Long-term safety and efficacy of veverimer in patients with metabolic acidosis in chronic kidney disease: a multicentre, randomised, blinded, placebo-controlled, 40-week extension

Donald E Wesson, Vandana Mathur, Navdeep Tangri, Yuri Stasiv, Dawn Parsell, Elizabeth Li, Gerrit Klaerner, David A Bushinsky

Summary

Background Metabolic acidosis, a complication of chronic kidney disease, causes protein catabolism and bone demineralisation and is associated with adverse kidney outcomes and mortality. Veverimer, a non-absorbed, counterion-free, polymeric drug candidate selectively binds and removes hydrochloric acid from the gastrointestinal lumen.

Methods We did a multicentre, randomised, blinded, placebo-controlled, 40-week extension of a 12-week parent study at 29 sites (hospitals and specialty clinics) in seven countries (Bulgaria, Georgia, Hungary, Serbia, Slovenia, Ukraine, and the USA). Eligible patients were those with chronic kidney disease (estimated glomerular filtration rate 20–40 mL/min per 1·73 m²) and metabolic acidosis (serum bicarbonate 12–20 mmol/L), who had completed the 12-week parent study, for which they were randomly assigned (4:3) to veverimer (6 g/day) or placebo as oral suspensions in water with food. Participants in the extension continued with the same treatment assignment as in the parent study. The primary endpoint was safety; the four secondary endpoints assessed the long-term effects of veverimer on serum bicarbonate concentration and physical functioning. The safety analysis set was defined as all patients who received any amount of study drug. This trial is registered at ClinicalTrials.gov, number NCT03390842, and has now completed.

Findings Participants entered the study between Dec 20, 2017, and May 4, 2018. Of the 217 patients randomly assigned to treatment in the parent study (124 to veverimer and 93 to placebo), 196 patients (114 veverimer and 82 placebo) continued on their blinded randomised treatment assignment into this 40-week extension study. Compared with placebo, fewer patients on veverimer discontinued treatment prematurely (3% *vs* 10%, respectively), and no patients on veverimer discontinued because of an adverse event. Serious adverse events occurred in 2% of veverimer-treated patients and in 5% of placebo patients (two of whom died). Renal system adverse events were reported in 8% and 15% in the veverimer and placebo groups, respectively. More patients on veverimer than placebo had an increase in bicarbonate (≥4 mmol/L or normalisation) at week 52 (63% *vs* 38%, p=0·0015) and higher bicarbonate concentrations were observed with veverimer than placebo at all timepoints starting at week 1 (p<0·001). Veverimer resulted in improved patient-reported physical functioning (Kidney Disease and Quality of Life–Physical Function Domain) versus placebo with a mean placebo-subtracted change at end of treatment of 12·1 points (SE 3·3; p<0·0001). Time to do the repeat chair stand test improved by 4·3 s (1·2) on veverimer versus 1·4 s (1·2) on placebo (p<0·0001).

Interpretation In patients with chronic kidney disease and metabolic acidosis, veverimer safely and effectively corrected metabolic acidosis and improved subjective and objective measures of physical function.

Funding Tricida.

Published Online
June 24, 2019
http://dx.doi.org/10.1016/S0140-6736(19)31388-1

See Online/Comment
http://dx.doi.org/10.1016/S0140-6736(19)31473-4

Baylor Scott & White Health and Wellness Center, Dallas, TX, USA (Prof D E Wesson MD); **MathurConsulting, Woodside, CA, USA** (V Mathur MD); **Division of Nephrology, University of Manitoba, Winnipeg, MB, Canada** (N Tangri MD); **Tricida, South San Francisco, CA, USA** (Y Stasiv PhD, D Parsell PhD, G Klaerner PhD); **PharmaStat, Newark, CA, USA** (E Li MS); **and University of Rochester School of Medicine, Rochester, NY, USA** (Prof D A Bushinsky MD)

Correspondence to:
Prof Donald E Wesson, Baylor Scott & White Health and Wellness Center, Dallas, TX 75210, USA
donald.wesson@bswhealth.org

Introduction

Metabolic acidosis is a common complication of chronic kidney disease that is associated with chronic kidney disease progression, all-cause mortality, and adverse effects on bone and muscle.[1] As kidney function declines, acid accumulates and is buffered by bone and muscle. Acid buffering leads to bone demineralisation, protein catabolism, and reduced muscle mass, all of which might contribute to worsening physical function.[1]

Treatment of metabolic acidosis is limited by a scarcity of approved therapies. Oral alkali supplements, typically containing sodium, neutralise acid but might cause volume-related adverse effects.[2,3] Diets low in animal protein and high in fruits and vegetables reduce net acid intake, but the effectiveness of this approach is limited by inconsistent adherence to these diets, which differ markedly from the acid-producing diets typical of developed societies.[4]

Veverimer is an oral non-absorbed polymer that selectively binds and eliminates hydrochloric acid from the gastrointestinal tract, leading to increased serum bicarbonate. It is not an ion-exchange resin and does not introduce unwanted cations such as sodium or potassium. Veverimer has been shown to increase serum bicarbonate in 2-week[5] and 12-week,[6] multicentre, randomised, double-blind, placebo-controlled trials. We present the long-term safety of veverimer and its effects on serum bicarbonate and physical function from a

Research in context

Evidence before this study

Metabolic acidosis is a common complication of chronic kidney disease that is associated with protein catabolism, bone demineralisation, chronic kidney disease progression, and all-cause mortality. As kidney function declines, the ability to excrete endogeneous acids diminishes, and the risk of developing both metabolic acidosis and frailty increases. Current strategies for treating metabolic acidosis in patients with chronic kidney disease include neutralising the accumulated acid with oral alkali salts (primarily sodium bicarbonate) and reducing acid intake with diets rich in base-producing fruits and vegetables. To determine the effects of these strategies on physical function, we did a PubMed search of publications of clinical trials from Jan 1, 1970, to April 30, 2019, without limits on language, using the terms "bicarbonate" AND "chronic kidney disease" AND "randomized" AND "physical function" and another otherwise identical search in which "bicarbonate" was replaced by "diet". The one study that was identified was of the investigational hydrochloric acid binder, veverimer. Veverimer is a non-absorbed, counterion-free, polymeric drug that selectively binds and removes hydrochloric acid from the gastrointestinal lumen, and it is being studied for the treatment of metabolic acidosis in patients with chronic kidney disease. In the 12-week study reported, treatment with veverimer (*vs* placebo) increased serum bicarbonate (primary endpoint) and physical functioning (exploratory endpoint) in patients with chronic kidney disease with metabolic acidosis.

Added value of this study

Our multicentre, blinded, placebo-controlled, 40-week extension study, showed that veverimer was well tolerated with a long-term safety profile similar to placebo, and its efficacy in increasing serum bicarbonate was sustained over 52 weeks of treatment. This is, to the best of our knowledge, the first randomised, controlled study to show the sustained effects of treatment of metabolic acidosis on physical function and its effect on daily activities. Patients treated with veverimer reported improvement in their physical function-related quality of life starting at week 12 that continued through the end of treatment, whereas there was no change reported by patients on placebo. Objectively measured physical functioning, assessed by the five-times repeated chair stand test, also improved on veverimer starting at week 12 and improvement continued through the study. The improvements observed in subjectively and objectively measured physical functioning in veverimer-treated patients were both statistically significant versus placebo and exceeded minimal clinically important differences for the measurements. Although our study was not powered to evaluate the effects of veverimer on chronic kidney disease progression or mortality, veverimer was associated with improved time to the composite clinical endpoint of death, renal replacement therapy, or a confirmed decline in estimated glomerular filtration rate of at least 50%. Thus, our study adds to the body of evidence from several single-centre, open-label studies, suggesting treating metabolic acidosis slows progression of chronic kidney disease.

