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Safety and Efficacy of Patiromer in Hyperkalemic Patients with CKD: A Pooled Analysis of Three Randomized Trials

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Hermann Haller, Stefano Bianchi, Kieran McCafferty, Susan Arthur, Carol Quinn, Jeffrey Budden, and Matthew Weir

Key Points:
*Hyperkalemia is frequently observed in patients with CKD, and its frequency and severity increase as CKD progresses.

*Patiromer is an effective and well tolerated treatment option for hyperkalemia in patients with advanced or mild/moderate CKD on RAASi.

Abstract:
Background: Hyperkalemia is a common electrolyte abnormality in patients with chronic kidney disease (CKD), which is associated with worse outcomes and limits use of renin-angiotensin-aldosterone system inhibitors (RAASi). This post hoc subgroup analysis of three clinical trials evaluated the efficacy and safety of the sodium-free, potassium-binding polymer, patiromer, for the treatment of hyperkalemia in adults with non-dialysis CKD. Methods: Data from the 4-week treatment periods of AMETHYST-DN, OPAL-HK, and TOURMALINE studies were combined. Patients had baseline diagnosis of CKD, hyperkalemia (serum potassium >5.0 mEq/L) and received patiromer 8.4-33.6 g/day. Patients were stratified by baseline estimated glomerular filtration rate (eGFR) into two subgroups: severe/end-stage CKD (Stage 3b-5; eGFR<45 mL/min/1.73m2) and mild/moderate CKD (Stage 1-3a; eGFR {greater than or equal to}45 mL/min/1.73m2). Efficacy was assessed by the change in serum potassium (mean{plus minus}standard error [SE]) from baseline to week 4. Safety assessments included incidence and severity of adverse events (AEs). Results: Efficacy analyses (N=626; 62% male, mean age 66 years) included 417 (67%) patients with severe/end-stage CKD and 209 (33%) with mild/moderate CKD. Most patients were receiving RAASi therapy at baseline (severe/end-stage CKD: 92%; mild/moderate CKD: 98%). The mean{plus minus}SE change in serum potassium (baseline to week 4) was −0.84{plus minus}0.03 in the severe/end-stage CKD subgroup, and −0.60{plus minus}0.04 mEq/L in the mild/moderate CKD subgroup. AEs were reported for 40% and 27% patients in the severe/end-stage and mild/moderate CKD subgroups, respectively, with 16% and 12% reporting AEs considered related to patiromer. The most frequent AEs were mild-to-moderate constipation (8% and 3%) and diarrhea (4% and 2%). AEs leading to patiromer discontinuation occurred in 6% and 2% of patients with severe/end-stage CKD, and mild/moderate CKD, respectively. Conclusions: Patiromer was effective for treatment of hyperkalemia and well tolerated in patients across stages of CKD, most of whom were receiving guideline-recommended RAASi therapy.

Disclosures: H. Haller reports the following: Consultancy: Bayer Pharma, MedWiss, Phenos, Alexion, Boehringer, AstraZeneca, Vifor-Fresenius; Honoraria: Alexion, AstraZeneca, Novartis, Bayer Pharma, MedWiss, Phenos, Boehringer, Vifor-Fresenius; Advisory or Leadership Role: Der Internist, Der Nephrologe, Bayer Pharma, Alexion; and Speakers Bureau: Amgen, Novartis, Bayer Pharma, MedWiss, Phenos, Alexion, Boehringer, AstraZeneca, Vifor-Fresenius. Stefano Bianchi reports consultancy and lectures fees from AstraZeneca, Bayer Pharma AG, Boehringer, Lilly, Novo Nordisk, Pfizer, Vifor Pharma AG, and is a grant holder for The Italian Ministry of Health. K. Mccafferty reports the following: Employer: NHS; Consultancy: Oncacare.; Research Funding: AstraZeneca; Honoraria: Vifor Fresenius, Bayer, Pharmacosmos, Napp, AstraZeneca; and Speakers Bureau: AstraZeneca, Bayer. S. Arthur and J. Budden report the following: Employer: Vifor Pharma, Inc.; and Ownership Interest: Vifor Pharma; Vifor Pharma, Inc. C. Moreno Quinn reports the following: Employer: Vifor Pharma; Ownership Interest: AstraZeneca; Vifor Pharma; Research Funding: CARE-HK in Heart Failure registry; Patents or Royalties: AstraZeneca; and Advisory or Leadership Role: Precision medicine journal editorial board. M. Weir reports the following: Consultancy: Vifor Pharma, Merck, Janssen, AstraZeneca, Boehringer-Ingelheim, Bayer, NovoNordisk, CareDx, Akebia. All are modest (less than $10000); Honoraria: Same as above for ad hoc advisory board meetings; and Advisory or Leadership Role: same as above for ad hoc advisory board.

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Safety and Efficacy of Patiromer in Hyperkalemic Patients with CKD: A Pooled Analysis of Three Randomized Trials

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Key Points

- Hyperkalemia is frequently observed in patients with CKD, and its frequency and severity increase as CKD progresses.
- Patiromer is an effective and well tolerated treatment option for hyperkalemia in patients with advanced or mild/moderate CKD on RAASi.

Abstract

Background: Hyperkalemia is a common electrolyte abnormality in patients with chronic kidney disease (CKD), which is associated with worse outcomes and limits use of renin–angiotensin–aldosterone system inhibitors (RAASi). This post hoc subgroup analysis of three clinical trials evaluated the efficacy and safety of the sodium-free, potassium-binding polymer, patiromer, for the treatment of hyperkalemia in adults with non-dialysis CKD.

Methods: Data from the 4-week treatment periods of AMETHYST-DN, OPAL-HK, and TOURMALINE studies were combined. Patients had baseline diagnosis of CKD, hyperkalemia (serum potassium >5.0 mEq/L) and received patiromer 8.4–33.6 g/day. Patients were stratified by baseline estimated glomerular filtration rate (eGFR) into two subgroups: severe/end-stage CKD (Stage 3b–5; eGFR<45 mL/min/1.73m^2) and mild/moderate CKD (Stage 1–3a; eGFR ≥45 mL/min/1.73m^2). Efficacy was assessed by the change in serum potassium (mean±standard error [SE]) from baseline to week 4. Safety assessments included incidence and severity of adverse events (AEs).

