidney disease clinical practice guidelines to treat serum bicarbonate concentrations of less than 22 mmol/L, a low proportion of study patients (9%), both in the USA and Europe, were receiving alkali treatment despite their substantial metabolic acidosis. Our study was not designed to determine why patients were not receiving guideline-recommended therapy, but this lack of alkali use might reflect the difficulty in administering the required doses of sodium bicarbonate in the wider chronic kidney disease population.

The direct effects of acidemia on skeletal muscle catabolism and bone demineralisation maintain serum bicarbonate at the expense of bone and muscle. Thus, a low serum bicarbonate represents a late finding in the acid retention process.[2–5,30] Previous studies in women older than 50 years and in patients with chronic kidney disease have shown that bicarbonate supplementation improved muscle strength.[31,32] We hypothesised that muscle catabolism might be reduced with veverimer-mediated increases in bicarbonate and were particularly interested in whether such effects might improve how patients feel and function. After 12 weeks of treatment with veverimer, there was a clinically meaningful improvement in patient-reported physical functioning; however, duration of the repeated chair-stand test did not improve. These findings are worthy of future study, given the burden of symptoms in late stage chronic kidney disease and the failure of other interventions, such as correction of anaemia with erythropoiesis-stimulating agents and treatment of hyperparathyroidism in improving physical functioning.[23,33] These findings will need to be confirmed in longer term studies of veverimer; however, they suggest an important role of metabolic

acidosis in muscle function and identify a clinical endpoint which should be assessed in trials that include patients with later stages of chronic kidney disease.

The limitations of our study include the racial homogeneity of the study population and the short treatment duration (12 weeks). Although meaningful effects of veverimer on increasing serum bicarbonate levels and self-reported physical functioning were achieved at 12 weeks, the sustainability of these effects over a longer time horizon needs to be confirmed in longer-term studies.

Gastrointestinal hydrochloric acid binding with a non-absorbed polymer is a novel approach to treatment of metabolic acidosis associated with chronic kidney disease. In this study, we showed that veverimer was well tolerated and significantly increased serum bicarbonate. Patient-reported physical functioning also improved after 12 weeks of treatment. Longer-term studies to further assess the effects of veverimer on reducing deleterious consequences of metabolic acidosis, including progression of chronic kidney disease and adverse effects on bone and muscle health, are warranted.

Contributors

VM, YS, DP, EL, and GK developed the study protocol and statistical analysis plan. VM and YS were responsible for management and execution of the clinical trial. EL did the statistical analyses. All authors (DEW, VM, NT, YS, DP, EL, GK, and DAB) contributed to the interpretation of the results and writing the manuscript.

Declaration of interests

DEW reports other compensation from Tricida. VM reports personal fees and other compensation from Tricida. NT reports personal fees from Tricida and other compensation from Tricida, personal fees from Otsuka, and a grant and personal fees from AstraZeneca. DAB reports personal fees and other compensation from Tricida and Amgen; personal fees from Sanofi and Relypsa; and grant support from the National Institutes of Health and Renal Research Institute. EL reports personal fees from Tricida. YS, DP and GK are Tricida employees and own stock or stock options in the company. VM, YS, DP, and GK are listed on granted or pending Tricida patents.

Data sharing

All data other than the protocol, including study participant data, data dictionary, statistical analysis plan, and informed consent, will not be shared.

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