Implications of all the available evidence

Treatment with veverimer sustainably and safely treats metabolic acidosis in patients with chronic kidney disease. It does so through a physiologically desirable mechanism, acid removal, and treatment results in an improvement in physical functioning. Improvement in the ability to rise from a chair and conduct activities of daily living are highly relevant as loss of these abilities might determine whether or not a patient can continue to live independently. Our findings show that chronic metabolic acidosis, which is known to cause protein catabolism and is implicated in the development of frailty, is an important and treatable determinant of poor physical function in patients with chronic kidney disease. Because the decision to initiate dialysis is based on an overall clinical assessment, including physical functioning and the ability to manage complications such as acidosis, our findings raise the possibility that use of veverimer could not only safely correct acidosis and improve physical functioning, but could also forestall initiation of dialysis. Larger studies of longer duration will be necessary to test this hypothesis.

40-week, blinded extension (n=196) of the 12-week parent study[6] (n=217) in patients with chronic kidney disease and chronic metabolic acidosis.

Methods

Study design and participants

See Online for appendix

We did a multicentre, randomised, blinded, placebo-controlled, 40-week extension of our 12-week parent study[6] at 29 sites (hospitals and specialty clinics) in seven countries (Bulgaria, Georgia, Hungary, Serbia, Slovenia, Ukraine, and the USA). The study protocol (appendix p 22) was approved by each site's relevant institutional review board or ethics committee and appropriate regulatory authorities in accordance with applicable laws and regulations.

During the up to 2-week screening period of the parent study, three qualifying bicarbonate values were required; the first two values and the average of all three were required to be within the range of 12–20 mmol/L. Two qualifying screening estimated glomerular filtration rate (eGFR) values not different by more than 20% and in the range of 20–40 mL/min per 1·73 m² were also required (see appendix p 5 for all criteria). Full eligibility criteria for the parent study have been previously published.[6] Eligible participants for the extension study were patients with non-dialysis-dependent chronic kidney disease with adequate peripheral venous access, who completed the 12-week parent study, with a serum bicarbonate value of at least 12 mmol/L. Exclusion criteria were: serum bicarbonate concentration low

enough to need emergency intervention or assessment for an acute acidotic process; a requirement for dialysis for acute kidney injury or worsening chronic kidney disease during the parent study; planned kidney replacement therapy within 6 months; recent history or current diagnosis of cancer, clinically significant diabetic gastroparesis, bariatric surgery, bowel obstruction, swallowing disorders, severe gastrointestinal disorders, inflammatory bowel disease, major gastrointestinal surgery or active gastric or duodenal ulcers, or both; or a serum calcium concentration of 2 mmol/L or less at week 10 of the parent study. Patients who continued from the parent study into the extension study did so with no gap in their study treatment. Dosing of oral concomitant medications and study drug was separated by at least 4 h. All patients provided written informed consent before their participation in the extension study. A diagram of the study design is given in the appendix (p 3).

Randomisation and masking

In the parent study, patients were centrally randomised via an interactive web-based response system in a 4:3 ratio to treatment with veverimer or placebo, stratified by screening bicarbonate concentration (≤18 or >18 mmol/L). Further information regarding randomisation into the parent study has been previously published.[6] Although veverimer and placebo were administered as powders suspended in water, the powders were not identical in appearance. Therefore, study drug dispensing, preparation, and accountability were done by an unmasked designated site staff member who had no other responsibilities for the study. A masking plan was in place, requiring sequestration of drug accountability records and return of study drug to a location inaccessible to the masked site staff. Site personnel were trained on masking requirements. The study sponsor and statisticians were masked for the duration of the parent study but were required to become unmasked following database lock for the parent study to allow reporting of the results of the parent study. The investigators, patients, and personnel responsible for monitoring study records (other than drug accountability) remained masked to treatment assignment throughout both the parent and extension studies.

Procedures

Participants received the same masked treatment that they had received in the parent study. The starting study drug dose in the parent study was 6 g veverimer once daily (two packets per day) or placebo once daily (two packets per day; microcrystalline cellulose, National Formulary Grade). Both were administered orally as a suspension in water with food. The study drug dose was algorithmically titrated by the interactive response technology system in the range of 0–9 g/day (or equivalent number of placebo packets) to a target bicarbonate concentration of 22–29 mmol/L based on the bicarbonate measurement at each visit (appendix p 4). Study drug was administered at approximately the same time each day. The starting dose of study drug in the 40-week treatment period of this extension study was the same as the ending dose of study drug in the parent study (ie, at week 12), unless the patient met the criteria for a dose adjustment (appendix p 4).

Following enrolment, participants attended scheduled visits at weeks 14, 16, 20, 24, 28, 34, 40, 46, and 52 for assessments. Participants who completed the treatment period or discontinued it early while continuing participation in the study attended off-treatment follow-up visits at weeks 53 and 54. Patients who discontinued study drug before week 52 and did not withdraw informed consent were to be contacted by telephone 40 weeks after their week 12 visit to ascertain vital status and renal status (ie, receiving renal replacement therapy or not).

During the course of the study, no addition or up-titration of any other concomitant therapy to raise serum bicarbonate was allowed. Patients who entered the study at the week 12 visit on an oral alkali supplement were taken off the supplement if their serum bicarbonate was within or above the normal range. If, after removal of alkali supplementation, serum bicarbonate fell below the normal range, the study drug dose was increased in a step-wise fashion to the maximum dose of three packets once daily and, if serum bicarbonate was still below normal, the oral alkali therapy the patient was taking at the week 12 visit was reinstated at the same dose the patient was taking at the week 12 visit.

Following a fast of at least 4 h, at each scheduled visit venous blood for bicarbonate was drawn and kept capped until transfer within 10 min into a calibrated iSTAT Handheld Blood Analyzer (Abbott Point of Care, Princeton, NJ, USA) at each site. All other clinical laboratory measurements were done by a central laboratory. The Kidney Disease and Quality of Life Short Form-36, question 3 (Physical Function Domain; KDQoL-PFD) and standardised repeated chair stand test were administered at baseline and weeks 12, 40 and 52. The KDQoL-PFD (appendix p 3) was forward and backwards translated, linguistically validated (including clinician's review), culturally adapted, and cognitively debriefed in patients with chronic kidney disease. The paper questionnaires were completed by patients by themselves, while they were at the study site. Study site personnel were trained on administering the repeated chair stand test. They used a verbatim written script (in the patient's spoken language) to instruct patients during the test. They measured time (with a stopwatch) for the patient to complete five repeated sit-stands with arms folded across the chest from an armless chair. There were no protocol-specified dietary restrictions. Dietary counselling was provided to patients in accordance with dietary recommendations for patients with chronic kidney disease (eg, Kidney Disease Improving Global Outcome 2013).