Results: Efficacy analyses (N=626; 62% male, mean age 66 years) included 417 (67%) patients with severe/end-stage CKD and 209 (33%) with mild/moderate CKD. Most patients were receiving RAASi therapy at baseline (severe/end-stage CKD: 92%;

mild/moderate CKD: 98%). The mean±SE change in serum potassium (baseline to week 4) was −0.84±0.03 in the severe/end-stage CKD subgroup, and −0.60±0.04 mEq/L in the mild/moderate CKD subgroup. AEs were reported for 40% and 27% patients in the severe/end-stage and mild/moderate CKD subgroups, respectively, with 16% and 12% reporting AEs considered related to patiromer. The most frequent AEs were mild-to-moderate constipation (8% and 3%) and diarrhea (4% and 2%). AEs leading to patiromer discontinuation occurred in 6% and 2% of patients with severe/end-stage CKD, and mild/moderate CKD, respectively.

Conclusions: Patiromer was effective for treatment of hyperkalemia and well tolerated in patients across stages of CKD, most of whom were receiving guideline-recommended RAASi therapy.

Introduction

Hyperkalemia (serum potassium >5.0 mEq/L) is a frequently observed electrolyte abnormality in patients with chronic kidney disease (CKD), and its frequency and severity increases as CKD progresses [1]. Chronic hyperkalemia increases secretion of aldosterone, which can lead to deleterious effects on the kidney and cardiovascular system, including vascular inflammation, renal and myocardial fibrosis, and ventricular hypertrophy [2]. Hyperkalemia has consistently been linked to increased hospitalization and worse clinical outcomes in patients with heart failure [3].

The Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines recommend that treatment with an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB) should be initiated in patients with non-dialysis CKD with or without diabetes who have hypertension and either severely or moderately increased albuminuria, and that these medications should be titrated to the highest approved tolerated dose [4, 5]. These recommendations are based on several pivotal trials reporting benefits of renin–angiotensin–aldosterone inhibitors (RAASi) in reducing blood pressure, decreasing albuminuria, delaying kidney disease progression and reducing cardiovascular complications [6-11].

RAASi increases the risk of hyperkalemia, which frequently leads to downtitration or discontinuation of guideline-recommended RAASi therapy in patients with CKD [12-14]. Observational studies have shown that dose reduction or cessation of RAASi therapy is associated with increased morbidity and mortality in this population [15]. The KDIGO clinical practice guidelines recommend that the dose of an ACEi or ARB should be

reduced or discontinued only as a last resort in CKD patients with hyperkalemia [4], and to consider the use of potassium binders for the treatment of hyperkalemia.

Patients with reduced kidney function can be susceptible to further kidney injury and increased metabolic derangements, with impact and sensitivity to specific risk factors linked to remaining levels of kidney function [16, 17]. It is therefore particularly important to assess the safety and efficacy of medications in patient subpopulations with both early and late-stage disease.

Patiromer is a non-absorbed, sodium-free, potassium-binding polymer shown to reduce serum potassium to normal levels in clinical trials in patients with hyperkalemia, and thereby enable RAASi therapy [18-20]. The vast majority of patients enrolled in these studies had CKD; however, the effect of patiromer has not previously been evaluated between patients across different stages of kidney disease. We conducted a post hoc subgroup analysis of three clinical trials (AMETHYST-DN, OPAL-HK, and TOURMALINE)[18-20] to evaluate the efficacy and safety of patiromer for the treatment of hyperkalemia in adult patients with Stage 3b–5 CKD and those with Stage 1−3a CKD over a 4-week treatment period.

Materials and methods

Study designs and patients

This post hoc analysis was performed using pooled data from the initial 4-week treatment phases of the AMETHYST-DN and OPAL-HK studies [18, 19], and the complete 4-week treatment period of the TOURMALINE study [20]. All three trials evaluated the efficacy and safety of patiromer for the treatment of hyperkalemia and enrolled adult patients with a baseline serum potassium value >5.0 mEq/L, as evaluated by local laboratory measurement. None of the trials used a placebo arm for the initial 4-week treatment phases. The methods and results of AMETHYST-DN, OPAL-HK and TOURMALINE have been described previously [18-20]. A brief overview of the design and key inclusion criteria for each study is provided below and in **Supplemental Table 1**. This study was exempt from IRB review due to the use of public, deidentified data.

AMETHYST-DN (NCT01371747) was a 52-week, phase 2, open-label, randomized, dose-ranging study that evaluated patiromer in 304 adults with type 2 diabetes mellitus (T2DM), CKD (mean ±standard deviation [SD] estimated glomerular filtration rate [eGFR] 40.6 ±50.7 mL/min/1.73 m^2) and hyperkalemia who were receiving RAASi therapy [18]. Patients were stratified according to their baseline serum potassium levels and assigned into two separate groups (mild hyperkalemia: serum potassium >5.0–5.5 mEq/L or moderate hyperkalemia: >5.5–<6.0 mEq/L). Patients with mild hyperkalemia received patiromer at starting doses of 8.4 g to 25.2 g/day, while those with moderate hyperkalemia received 16.8 g to 33.6 g/day. Patiromer was titrated during the treatment period to reach and maintain serum potassium ≤5.0 mEq/L.

OPAL-HK (NCT01810939) was a 12-week, phase 3, two-phase, single-blind, randomized withdrawal trial that evaluated patiromer in 243 patients with CKD (mean ±SD eGFR: 35.4 ±16.2 ml/min/1.73 m^2) and hyperkalemia who were receiving RAASi[19]. During the initial 4-week treatment phase, patiromer was administered at a starting dose of either 8.4 g/day for patients with mild hyperkalemia at baseline (serum potassium 5.1–<5.5 mEq/L), or 16.8 g/day for those with moderate-to-severe hyperkalemia (≥5.5–<6.5 mEq/L). Patiromer was titrated to achieve and maintain serum potassium within the target range (3.8–<5.1 mEq/L). After the initial 4-week treatment phase, eligible patients entered a randomized withdrawal phase, and continued patiromer treatment or were switched to placebo for 8 weeks.

TOURMALINE (NCT02694744) was a 4-week, phase 4, open-label, randomized trial that evaluated patiromer administered without food versus with food in 112 patients with hyperkalemia. Most patients who participated in the study (n=85, 76%) had a baseline diagnosis of CKD (mean ±SD: eGFR 31.8 ±18.3 ml/min/1.73 m^2). Patiromer was administered at a starting dose of 8.4 g/day and titrated in increments of 8.4 g/day (to a maximum of 25.2 g/day) to reach and maintain serum potassium levels in the target range of 3.8–5.0 mEq/L. In contrast with AMETHYST-DN and OPAL-HK, patients in TOURMALINE were not required to be taking RAASi therapy prior to and during the study.

CKD subgroups and analysis populations

In the present pooled analysis, patients with an investigator determined diagnosis of CKD at screening (defined as eGFR 15 mL/min/1.73 m^2 to < 60 mL/min/1.73 m^2 at

screening) from the AMETHYST-DN, OPAL-HK and TOURMALINE studies were stratified according to central laboratory-measured baseline eGFR into two subgroups: (1) Stage 3b–5 CKD (non-dialysis; eGFR <45 mL/min/1.73m^2) or (2) Stage 1–3a CKD (eGFR ≥45 mL/min/1.73m^2).

All safety assessments were performed on the safety population (N=632), which comprised all randomized CKD patients from AMETHYST-DN, OPAL-HK and TOURMALINE who received ≥1 dose of patiromer. Evaluation of baseline characteristics and efficacy assessments was performed on the efficacy population (N=626), comprising all randomized CKD patients from the three trials who received ≥1 dose patiromer and had ≥1 post-baseline weekly serum potassium assessment available (AMETHYST-DN: n=304/304; OPAL-HK: n=237/237; TOURMALINE: n=85/112). The efficacy population excluded six patients from the OPAL-HK study without a weekly post-baseline serum potassium measurement available. Six patients from the AMETHYST-DN study did not have a baseline eGFR value available; therefore, for the purposes of this analysis, the earliest available assessment of eGFR was used to impute their CKD stage.

Efficacy and safety assessments

Efficacy was evaluated as the mean ± standard error (SE) change in central laboratory serum potassium from baseline to week 4, which was the primary endpoint of the AMETHYST-DN and OPAL-HK studies, and a secondary endpoint of the TOURMALINE study. Changes in serum potassium during the 4-week treatment period and the

proportion of patients who achieved target serum potassium levels (≥1 serum potassium measurement 3.8–5.0 mEq/L) were also evaluated.

Safety outcomes included the frequency and severity of adverse events (AEs) with onset during the 4-week treatment period. All AEs were recorded based on reports from the study investigator and separately based on prespecified laboratory values of interest.

All efficacy and safety results are presented separately for the Stage 3b–5 CKD and Stage 1–3a CKD patient subgroups.

Statistical analyses

Descriptive statistics were summarized as means ± SD or SE for continuous variables, or as proportions for categorical variables. All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Baseline demographics and clinical characteristics

Baseline serum potassium (mean ±SD) was comparable in all three trials: In OPAL-HK, it was 5.6 ±0.5 mmol/L; in AMETHYST-DN it was 5.3 ±0.4 mmol/L; and in TOURMALINE it was 5.4 ±0.4 and 5.3 ±0.4 mmol/L in the with and without food groups, respectively. Of the 626 patients included in the efficacy population, 417 patients (67%) had Stage 3b–5 CKD (including 27 patients [6%] with Stage 5 CKD) and 209 patients (33%) had Stage 1–3a CKD. Baseline characteristics were generally balanced between the subgroups, with some notable differences (**Table 1**). Mean ±SD serum potassium was higher among patients with Stage 3b–5 CKD than in those with Stage 1−3a CKD (5.47 ±0.41 and 5.32 ±0.42 mEq/L, respectively). Patients in the Stage 3b–5 CKD subgroup also had a higher mean spot urine albumin-to-creatinine ratio (ACR) than patients in the Stage 1–3a CKD subgroup. Most patients in the Stage 3b–5 CKD and Stage 1–3a subgroups had comorbid hypertension (99% and 98%, respectively) and comorbid diabetes (80% and 88%, respectively). Approximately one-third of patients with Stage 3b–5 and Stage 1–3a CKD had heart failure (34% and 35%, respectively), predominantly New York Heart Association (NYHA) class II. The mean age was 66 years in both subgroups.

Overall, 92% of patients with Stage 3b−5 CKD and 98% of patients with Stage 1−3a CKD were receiving RAASi therapy at baseline (**Table 2**). In the Stage 3b–5 CKD subgroup, the most frequently prescribed RAASi medications were ACEi (60%) and ARB (41%). Approximately one-third of patients with Stage 3b–5 CKD (37%) were receiving a beta blocker and 41% a loop diuretic.

Efficacy

Treatment with patiromer induced early reductions in serum potassium in both subgroups, with mean levels decreasing from baseline to <5.0 mEq/L by Week 1 or Day 3 in the Stage 3b–5 and Stage 1–3a CKD subgroups, respectively (**Figure 1**). The mean ±SD change in serum potassium from baseline to week 4 was −0.84 ±0.03 and −0.60 ±0.04 mEq/L among patients with Stage 3b–5 and Stage 1–3a CKD, respectively. The proportion of patients who achieved normokalemia (at least one serum potassium value in the range 3.8–5.0 mEq/L) at any time during the 4-week treatment period was 96% in the Stage 3b–5 CKD subgroup (86.1% at Week 4) and 99% in the CKD Stage 1–3a subgroup (88.3% at Week 4).

The mean ±SD change in systolic blood pressure from baseline to week 4 was -6.2 ±19.2 and −10.7 ±17.5 mmHg (-4.0 ±12.0 and -6.5 ±12.2 for diastolic blood pressure) among patients with Stage 3b–5 and Stage 1–3a CKD, respectively.