Outcomes

The primary endpoint was an evaluation of long-term safety based on the incidence of adverse events, serious adverse events, and adverse events leading to withdrawal. The four secondary endpoints assessed the change from baseline (pre-randomisation in the parent study) to end of treatment (week 52) in: the difference (veverimer minus placebo) in the proportion of responders—ie, patients achieving at least a 4 mmol/L increase from baseline in serum bicarbonate or a serum bicarbonate in the normal range (22–29 mmol/L); the least squares mean change from baseline in serum bicarbonate; the total score of the KDQoL-PFD; and the time to complete the repeated chair stand test. The change from baseline in the ten individual items comprising the KDQoL-PFD was assessed at weeks 12, 40, and 52 in a prespecified exploratory analysis. Kidney and mortality outcomes were evaluated with prespecified time-to-event analyses of death; death or renal replacement therapy; or the composite outcome of death, renal replacement therapy, or a confirmed decline in eGFR of at least 50%.

Statistical analysis

The sample size of this study was determined by the number of eligible patients electing to continue into this study after completing the parent study.[6] We analysed primary and secondary endpoints and did exploratory analyses according to the prespecified statistical analysis plan that was finalised before database lock. The individual component analyses of the secondary bicarbonate responder endpoint were prespecified but not adjusted for multiple comparisons.

The safety analysis set was defined as all patients who received any amount of study drug (veverimer or placebo) in the extension study and was used for assessment of safety (primary endpoint) based on the actual treatment received. Adverse events were coded using the Medical Dictionary for Regulatory Activities, version 20.0, and safety parameters were summarised descriptively. All patients randomly assigned into the parent study were included in the time-to-event analyses.

A modified intention-to-treat analysis set, defined as all randomly assigned patients who had both baseline and at least one post-baseline serum bicarbonate value in the parent study and at least one serum bicarbonate value after the week 12 visit in the extension study, was used for evaluation of efficacy (secondary endpoints), based on planned treatment assignment. To control family-wise error rate, hypothesis testing for the four durability of effect (secondary) endpoints was prespecified to be done sequentially, with subsequent tests only done when all previous tests were statistically significant at the two-sided 0·05 level: responder analysis at week 52 using Fisher's exact test; change from baseline to week 52 in serum bicarbonate using a mixed model for repeated measurements; change from baseline to week 52 in the total score of the KDQoL-PFD using a rank-based ANCOVA model; and change from baseline to week 52 in the duration of the repeated chair stand test using a rank-based ANCOVA model. Baseline bicarbonate was defined as the parent study mean of the bicarbonate values from screening 1, screening 2, and day 1 (pre-dose) visits.

If serum bicarbonate data were missing from either treatment group, such data were considered missing at random. Missing data were not imputed for the analysis of change from baseline in serum bicarbonate. To evaluate the potential effect of missing data on the durability of the effect of veverimer on serum bicarbonate, sensitivity analyses for responders and change from baseline in serum bicarbonate were done using multiple imputation models under a missing not at random assumption. For analysis of both the KDQoL-PFD and the repeated chair stand test, for patients with no data after the week 40 visit, the week 40 visit value was used in the analysis. The reasons for missing time to complete repeated chair stand test results were: (1) the patient was weak and thus unable to stand up from the chair once; (2) the patient could stand up from the chair once, but was unable to do so five times as required for the repeated chair stand test; (3) the patient was physically unable to do the test, for example because of below the knee amputation of both lower extremities; and (4) the patient missed a visit. For the purposes of the main analysis of change from baseline in time to complete the repeated chair stand test, the missing chair stand time for patients who were unable to do the chair stand test because of reasons (1) or (2) were set to 60 s, which is the maximum time period allowed for the test. The change from baseline value was calculated after the imputed values at baseline or post-baseline timepoint, or both. A sensitivity analysis was done that excluded missing data from patients who were unable to do the chair stand test.

Prespecified exploratory analysis of individual KDQoL-PFD items was done using Cochran-Mantel-Haenszel statistics (modified ridit scores), adjusting for baseline bicarbonate (≤18 or >18 mmol/L) and screening eGFR (<30 or ≥30 mL/min per 1·73 m²).

The decline in eGFR of at least 50% outcome was defined as two consecutive qualifying eGFR values at least 28 days apart that met the threshold, with no intervening values that did not meet the threshold. The event onset date was the first collection date of the two qualifying values. A single qualifying value counted only if there was at least one qualifying value less than 28 days before the last eGFR value and the immediately preceding value represented a decline of at least 40%. These two values must have been at least 7 days apart. In this case, the first of the two values representing a decline in eGFR of at least 50% was considered the start date of the event. The time to event was defined as the duration between the date of first dose of study drug in the parent study to the date of first occurrence of the

	Veverimer (n=114)	Placebo (n=82)
Age (years)	62·9 (12·1)	61·7 (11·9)
≥65	58 (51%)	38 (46%)
Sex		
Male	68 (60%)	51 (62%)
Female	46 (40%)	31 (38%)
Race		
White	113 (99%)	79 (96%)
Black or African American	1 (1%)	3 (4%)
Region		
Europe	108 (95%)	71 (87%)
USA	6 (5%)	11 (13%)
Body-mass index (kg/m²)	28·6 (4·0)	27·9 (3·9)
Systolic blood pressure (mm Hg)	135·9 (8·9)	136·5 (9·0)
Selected medical history		
Hypertension	110 (96%)	79 (96%)
Diabetes	70 (61%)	57 (70%)
Dyslipidaemia, hyperlipidaemia, or hypercholesterolaemia	70 (61%)	48 (59%)
Left ventricular hypertrophy	56 (49%)	35 (43%)
Congestive heart failure	34 (30%)	28 (34%)
Percutaneous coronary intervention or coronary bypass graft	19 (17%)	14 (17%)
Myocardial infarction	17 (15%)	10 (12%)
Stroke	8 (7%)	8 (10%)
Atrial fibrillation or atrial flutter	7 (6%)	6 (7%)
Peripheral vascular disease	5 (4%)	6 (7%)
Peripheral vascular disease intervention or surgical arterial bypass	1 (1%)	3 (4%)
Transient ischaemic attack	1 (1%)	0
Cause of chronic kidney disease		
Hypertension	36 (32%)	27 (33%)
Diabetes and hypertension	37 (32%)	23 (28%)
Diabetes	15 (13%)	18 (22%)
Glomerulonephritis	7 (6%)	7 (9%)
Interstitial nephritis	6 (5%)	3 (4%)
Cystic renal disease	5 (4%)	3 (4%)
Other, unknown, or urological	8 (7%)	1 (1%)
Medication use		
Sodium bicarbonate	10 (9%)	5 (6%)
ACE inhibitors or ARBs	74 (65%)	66 (80%)
Diuretics	70 (61%)	52 (63%)
Calcium channel blockers	65 (57%)	49 (60%)
Anti-diabetic drugs	62 (54%)	45 (55%)
β blockers	53 (46%)	46 (56%)
Lipid modifying agents	49 (43%)	41 (50%)
Anti-thrombotic agents	44 (39%)	41 (50%)

(Table 1 continues in next column)

(Continued from previous column)