In hyperkalemic patients, RAASi medication use at Week 4 was reported in 85.1% and 94.7% of patients in the Stage 3b–5 and Stage 1–3a CKD groups, respectively.

Safety and tolerability

In total, 421 patients with Stage 3b–5 CKD and 211 patients with Stage 1–3a CKD were included in the safety population. During the 4-week treatment period, 16% of patients with Stage 3b–5 CKD and 12% of patients with Stage 1–3a CKD reported ≥1 treatment-emergent AE (TEAE) related to patiromer (**Table 3**). The most frequent TEAEs related

to patiromer in the Stage 3b–5 CKD and Stage 1–3a CKD subgroups, respectively, were constipation (7% and 3%) and diarrhea (3% and 2%), none of which were severe. AEs leading to discontinuation of patiromer were reported for 24 (6%) patients with Stage 3b–5 CKD and 5 (2%) of patients with Stage 1–3a CKD. (**Supplemental Table 2**).

Overall, 19 patients had ≥1 serious AE (16 in the Stage 3b–5 CKD subgroup and 3 in the Stage 1–3a CKD subgroup); none of these were related to patiromer, based on investigator assessment (**Supplemental Table 3**).

Mean serum magnesium, calcium and phosphate levels remained unchanged and within the normal range in both subgroups during the 4-week treatment period (**Supplemental Table 4**).

Hypomagnesemia was reported for 9 patients (2%) in the Stage 3b–5 CKD subgroup and for 5 patients (3%) in the Stage 1–3a CKD subgroup. During the treatment period, 19 patients (5%) in the Stage CKD 3b−5 subgroup and 18 patients (9%) in the Stage 1–3 CKD subgroup had serum magnesium <1.4 mg/dL (**Table 4**). One patient from the Stage 3b–5 CKD subgroup had a serum magnesium value <1.2 mg/dL (1.05 mg/dL).

AEs of hypokalemia were reported for 7 patients (2%) with Stage 3b–5 CKD (serum potassium 3.0–4.9 mEq/L) and one patient (0.5%) with Stage 1–3a CKD. The proportion of patients with serum potassium <3.5 mEq/L during the 4-week treatment period was similarly low in both the Stage 3b–5 CKD and Stage 1–3a CKD subgroups (2% and 1%, respectively) (**Table 4**).

No AEs of hypercalcemia were reported for patients in either subgroup and no clinically relevant increases in serum calcium or post-baseline values >12.0 mg/dL were observed. Serum calcium values above the upper limit of normal (ULN) were recorded for 21 patients (5%) with Stage 3b–5 CKD and 13 patients (6%) with Stage 1–3a CKD (**Table 4**). One patient had an AE of hypocalcemia in the Stage 3b–5 CKD subgroup. The highest post-baseline calcium value was 11.9 mg/dL, recorded for a patient with elevated serum calcium at study baseline (12.7 mg/dL).

No AEs of hyperphosphatemia were reported for patients in either subgroup. Any serum phosphate values >ULN was reported for 29% of patients in the Stage 3b–5 CKD subgroup and 11% in the Stage 1–3a subgroup (**Table 4**).

Overall, there were no clinically meaningful changes from baseline in mean eGFR during the 4-week treatment period in either subgroup (**Supplemental Table 5**). A reduction from baseline to Week 4 in mean spot urine ACR was observed in the Stage 3b–5 CKD subgroup, while levels remained unchanged in the Stage 1–3a CKD subgroup (**Supplemental Table 5**).

Discussion

Patiromer, a sodium-free potassium binder, may be an appropriate treatment option to treat hyperkalemia in patients with CKD on RAASi. Patients with CKD may be at risk of volume overload and are often on sodium-restricted diets to help control hypertension and albuminuria[21]. Sodium may also blunt the response to RAAS blockade [21].

Given the potential variability in both efficacy and safety of treatments in patients with early vs advanced CKD, it is important to assess the safety and efficacy of medications in both these subpopulations [16, 17].

This subgroup analysis demonstrated that patiromer provided effective reduction of serum potassium in hyperkalemic patients with either mild/moderate or advanced/end-stage CKD, over 92% of whom were receiving RAASi therapy at baseline. Most patients responded to the 8.4g starting dose, with reductions in mean serum potassium occurring early during treatment and reaching normal levels in both the mild/moderate and advanced/end-stage CKD patient subgroups, regardless of initial serum potassium levels.

This analysis showed that patiromer was generally well tolerated by patients with either mild/moderate or advanced/end-stage CKD over the 4-week treatment period, with a minimal risk of hypokalemia. Consistent with previous reports for the overall patient populations from these three studies [18-20], the most frequent AEs in both subgroups were gastrointestinal in nature, comprising mainly mild-to-moderate constipation and diarrhea.

Overall, the proportion of patients with AEs and serious AEs was numerically higher among patients with advanced/end-stage CKD versus patients with mild/moderate CKD. However, this finding was not unexpected, given that a higher incidence of AEs among patients with advanced versus earlier stages of CKD has been reported in several other studies; [22-26] indicating that patients with advanced CKD typically have a greater burden of comorbidities than those with earlier stages of CKD. None of the serious AEs recorded for patients in either subgroup was considered by investigators to be related to treatment with patiromer. The profile of the serious AEs that occurred more frequently in Stage 3b–5 CKD patients (renal and urinary disorders, cardiac disorders, and vascular disorders), was consistent with the profile expected for patients with lower eGFR, and appeared to be related to underlying disease, rather than to any specific treatment effects with patiromer

In this subgroup analysis, mean serum magnesium levels remained within the target range during the 4-week treatment period in both the Stage 3b–5 CKD and Stage 1–3a CKD subgroups, which is consistent with serum magnesium levels observed in the AMBER study [27]. Reported AEs of hypomagnesemia occurred in approximately 2% of patients in each subgroup. However, at least one serum magnesium level <1.4 mg/dL was reported for fewer patients in the Stage 3b–5 CKD subgroup (5%) than in the Stage 1–3a CKD subgroup (9%), similar to findings reported in previous trials [28, 29]. AEs of hypokalemia were reported for more patients in the Stage 3b–5 CKD subgroup (2%) than in the Stage 1–3a CKD subgroup (0.5%), but the overall incidence was low. In the 12-week, placebo-controlled AMBER trial, rates of serum magnesium were 0.7% in placebo-treated patients vs. 2.1% in patiromer treated patients (data on file). The lower

rates of low serum magnesium in this advanced CKD population may be due to the lower starting dose of 8.4g of patiromer in all patients in the AMBER study.

The few phosphate measurements >ULN observed were likely due to the underlying CKD, and not to patiromer treatment. There is no mechanistic reason to expect patiromer treatment to result in increases in phosphate; patiromer has been shown to lower phosphate in previous studies [30, 31].

This present study had several limitations. It was a post hoc analysis, so the findings should be considered exploratory in nature. Additionally, duration of follow-up was limited to the 4-week treatment periods of the three trials; however, data from the overall AMETHYST-DN study have demonstrated that patiromer was well tolerated, long-term, and can control serum potassium levels among CKD patients over a 1-year treatment period [18]. Furthermore, a recent global pharmacovigilance database study of patiromer, which reviewed >17,000 individual case reports over a 4-year period, confirmed that the safety and tolerability profile of patiromer in the real-world setting is consistent with the clinical trial data [32]. The three trials that were the subject of the present analysis had no active comparator or placebo group; however, placebo-controlled data for patiromer in patients with advanced CKD were provided in the AMBER study, which showed similar rates of AEs in the patiromer and placebo groups (56% and 53%, respectively) over a 12-week treatment period [33].

In conclusion, this pooled analysis of three clinical trials showed that patiromer provided an effective treatment for patients with hyperkalemia across the spectrum of both early and advanced non-dialysis CKD, most of whom were receiving guideline-recommended RAASi. Patiromer was also well tolerated in both subpopulations, with mild-to-moderate

GI events being reported in a small proportion of patients, and relatively few treatment discontinuations.

Disclosures

H. Haller reports the following: Consultancy: Bayer Pharma, MedWiss, Phenos, Alexion, Boehringer, AstraZeneca, Vifor-Fresenius; Honoraria: Alexion, AstraZeneca, Novartis, Bayer Pharma, MedWiss, Phenos, Boehringer, Vifor-Fresenius; Advisory or Leadership Role: Der Internist, Der Nephrologe, Bayer Pharma, Alexion; and Speakers Bureau: Amgen, Novartis, Bayer Pharma, MedWiss, Phenos, Alexion, Boehringer, AstraZeneca, Vifor-Fresenius. Stefano Bianchi reports consultancy and lectures fees from AstraZeneca, Bayer Pharma AG, Boehringer, Lilly, Novo Nordisk, Pfizer, Vifor Pharma AG, and is a grant holder for The Italian Ministry of Health. K. Mccafferty reports the following: Employer: NHS; Consultancy: Oncacare.; Research Funding: AstraZeneca; Honoraria: Vifor Fresenius, Bayer, Pharmacosmos, Napp, AstraZeneca; and Speakers Bureau: AstraZeneca, Bayer. S. Arthur and J. Budden report the following: Employer: Vifor Pharma, Inc.; and Ownership Interest: Vifor Pharma; Vifor Pharma, Inc. C. Moreno Quinn reports the following: Employer: Vifor Pharma; Ownership Interest: AstraZeneca; Vifor Pharma; Research Funding: CARE-HK in Heart Failure registry; Patents or Royalties: AstraZeneca; and Advisory or Leadership Role: Precision medicine journal editorial board. M. Weir reports the following: Consultancy: Vifor Pharma, Merck, Janssen, AstraZeneca, Boehringer-Ingelheim, Bayer, NovoNordisk, CareDx, Akebia. All are modest (less than $10000); Honoraria: Same as above for ad hoc advisory board meetings; and Advisory or Leadership Role: same as above for ad hoc advisory board.

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Author Contributions

Hermann Haller: Writing - review and editing. Stefano Bianchi: Writing - review and editing. Kieran McCafferty: Writing - review and editing. Susan Arthur: Conceptualization; Data curation; Formal analysis; Methodology; Supervision; Validation; Visualization; Writing - original draft; Writing - review and editing. Carol Quinn: Writing - review and editing. Jeffrey Budden: Conceptualization; Writing - original draft; Writing - review and editing. Matthew Weir: Conceptualization; Writing - original draft; Writing - review and editing.

Supplemental Materials

Supplemental Table 1. Comparison of trial design for AMETHYST-DN, OPAL-HK, and TOURMALINE

Supplemental Table 2. Non-fatal treatment-emergent adverse events leading to treatment discontinuation, with onset during the first four weeks, by System Organ Class and Preferred Term

Supplemental Table 3: Serious treatment-emergent adverse events with onset during the first four weeks, by System Organ Class and Preferred Term

Supplemental Table 4. Mean (SD) serum calcium, phosphate and magnesium at baseline, Week 4 and change from baseline to Week 4 (safety population; N=632)

Supplemental Table 5. Mean (SD) eGFR and spot urine ACR at baseline, Week 4 and change from baseline to Week 4 (safety population; N=632)

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Tables and figures

Table 1. Baseline demographics and clinical characteristics (efficacy population; N=626)