	Veverimer (n=114)	Placebo (n=82)
Laboratory values		
Serum bicarbonate (mmol/L)	17·2 (1·4)	17·1 (1·5)
>18	37 (32%)	23 (28%)
≤18	77 (68%)	59 (72%)
Venous blood pH	7·30 (0·08)	7·30 (0·09)
Venous blood base excess (mmol/L)	−9·3 (2·2)	−9·3 (2·2)
Estimated GFR (mL/min per 1·73 m²)	29·4 (6·4)	27·9 (5·4)
Blood urea nitrogen (mmol/L)	13·7 (4·8)	13·6 (4·6)
Serum creatinine (μmol/L)	193·4 (47·5)	204·3 (51·8)
Serum sodium (mmol/L)	139·9 (2·6)	139·4 (2·9)
Serum potassium (mmol/L)	4·9 (0·6)	4·9 (0·6)
Serum chloride (mmol/L)	106·9 (3·7)	107·3 (4·8)
Serum calcium (mmol/L)	2·3 (0·1)	2·3 (0·1)
Serum phosphate (mmol/L)	1·2 (0·2)	1·2 (0·2)
Serum magnesium (mmol/L)	0·87 (0·11)	0·86 (0·11)
Serum anion gap (mmol/L)*	20·8 (3·9)	20·0 (4·1)
Haemoglobin (g/L)	125·7 (17·7)	125·6 (17·4)
Urine albumin-to-creatinine ratio (mg/mmol)†	23·5 (16·6–33·6)	34·5 (23·4–50·7)
Physical functioning		
KDQoL-PFD total score‡	52·6 (22·4)	55·7 (26·2)
Repeated chair stand (s)§	21·7 (16·9)	21·0 (17·1)

Data are mean (SD), n (%), or geometric mean (95% CI). Baseline characteristics were measured before randomisation in the parent study. ACE=angiotensin converting enzyme. ARBs=angiotensin II receptor blockers. GFR=glomerular filtration rate. KDQoL-PFD=Kidney Disease and Quality of Life–Physical Function Domain. *Serum anion gap was calculated as sodium plus potassium minus (chloride plus bicarbonate). †Values are from a spot urine collection. ‡Veverimer n=114; placebo n=82. §Veverimer n=114; placebo n=81.

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

event. Patients were censored to the earliest date at which the patient was last known to be alive, free from renal replacement therapy and free from a confirmed decline in eGFR of at least 50%. The Kaplan-Meier method was used for the analysis. A log-rank test was used to compare the event-free distributions between the treatment groups.

The protocol was amended three times (on Dec 11, 2017, May 31, 2018, and Oct 17, 2018). All analyses and summaries were produced using SAS, version 9.4. Amendment 1 was made to allow enrolment of patients aged up to 85 years, and to make several administrative clarifications; amendment 2 was made to add assessments of the KDQoL-PFD and repeated chair stand test at the week 40 visit and to eliminate the requirement for down-titration of study drug if bicarbonate was in the high-normal range (27–30 mmol/L); and amendment 3 clarified that the statistical analysis plan would specify analyses to be done in the event that the residuals from the mixed model for repeated measurements or ANCOVA models were not normally distributed. An unmasked, independent data monitoring committee did scheduled reviews of the safety data during the study. This study is registered with ClinicalTrials.gov (number NCT03390842).

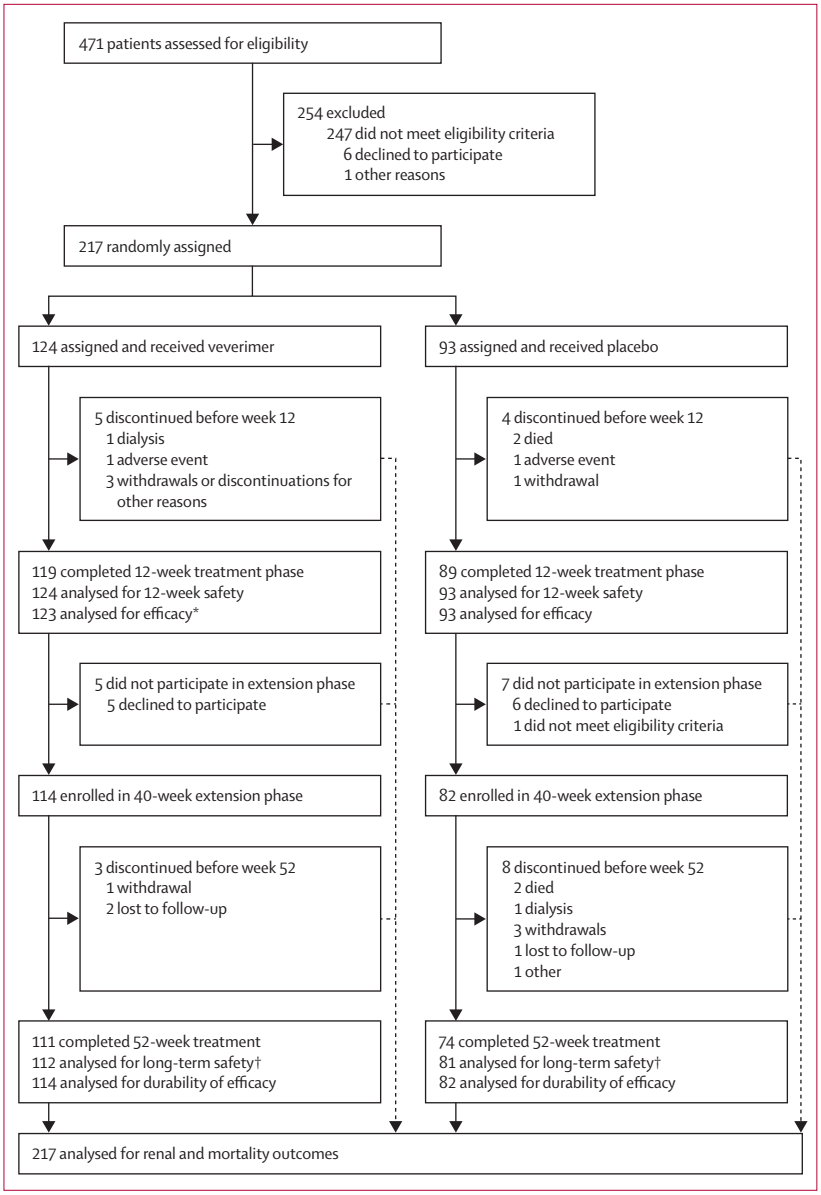

Figure 1: **Trial profile of patient flow through the parent and extension studies**
*One patient excluded from efficacy analysis because of no post-baseline bicarbonate values. †Three patients (two veverimer, one placebo) enrolled in the 40-week extension on a dose hold. Their serum bicarbonate concentrations remained in the normal range throughout the remainder of the study; therefore, they did not receive study drug during the extension study.

Role of the funding source
The funder of this study had a role in study design, data collection, data analysis, data interpretation, and writing of the Article. All authors had access to all the data in the study and had responsibility for the decision to submit for publication.

Results
Of 217 patients randomly assigned to treatment (124 to veverimer and 93 to placebo) in the parent 12-week study, 196 patients (114 veverimer and 82 placebo) continued on their blinded, randomised treatment assignment into this 40-week extension study between Dec 20, 2017, and May 4, 2018. The groups were well balanced with respect to demographics, common comorbidities, cause of chronic kidney disease, common concomitant medication use, and baseline kidney function and electrolytes (table 1). The key baseline characteristics of the 12 patients who did not continue into the extension study were similar to those of the 196 patients who did continue (appendix p 12). The baseline characteristics in the 217 patients randomly assigned into the parent study and evaluated for kidney and mortality outcomes were similar to those of the extension study population.[6]

111 (97%) of 114 patients in the veverimer group completed the 40-week treatment period, compared with 74 (90%) of 82 patients in the placebo group (figure 1). During the treatment period, patients receiving veverimer took a mean daily dose of 7·9 g (SD 1·8). Dosing compliance (defined as >80% of prescribed doses taken) was 100% and 99%, in the veverimer and placebo groups, respectively.