	Patients with Stage 3b–5 CKD (n=417)	**Patients with Stage 1–3a CKD (n=209)**
Male, n (%)	253 (61)	134 (64)
Age (years) mean (SD)	66 (10)	66 (9)
White, n (%)	398 (95)	207 (99)
Body weight (kg) mean (SD)	84.8 (15.0)	85.6 (14.1)
History of diabetes mellitus, n (%)	332 (80)	183 (88)
Hypertension, n (%)	411 (99)	205 (98)
Ejection fraction (%)[a], mean (SD)	49.8 (8.9)	50.0 (8.9)
Previous myocardial infarction, n (%)	72 (17)	47 (22)
History of heart failure	141 (34)	73 (35)
NYHA heart failure class[b], n (%)		
I	36 (9)	14 (7)
II	92 (22)	54 (26)
III	13 (3)	5 (2)
eGFR (mL/min/1.73m^2)[c], mean (SD)	27.9 (8.9)	58.0 (12.8)
CKD stage (eGFR) n (%)		
Stage 1 (≥90)	0	7 (3)
Stage 2 (60 to 89)	0	61 (29)
Stage 3a (45 to 59)	0	141 (67)
Stage 3b (30 to 44)	178 (43)	0
Stage 4 (15 to 29)	212 (51)	0
Stage 5 (<15)	27 (6)	0
Spot urine ACR (mg/g),[d] median (Q1, Q3)	412.0 (41.7, 1103.3)	599. (16.5, 545.3)

Serum potassium (mEq/L), mean (SD)	5.47 (0.41)	5.32 (0.42)

[a] Ejection fraction data were collected only in AMETHYST-DN (N=304).

[b] NYHA class IV heart failure patients were excluded.

[c] Central laboratory baseline eGFR was based on the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) formula. Seven subjects in AMETHYST-DN did not have a baseline value; for the purpose of this analysis, the earliest available assessment of eGFR was used to impute CKD stage at baseline.

[d] Spot urine ACR data were collected only in AMETHYST-DN (N=304) and OPAL-HK (N=243).

ACR, albumin–creatinine ratio; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; IQR, interquartile range; n/a, not applicable; NYHA, New York Heart Association; SD, standard deviation.

Table 2. Antihypertensive medications received by patients at baseline (efficacy population; N=626)

Medications	Patients with Stage 3b–5 CKD (n=417)	Patients with Stage 1–3a CKD (n=209)
Any RAASi, n (%)	383 (92)	204 (98)
ACE inhibitor	252 (60)	138 (66)
ARB	171 (41)	81 (39)
MRA	31 (7)	18 (9)
Renin inhibitor	1 (0.2)	1 (0.5)
Dual RAASi blockade[a]	67 (16)	31 (15)
ACE inhibitor + ARB	37 (9)	14 (7)
ACE inhibitor + MRA	10 (2)	5 (2)
ACE inhibitor + renin inhibitor	1 (0.2)	(0)
ARB + MRA	14 (3)	10 (5)
ACE inhibitor + ARB + MRA	5 (1)	1 (0.5)
ACE inhibitor + ARB + MRA + renin inhibitor	0 (0)	1 (0.5)
Beta blocker, n (%)	155 (37)	85 (41)
Diuretic, n (%)		
Thiazide	33 (8)	15 (7)
Loop	172 (41)	52 (25)

[a] Any combination of ≥2 of the following: ACE inhibitor, ARB, MRA, renin inhibitor.

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CKD, chronic kidney disease; MRA, mineralocorticoid receptor antagonist; RAASi, renin–angiotensin–aldosterone system inhibitor.

Table 3. Treatment-emergent adverse events related to patiromer[a] (safety population; N=632)

No. of patients (%)	Severity	Patients with Stage 3b–5 CKD (n=421)	Patients with Stage 1–3a CKD (n=211)
≥1 adverse event	Any severity	67 (15.9)	25 (11.8)
	Mild	45 (10.7)	18 (8.5)
	Moderate	22 (5.2)	7 (3.3)
	Severe	0 (0.0)	0 (0.0)
Gastrointestinal disorders	Any severity	54 (12.8)	13 (6.2)
	Mild	36 (8.6)	10 (4.7)
	Moderate	18 (4.3)	3 (1.4)
	Severe	0 (0.0)	0 (0.0)
Constipation	Any severity	30 (7.1)	6 (2.8)
	Mild	21 (5.0)	6 (2.8)
	Moderate	9 (2.1)	0 (0.0)
	Severe	0 (0.0)	0 (0.0)
Diarrhea	Any severity	12 (2.9)	4 (1.9)
	Mild	8 (1.9)	4 (1.9)
	Moderate	4 (1.0)	0 (0.0)
	Severe	0 (0.0)	0 (0.0)
Metabolism and nutrition disorders	Any severity	16 (3.8)	7 (3.3)
	Mild	13 (3.1)	4 (1.9)
	Moderate	3 (0.7)	3 (1.4)
	Severe	0 (0.0)	0 (0.0)
Hypomagnesemia	Any severity	9 (2.1)	5 (2.4)
	Mild	8 (1.9)	3 (1.4)
	Moderate	1 (0.2)	2 (0.9)
	Severe	0 (0.0)	0 (0.0)

[a] Adverse event that occurred in ≥2% of patients in either subgroup.

Note: This table summarizes adverse events during the first 4 weeks after the start of patiromer treatment (defined as onset on or before Study Day 32), regardless of the date of treatment discontinuation.

CKD, chronic kidney disease.

Table 4. Prespecified laboratory values of interest during 4-week treatment period[a] (safety population; N=632)

No. of patients (%)[a]	Patients with Stage 3b–5 CKD (n=421)	Patients with Stage 1–3a CKD (n=211)
Any serum K^+ value in target range (3.8–5.0 mEq/L)	403/418 (96)	209/211 (99)
Any serum K^+ value <3.5 mEq/L	8/418 (2)	3/211 (1)
Any serum value Mg^{2+}		
<1.4 mg/dL	19/412 (5)	18/209 (9)
<1.2 mg/dL	1/412 (0.2)	0/209 (0.0)
Any serum Ca^{2+} value >ULN[b]	21/412 (5)	13/209 (6)
Any serum phosphate value >ULN[c]	121/411 (29)	24/209 (11)

[a] Data summary is based on observed cases; for some patients, laboratory values were missing during the first 4 weeks of the study.

[b] Serum Ca^{2+} ULN >10.3 mg/dL for AMETHYST-DN, and >10.5 mg/dL for Studies OPAL-HK and TOURMALINE.

[c] Serum phosphate ULN >4.5 mg/dL in subjects aged <65 years, and >4.3 mg/dL in subjects aged ≥65 years for AMETHYST-DN and >4.8 mg/dL for OPAL-HK and TOURMALINE.