Veverimer was well tolerated with a safety profile that was not different from placebo. Fewer patients on veverimer than placebo discontinued treatment prematurely (3% *vs* 10%, respectively), and no patients on veverimer discontinued because of an adverse event. Serious adverse events occurred in 2% of veverimer-treated patients and 5% of placebo-treated patients; no serious adverse event was judged to be related to study drug by the investigators, medical monitor, or drug safety and pharmacovigilance team. The only adverse event with a between-group frequency difference of more than 5% was headache, which was more common on placebo (table 2). Gastrointestinal system adverse events, which were of interest given the association of such side-effects with polymer-binder drugs in general,[7–9] occurred in 21% of veverimer-treated patients and 26% of placebo-treated patients. Renal system adverse events, which were comprised of only events related to worsening kidney function and one of proteinuria, were reported in 8% and 15% in the veverimer and placebo groups, respectively. Only one patient on veverimer had an elevated (>30 mmol/L) serum bicarbonate concentration, and this occurred in the context of over diuresis. There were no apparent effects of veverimer on lipids or serum electrolytes that would indicate off-target effects (appendix p 13). The proportions of patients with a serum potassium concentration of more than 6·0 mmol/L were 4% and 2%, on veverimer and placebo, respectively, at randomisation and 4% and 3%, respectively, at week 52. There were no apparent effects of veverimer on vital signs, electrocardiogram intervals, haematology parameters, liver function tests, or urinalyses.

Over the entire treatment period (up to 52 weeks) in the 217 patients randomly assigned into the parent study,[6] a prespecified analysis showed that veverimer was associated with improved time to the composite clinical

endpoint of death, renal replacement therapy, or a confirmed decline in eGFR of at least 50% (annualised incidence rate of 4% in the veverimer group versus 12% in the placebo group, p=0·0224; figure 2; appendix p 18). The difference between treatment groups remained significant after (post-hoc) adjustment for screening eGFR (p=0·0358), baseline spot urine albumin-to-creatinine ratio (p=0·0428), and baseline diabetes status (p=0·0293). Time-to-event analyses of death and death or renal replacement therapy also favoured veverimer (p=0·0190 and p=0·0395, respectively).

Among the 196 patients enrolled in the extension study, 63% of veverimer-treated patients and 38% of placebo patients met the responder definition for durability of response (p=0·0015, 25% placebo-subtracted treatment difference, 95% CI 10–39). The placebo-subtracted treatment difference was similar for each of the two components of the composite endpoint (figure 3A). The change from baseline in serum bicarbonate was greater on veverimer than placebo at all timepoints starting at week 1 (p≤0·0005; figure 3B). At week 52, the least squares mean change from baseline was 4·7 mmol/L (SE 0·3) on veverimer versus 2·7 mmol/L (0·4) on placebo (a placebo-subtracted treatment difference of 2·0 mmol/L [0·5]). 2 weeks after discontinuation of treatment, mean serum bicarbonate was not different on veverimer (19·6 mmol/L [0·3]) and placebo (19·2 mmol/L [0·4]). Subgroup analyses by sex and age (<65 years and ≥65 years) were consistent with the overall population findings (appendix p 18). Prespecified sensitivity analyses using multiple imputation for the bicarbonate endpoints were consistent with the primary analyses (appendix p 19).

Patient-reported physical functioning, as measured by the total score of the KDQoL-PFD which quantifies the degree of limitation in performing daily activities such as climbing stairs and walking (appendix p 3), increased on veverimer compared with placebo (p<0·0001; figure 4A). Veverimer-treated patients had sustained improvement in physical function starting at week 12. By contrast, there was no change in reported physical function in patients on placebo. The mean change from randomisation to end of treatment in the total score of the KDQoL-PFD within the veverimer group was 11·4 points (SE 2·2), and the placebo-subtracted treatment effect was 12·1 points (3·3). Compared with placebo, veverimer significantly improved the daily activities of climbing a flight of stairs (p<0·0001); walking (one block [p=0·0020], several blocks [p=0·0003], and more than a mile [p<0·0001]); bending, kneeling, or stooping (p=0·0113); and lifting or carrying groceries (p=0·0488). Changes in the limitations related to vigorous activities such as participating in strenuous sports; moderate activities such as moving a table; climbing several flights of stairs; and bathing and dressing did not differ in the two treatment groups (appendix p 20).

Objectively measured physical functioning, assessed by the repeated chair stand test, also improved on veverimer starting at week 12 (figure 4B). At the end of treatment, the mean time for performing the chair stand test decreased from randomisation by 4·3 s (SE 1·2) on veverimer and by 1·4 s (1·2) on placebo (a placebo-subtracted treatment difference of 2·9 s [1·8]; p<0·0001). Among 20 patients with week 40 or 52 data who were too

	Veverimer (n=112)	Placebo (n=81)
Deaths	0	2 (2%)
Serious adverse events	2 (2%)	4 (5%)
Adverse events related to study drug	11 (10%)	12 (15%)
Premature discontinuation of study drug treatment due to adverse event	0	1 (1%)
Dialysis	0	1 (1%)
Adverse events ≥5% in either treatment group*		
Any	91 (81%)	65 (80%)
Headache	17 (15%)	20 (25%)
Hyperkalaemia	16 (14%)	9 (11%)
Influenza	12 (11%)	6 (7%)
Flatulence	8 (7%)	5 (6%)
Diarrhoea	7 (6%)	5 (6%)
Cough	7 (6%)	3 (4%)
Anaemia	6 (5%)	1 (1%)
Renal impairment	5 (4%)	7 (9%)

Data are n (%). Three patients enrolled in the 40-week extension were excluded from the safety population (two veverimer, one placebo) because they entered the extension study on a dose hold. Their serum bicarbonate levels remained in the normal range throughout the remainder of the study; therefore, they did not receive study drug during the extension study. *There was no significant difference between groups in the incidence of any common adverse event. Adverse events occurring during the first 12 weeks of treatment (parent study) have been previously reported.[6]

Table 2: **Safety summary**

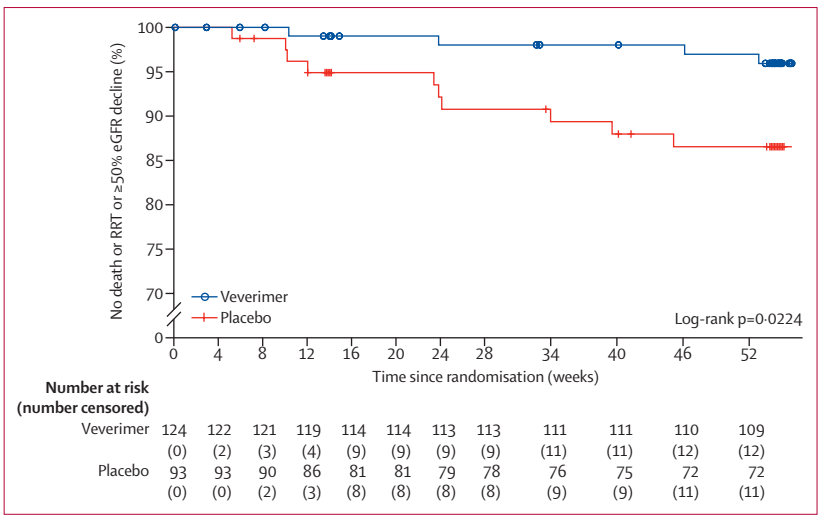

Figure 2: **Kaplan-Meier plot of time to first occurrence of death, renal replacement therapy, or a decline in eGFR of at least 50%**

The p value is based on a log-rank test that compares two survival distributions for the treatment effect (appendix p 18). In post-hoc analyses, the difference between treatment groups remained significant after adjustment for screening eGFR (p=0·0358), baseline spot urine albumin-to-creatinine ratio (p=0·0428), and baseline diabetes status (p=0·0293). eGFR=estimated glomerular filtration rate. RRT=renal replacement therapy (ie, dialysis or kidney transplantation).