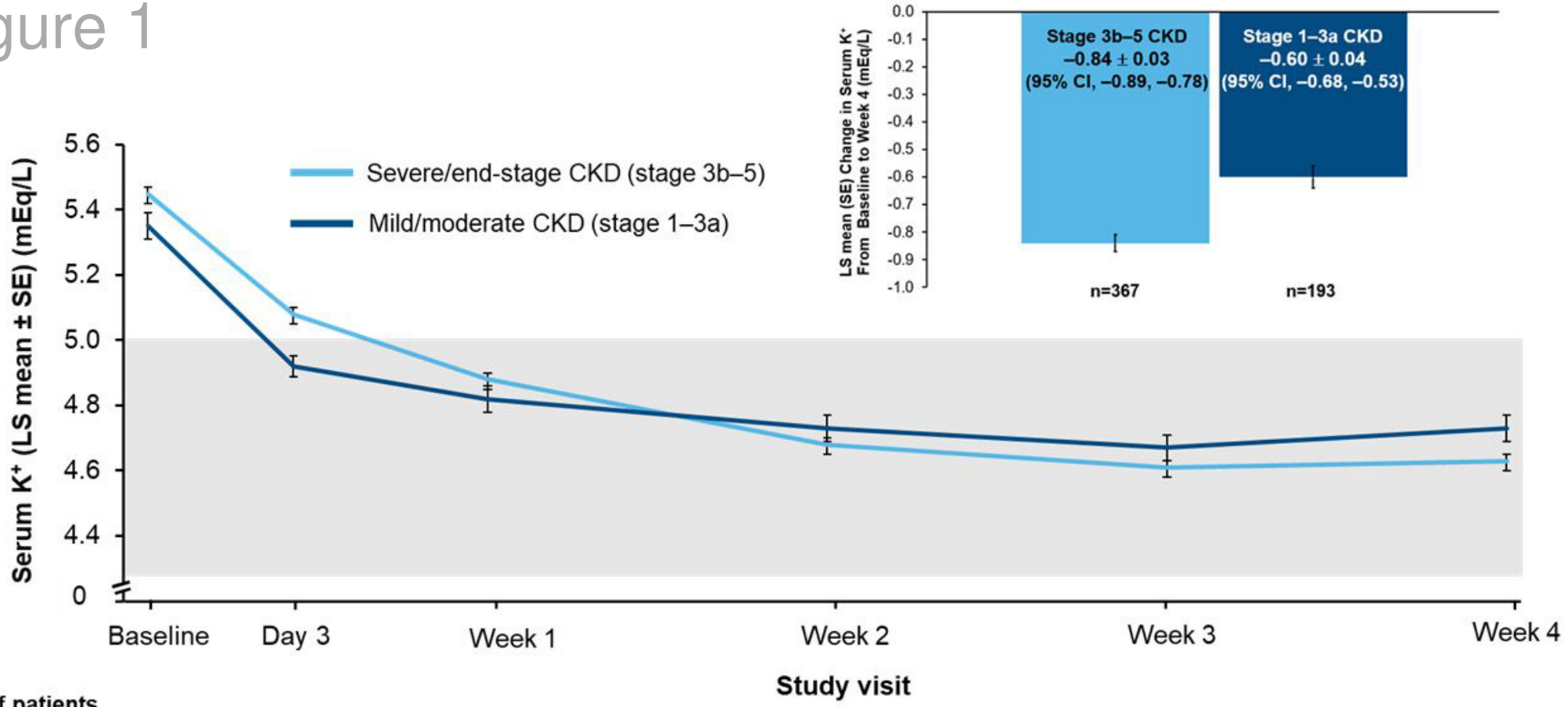
Ca^{2+}, calcium; CKD, chronic kidney disease; K^+, potassium; Mg^{2+}, magnesium, ULN, upper limit of normal.

Figure 1. Least squares mean (SE) serum potassium levels over time by study visit and change in serum potassium from baseline to Week 4 in patients with stage 3b–5 CKD or stage 1–3a CKD (Efficacy population; N=626)

Shaded area denotes target serum K^+ range: 3.8–5.0 mEq/L.

CI, confidence interval; CKD, chronic kidney disease; K^+, potassium; LS. least squares; SE, standard error of the mean.

Figure 1



No. of patients

Stage 3b–5 CKD:	417	404	406	390	378	367
Stage 1–3a CKD:	209	201	206	202	197	193

Supplemental Table 1. Comparison of trial design for AMETHYST-DN, OPAL-HK, and TOURMALINE

	AMETHYST-DN [18, 20]	OPAL-HK [19]	TOURMALINE
Design	52-week, phase 2, open-label, randomized study. The study had a run-in period of up to 4weeks, an 8-week treatment phase followed by a long-term maintenance phase of up to 44 weeks	12-week, phase 3, two-phase, single-blind, randomized withdrawal study. After the initial 4-week treatment phase, eligible patients entered a randomized withdrawal phase, and continued patiromer treatment or were switched to placebo for 8 weeks.	4-week, phase 4, open-label, randomized trial that evaluated patiromer administered without food versus with food
Patients	Adults with T2DM, CKD and hyperkalemia who were receiving RAASi	Patients with CKD and hyperkalemia who were receiving RAASi	Patients with hyperkalemia.
Patiromer dose	Patients with mild hyperkalemia (serum potassium >5.0–5.5 mEq/L) received patiromer at 8.4 g to 25.2 g/day, while those with moderate hyperkalemia (>5.5–<6.0 mEq/L) received 16.8 g to 33.6 g/day. Patiromer was titrated during the treatment period to reach and maintain serum potassium ≤5.0 mEq/L.	Patients with mild hyperkalemia (serum potassium 5.1–<5.5 mEq/L) received patiromer at 8.4 g, while those with moderate-to-severe hyperkalemia (≥5.5–<6.5 mEq/L) received 18.6 g/day. Patiromer was titrated to achieve and maintain serum potassium within the target range (3.8–<5.1mEq/L).	Patiromer was administered at a starting dose of 8.4 g/day and titrated in increments of 8.4 g/day (to a maximum of 25.2 g/day) to reach and maintain serum potassium levels in the target range of 3.8–5.0 mEq/L.
Main Inclusion criteria	1. Age 30 - 80 years old at screening 2. T2DM diagnosed after age 30 which has been treated with oral medications or insulin for at least 1 year 3. CKD: eGFR 15 - <60 mL/min/1.73m2 4. uACR: (Cohorts 1 and 2 only): ≥ 30 mg/g	1. Males and females ages 18 - 80 2. CKD - eGFR 15 to <60 mL/min/1.73m^2 3. Serum K+ 5.1 to <6.5 mEq/L 4. Receiving an ACE Inhibitor, an ARB, or an AA medication	5. Potassium concentration >5.0 mEq/L 6. Stable RAASi medication, if taking 7. Medications taken on a chronic basis are given once daily or twice daily