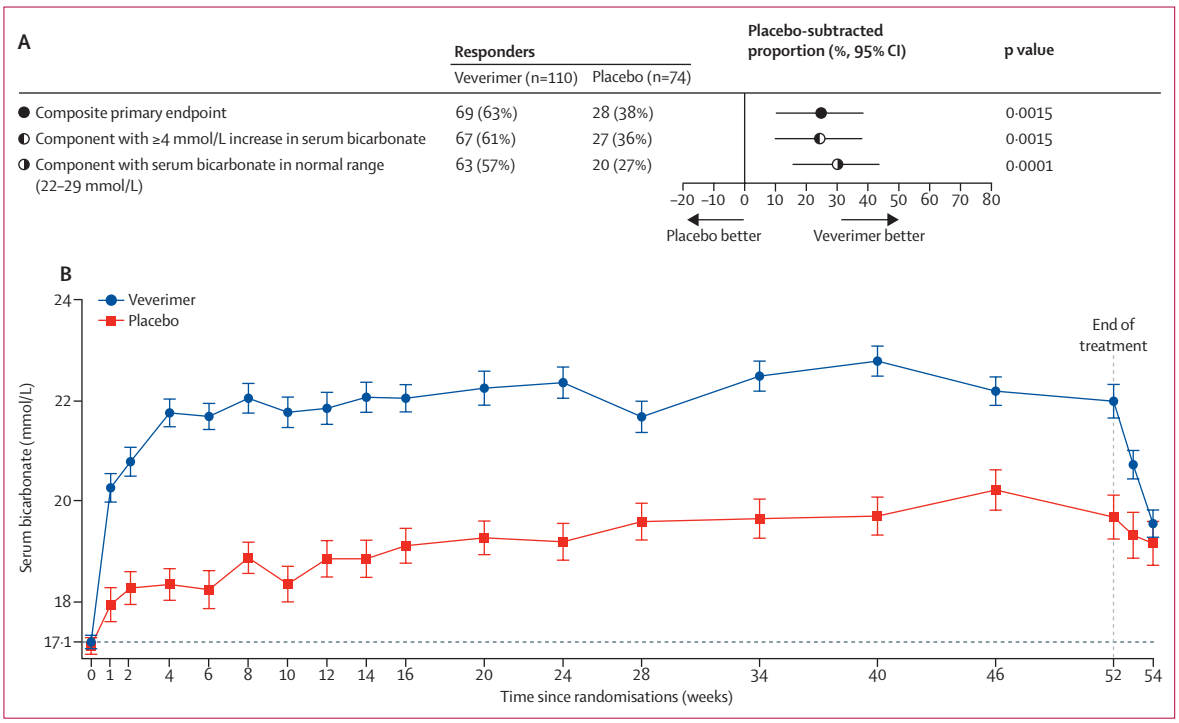

Figure 3: **Change in serum bicarbonate**

(A) The first secondary endpoint, durability of bicarbonate response, defined by the placebo-subtracted proportion of patients achieving a minimum of 4 mmol/L increase from baseline in serum bicarbonate or a serum bicarbonate in the normal range (22–29 mmol/L) at the end of treatment (week 52), is depicted as the top line. The two lower lines depict each component of the endpoint. The individual endpoint component analyses were prespecified but were not adjusted for multiple comparisons. p values are for the difference in proportions between veverimer and placebo groups (Fisher's exact test). (B) The baseline serum bicarbonate (treatment week 0), the mean of the screening 1, screening 2, and baseline day 1 values, was 17·2 mmol/L in the veverimer group and 17·1 mmol/L in the placebo group. Values depicted are the mean (SE).

weak to do the test at baseline, eight (73%) of 11 on veverimer versus four (44%) of nine on placebo were able to do the repeated chair stand test at end of treatment.

The significant improvements in physical function (KDQoL-PFD and repeated chair stand) in the veverimer-treated patients versus placebo were also evident in age (<65 years and ≥65 years) and sex subgroups (appendix p 19). A prespecified sensitivity analysis excluding data from patients unable to do the repeated chair stand test at baseline was consistent with the findings from the primary analyses (appendix p 19).

Discussion

In patients with non-dialysis-dependent chronic kidney disease and metabolic acidosis, treatment with veverimer for up to 1 year safely and effectively corrected acidosis and improved subjective and objective measures of physical function. Veverimer was well tolerated, with high adherence to treatment and a safety profile similar to placebo. The mechanism of action of this non-absorbed polymer is novel. Rather than neutralising acid or reducing acid intake, veverimer selectively binds and removes hydrochloric acid from the gastrointestinal tract, resulting in increased serum bicarbonate concentrations.

Metabolic acidosis in patients with chronic kidney disease is chronic and thus requires long-term treatment to mitigate its deleterious consequences.[1] In this study, we showed that the effect of veverimer on increasing serum bicarbonate was sustained over 1 year. The proportion of veverimer-treated patients achieving at least a 4 mmol/L increase or normalisation of serum bicarbonate was similar in the extension study (63% at week 52) and the parent study (59% at week 12).[6] Similarly, the least squares mean change from baseline in serum bicarbonate in veverimer-treated patients was similar in the two studies: 4·7 mmol/L (SE 0·3) at week 52 in the extension study versus 4·4 mmol/L (0·3) at week 12 in the parent study.[6] Mean serum bicarbonate was increased to maximum concentration by 4 weeks and remained stable for the remainder of the study. This might be an advantage to clinicians (compared with titrating alkali therapy). We observed a gradual increase in serum bicarbonate in patients treated with placebo; nevertheless, the mean bicarbonate concentration in placebo-treated patients remained less than 20 mmol/L at the end of the study. The reason for the slow increase is not clear but might be related to increased attention to bicarbonate concentrations leading to a reduction in dietary protein intake.

Metabolic acidosis in non-dialysis-dependent patients with chronic kidney disease has been traditionally treated with sodium-based alkali supplements, which

might cause gastrointestinal and volume related-adverse effects.[2,3,15,16] Previous studies using sodium bicarbonate to treat metabolic acidosis in chronic kidney disease typically excluded patients with sodium-sensitive comorbid conditions, such as heart failure, poorly controlled hypertension, and oedema, and primarily included patients with mild acidosis (mean serum bicarbonate 20–23 mmol/L).[17–22] By contrast, our study population had more severe acidosis (mean bicarbonate 17·2 mmol/L) and included patients with most common sodium-sensitive comorbidities. Accordingly, our results extend the findings of the benefits of treatment of metabolic acidosis to a more representative chronic kidney disease patient population.

Patients with chronic kidney disease are often frail and have impaired physical function.[21–25] Multiple studies show that acidosis impairs muscle metabolism.[26–28] These data served as the rationale for the selection of the specific subjective and objective measures of physical function assessed in this study. We found that treatment with veverimer improved both patient-reported and objectively measured physical function. After 52 weeks, although there was no change in the placebo group, patients on veverimer had a more than 11-point improvement on average in the total score of the KDQoL-PFD, exceeding the 3 to 5-point change considered the minimal clinically important difference for KDQoL subscales.[10–13] These findings are novel in the chronic kidney disease population given the relative failure of other interventions, such as correction of anaemia and treatment of hyperparathyroidism, to improve physical function to a clinically meaningful extent.[11,29] Consistent with the patient-reported change in physical function, we also found an objective improvement in chair stand time of 4·3 s that exceeded the minimal clinically important difference of 1·7 s, based on anchor-based methods assessed during the time frame of the intervention.[14] The improvement in the ability to rise from a chair, walking a block or several blocks, and climbing a flight of stairs, in particular, are highly relevant clinically because loss of these abilities often determines whether or not a patient can continue to live independently. The decision to initiate dialysis is based on an overall clinical assessment of uraemic signs and symptoms, including physical functioning and the ability to manage complications such as acidosis (KDOQI 2015).[30] Our findings raise the possibility that use of veverimer could not only correct acidosis and improve physical functioning, but could also forestall initiation of dialysis.

Although this study was not powered to evaluate the effects of veverimer on chronic kidney disease progression or mortality, the observation of a lower incidence of these events over 52 weeks in patients treated with veverimer warrants further examination in larger trials of longer duration. Our multicentre, blinded, placebo-controlled study adds to the body of evidence from several single-centre, open-label studies, suggesting that treating metabolic acidosis slows progression of chronic kidney disease.[2,4,17–20]

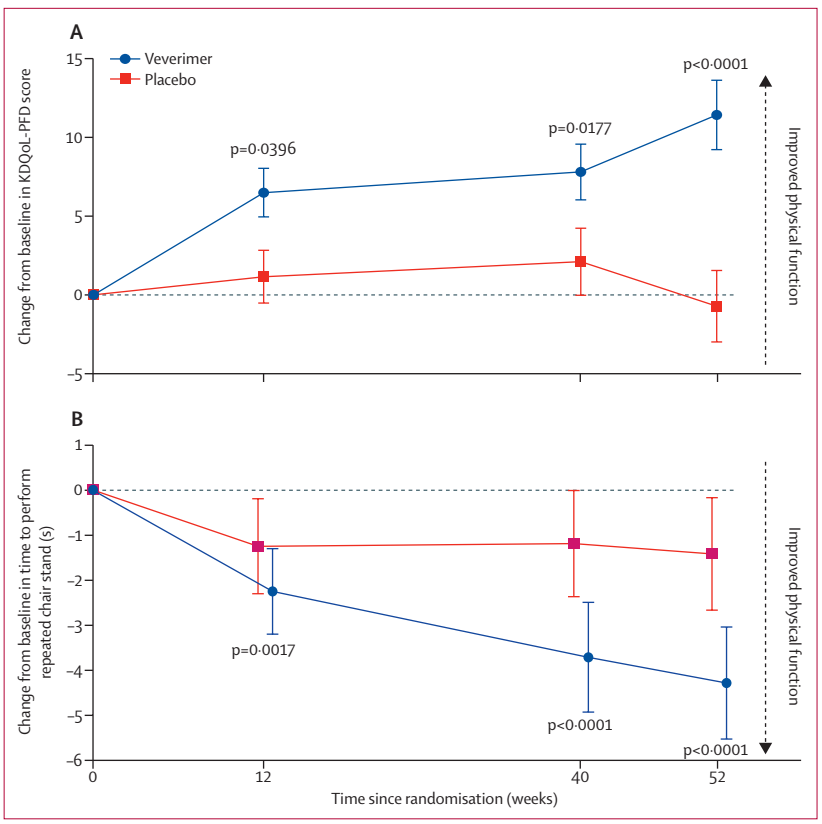

Figure 4: **Change in physical functioning**
(A) Patients reported how limited they were on the ten items of the Physical Functioning Domain of the Kidney Disease and Quality of Life (KDQoL-PFD) at baseline, and at weeks 12, 40, and 52 (appendix p 3). A higher score reflects better physical functioning. The observed mean change from baseline on veverimer and placebo at week 52 was positive 11·42 points and negative 0·71 points, respectively. The minimal clinically important difference reported for the KDQoL subscales is 3–5 points.[10–13] Data shown are mean (SE). p values were based on rank-based ANCOVA models. (B) Patients were timed on the speed with which they could repeatedly stand from a chair five times at baseline, and at weeks 12, 40, and 52. The data points for veverimer are slightly offset from the corresponding times for greater visibility. A shorter time for the test reflects better physical functioning. The observed mean change from baseline on veverimer and placebo at week 52 was −4·3 s and −1·4 s, respectively. The minimal clinically important difference reported for the repeated chair stand test is 1·7 s.[14] Data shown are means (SE). p values were based on rank-based ANCOVA models. Week 52 results included week 40 data, if week 52 data were not available.

Limitations of this study include a study population that was predominantly white, with very few African American or Hispanic patients, 1-year treatment duration and absence of an active comparator group. Although the 1-year duration of this study was appropriate to assess durability of increase in serum bicarbonate and improvement in physical function, longer-term and larger studies are needed to establish benefit of treatment of metabolic acidosis on chronic kidney disease progression and mortality. Our study eligibility criteria allowed inclusion of patients with sodium-sensitive comorbidities, such as hypertension, New York Heart Association Class I–III heart failure, and oedema, which limited use of sodium-based oral alkali as a treatment group. Oral sodium bicarbonate is not approved for the chronic treatment of

metabolic acidosis in the USA and fewer than 10% of patients with chronic kidney disease with metabolic acidosis are treated with alkali supplementation.[31] The Kidney Disease Improving Global Outcomes guideline suggests that patients with chronic kidney disease-related metabolic acidosis receive oral bicarbonate supplementation to maintain serum bicarbonate within the normal range, but assign the suggestion to level 2B, defined as "likely to require substantial debate and involvement of stakeholders before policy can be determined". The lack of policy reflects the insufficient published data from randomised, placebo-controlled studies like ours to test the effectiveness and safety of chronic treatments for metabolic acidosis. The need for effective treatments in addition to sodium bicarbonate is particularly important, recognising the potential harm to which patients with chronic kidney disease might be subjected given their common sodium-sensitive comorbid conditions that sodium bicarbonate might exacerbate.[3] Another limitation of our study is that only patients with eGFR 20–40 mL/min per 1·73 m² were enrolled. Since metabolic acidosis is more prevalent with more severe chronic kidney disease, it will also be important to study veverimer in patients with lower eGFR in future studies. Finally, although there were no adverse events related to soft tissue calcification or apparent effects of veverimer on calcium, phosphate, vitamin D, or parathyroid hormone levels, we did not specifically measure soft tissue calcification. Given that alterations in acid–base homoeostasis might affect soft tissue calcification, such measurements might be worthwhile in future studies.

In conclusion, we showed that treatment with veverimer safely and effectively treated metabolic acidosis in patients with chronic kidney disease and improved how these patients felt and functioned. Larger studies of longer duration are needed to further evaluate the effects of veverimer on chronic kidney disease progression and mortality.

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 analysis. All authors (DEW, VM, NT, YS, DP, EL, GK, and DAB) contributed to the interpretation of the results and writing the Article.

Declaration of interests

DEW reports personal fees from Tricida and grant support from the National Institutes of Health. VM reports personal fees and other compensation from Tricida; and personal fees from Corvidia Therapeutics, Equilliumbio, Rigel, Trevi Therapeutics, Cara Therapeutics, and Sanifit, outside the submitted work. NT reports personal fees and other compensation from Tricida; grants and personal fees from AstraZeneca; and personal fees from Otsuka, Janssen, Boehringer Ingelheim/Lilly, outside the submitted work. DAB reports personal fees and other compensation from Tricida and Amgen; personal fees from Sanifit, Sanofi/Genzyme, and Fresenius/Vifor/ Relypsa; and grant support from the National Institutes of Health and Renal Research Institute, all outside the submitted work. EL reports personal fees from PharmaStat. 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.

Acknowledgments

This study was financially supported by Tricida. We thank the investigators, site personnel, and patients who participated in the study, members of the Tricida clinical operations, regulatory, and chemistry, manufacturing and controls teams and contract research organisation personnel at Worldwide Clinical Trials and Comac Medical for execution of the study, and Jun Shao for generating figures.

References

1 Kraut JA, Madias NE. Adverse effects of the metabolic acidosis of chronic kidney disease. *Adv Chronic Kidney Dis* 2017; **24:** 289–97.

2 Dubey AK, Sahoo J, Vairappan B, Haridasan S, Parameswaran S, Priyamvada PS. Correction of metabolic acidosis improves muscle mass and renal function in chronic kidney disease stages 3 and 4: a randomized controlled trial. *Nephrol Dial Transplant* 2018; published online July 24. DOI:10.1093/ndt/gfy214.

3 Bushinsky DA. Tolerance to sodium in patients with CKD-induced metabolic acidosis: does the accompanying anion matter? *Am J Kidney Dis* 2019; **73:** 858–65.

4 Garneata L, Stancu A, Dragomir D, Stefan G, Mircescu G. Ketoanalogue-supplemented vegetarian very low-protein diet and CKD progression. *J Am Soc Nephrol* 2016; **27:** 2164–76.

5 Bushinsky DA, Hostetter T, Klaerner G, et al. Randomized, controlled trial of TRC101 to increase serum bicarbonate in patients with CKD. *Clin J Am Soc Nephrol* 2018; **13:** 26–35.

6 Wesson DE, Mathur V, Tangri N, et al. Veverimer versus placebo in patients with metabolic acidosis associated with chronic kidney disease: a multicentre, randomised, double-blind, controlled, phase 3 trial. *Lancet* 2019; **393:** 1417–27.

7 Veltassa (patiromer) [package insert]. Redwood City, CA: Relypsa; 2018.

8 Renvela (sevelamer carbonate) [package insert]. Cambridge, MA: Genzyme Corporation; 2018.

9 Welchol (colesevelam hydrochloride) [package insert]. Baskin Ridge, NJ: Daiichi Sankyo; 2019.

10 Clement FM, Klarenbach S, Tonelli M, Johnson JA, Manns BJ. The impact of selecting a high hemoglobin target level on health-related quality of life for patients with chronic kidney disease: a systematic review and meta-analysis. *Arch Intern Med* 2009; **169:** 1104–12.

11 Collister D, Komenda P, Hiebert B, et al. The effect of erythropoietin-stimulating agents on health-related quality of life in anemia of chronic kidney disease: a systematic review and meta-analysis. *Ann Intern Med* 2016; **164:** 472–78.

12 Leaf DE, Goldfarb DS. Interpretation and review of health-related quality of life data in CKD patients receiving treatment for anemia. *Kidney Int* 2009; **75:** 15–24.

13 Samsa G, Edelman D, Rothman ML, Williams GR, Lipscomb J, Matchar D. Determining clinically important differences in health status measures: a general approach with illustration to the Health Utilities Index Mark II. *Pharmacoeconomics* 1999; **15:** 141–55.

14 Jones SE, Kon SS, Canavan JL, et al. The five-repetition sit-to-stand test as a functional outcome measure in COPD. *Thorax* 2013; **68:** 1015–20.

15 Loniewski I, Wesson DE. Bicarbonate therapy for prevention of chronic kidney disease progression. *Kidney Int* 2014; **85:** 529–35.

16 Siegler JC, Marshall PW, Bray J, Towlson C. Sodium bicarbonate supplementation and ingestion timing: does it matter? *J Strength Cond Res* 2012; **26:** 1953–58.

17 de Brito-Ashurst I, Varagunam M, Raftery MJ, Yaqoob MM. Bicarbonate supplementation slows progression of CKD and improves nutritional status. *J Am Soc Nephrol* 2009; **20:** 2075–84.

18 Goraya N, Simoni J, Jo CH, Wesson DE. Treatment of metabolic acidosis in patients with stage 3 chronic kidney disease with fruits and vegetables or oral bicarbonate reduces urine angiotensinogen and preserves glomerular filtration rate. *Kidney Int* 2014; **86:** 1031–38.

19 Mahajan A, Simoni J, Sheather SJ, Broglio KR, Rajab MH, Wesson DE. Daily oral sodium bicarbonate preserves glomerular filtration rate by slowing its decline in early hypertensive nephropathy. *Kidney Int* 2010; **78:** 303–09.

20 Phisitkul S, Khanna A, Simoni J, et al. Amelioration of metabolic acidosis in patients with low GFR reduced kidney endothelin production and kidney injury, and better preserved GFR. *Kidney Int* 2010; **77:** 617–23.

21 Chowdhury R, Peel NM, Krosch M, Hubbard RE. Frailty and chronic kidney disease: a systematic review. *Arch Gerontol Geriatr* 2017; **68**: 135–42.

22 Jhamb M, Weiner DE. Exercise to improve physical function and quality of life in CKD. *Clin J Am Soc Nephrol* 2014; **9:** 2023–24.

23 Kim JC, Kalantar-Zadeh K, Kopple JD. Frailty and protein-energy wasting in elderly patients with end stage kidney disease. *J Am Soc Nephrol* 2013; **24:** 337–51.

24 Weiner DE, Seliger SL. Cognitive and physical function in chronic kidney disease. *Curr Opin Nephrol Hypertens* 2014; **23:** 291–97.

25 Walker SR, Gill K, Macdonald K, et al. Association of frailty and physical function in patients with non-dialysis CKD: a systematic review. *BMC Nephrol* 2013; **14**: 228.

26 Du J, Hu Z, Mitch WE. Cellular signals activating muscle proteolysis in chronic kidney disease: a two-stage process. *Int J Biochem Cell Biol* 2005; **37:** 2147–55.

27 Reaich D, Price SR, England BK, Mitch WE. Mechanisms causing muscle loss in chronic renal failure. *Am J Kidney Dis* 1995; **26:** 242–47.

28 Workeneh BT, Mitch WE. Review of muscle wasting associated with chronic kidney disease. *Am J Clin Nutr* 2010; **91:** 1128s–32s.

29 Cunningham J, Danese M, Olson K, Klassen P, Chertow GM. Effects of the calcimimetic cinacalcet HCl on cardiovascular disease, fracture, and health-related quality of life in secondary hyperparathyroidism. *Kidney Int* 2005; **68:** 1793–800.

30 Daugirdas JT, Depner TA, Inrig J, et al. KDOQI clinical practice guideline for hemodialysis adequacy: 2015 update. *Am J Kidney Dis* 2015; **66:** 884–930.

31 Dobre M, Yang W, Chen J, et al. Association of serum bicarbonate with risk of renal and cardiovascular outcomes in CKD: a report from the Chronic Renal Insufficiency Cohort (CRIC) study. *Am J Kidney Dis* 2013; **62:** 670–78.