	5. Serum K+ values: Cohorts 1 and 2: 4.3 - 5.0 mEq/L at screening AND 4.5 - 5.0 mEq/L at randomisation AND >5.0 - <6.0 mEq/L at randomization to patiromer; Cohort 3: >5.0 - <6.0 mEq/L 6. Receiving an ACEI and/or ARB for at least 28 days prior to screening 7. SBP ≥130 - <180 mmHg AND average DBP ≥80 - <110 mmHg		
Main Exclusion criteria	1. Type 1 diabetes mellitus 2. HBa1C >12% (Cohort 1 and 2) 3. Emergency treatment for T2DM within the last 3 months 4. SBP >180 mmHg or DBP >110 mmHg 5. serum magnesium <1.4 mg/dL (<0.58 mmol/L) 6. uACR ≥10000 mg/g (Cohort 1 and 2) 7. Renal artery stenosis, diabetic gastroparesis, non-diabetic CKD 8. History of gastrointestinal disorders 9. NYHA Class III or IV heart failure 10. BMI ≥40 kg/m^2 11. Unstable angina, unresolved acute coronary syndrome, cardiac arrest or clinically significant ventricular arrhythmias, TIA or stroke, IV cardiac medication	1. Auto-immune related CKD 2. Uncontrolled Type 1 diabetes or HbA1c >10.0% 3. NYHA class IV heart failure 4. Major surgery or heart or kidney transplant in the past 3 months 5. Significant cardiovascular or cerebrovascular events in the past 2 months 6. BMI ≥ 40 kg/m^2	1. Expected need for dialysis 2. Major organ transplant 3. History of conditions associated with pseudohyperkalemia 4. History of gastrointestinal disorders 5. Cancer or unstable medical condition

	12. Kidney transplant, cancer, alcoholism, or drug/chemical abuse, raised liver enzymes 13. New or changed prescriptions for loop and thiazide diuretics or other antihypertensive medications 14. Use of polymer-based drugs, phosphate binders, other potassium binders, lithium, potassium sparing medications, potassium supplements, bicarbonate or baking soda	

AA: aldosterone antagonist; ACE: angiotensin-converting enzyme; ARB: angiotensin II receptor blocker; BMI: body mass index; CKD: chronic kidney disease; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration; HbA1c: haemoglobin A1c; K+: potassium; NYHA: New York Heart Association; RAASi: renin angiotensin aldosterone system inhibitors; SBP: systolic blood pressure; T2DM: Type 2 diabetes mellitus; uACR: urine albumin creatinine ratio.

Supplemental Table 2. Non-fatal treatment-emergent adverse events leading to treatment discontinuation, with onset during the first four weeks, by System Organ Class and Preferred Term

Adverse event	n (%) of patients	
	Patients with Stage 3b–5 CKD (n=421)	**Patients with Stage 1–3a CKD (n=211)**
≥ 1 AE leading to discontinuation of patiromer[a,b]	24 (6)	5 (2)
Renal and urinary disorders		
Worsening renal function	5 (1)	0
Acute kidney injury	1 (0.2)	0
Gastrointestinal disorders		
Vomiting	3 (0.7)	0
Diarrhea	2 (0.5)	1 (0.5)
Constipation	2 (0.5)	0
Flatulence	2 (0.5)	0
Nausea	1 (0.2)	0
Abdominal pain	1 (0.2)	0
Abdominal distension	0	1 (0.5)

Abdominal pain upper	0	1 (0.5)
Cardiac disorders		
Angina pectoris	1 (0.2)	0
Atrial fibrillation	0	1 (0.5)
General disorders and administration site conditions		
Fatigue	1 (0.2)	0
Vascular disorders		
Hypertensive crisis	1 (0.2)	0
Metabolism and Nutrition Disorders		
Hypokalemia	2 (0.5)	0
Anorexia	1 (0.2)	0
Infections and infestations		
Urinary tract infection	1 (0.2)	0
Musculoskeletal and connective tissue disorders		
Muscle spasms	1 (0.2)	0
Immune system disorders		
Hypersensitivity	0	1 (0.5)
Investigations		
Glomerular filtration rate decreased	2 (0.5)	0

[a]Some patients may have discontinued patiromer due to >1 adverse event.

[b]In 9 patients, these events were adjudicated by the investigator to be treatment-related: abdominal pain (one patient), constipation (two patients), diarrhea (two patients),

flatulence (two patients), vomiting (two patients); none of these events were serious or severe.

AE, adverse event; CKD, chronic kidney disease.

Supplemental Table 3: Serious treatment-emergent adverse events with onset during the first four weeks, by System Organ Class and Preferred Term

No. of patients (%)	Patients with CKD stage 3b–5 (n=421)	Patients with CKD stage 1–3a (n=211)
≥1 serious adverse event[a]	**16 (4)**	**3 (1)**
Cardiac disorders	**4 (1.0)**	**1 (0.5)**
Atrial fibrillation	1 (0.2)	1 (0.5)
Angina pectoris	1 (0.2)	0
Cardiorespiratory arrest[b]	1 (0.2)	0
Myocardial infarction[b]	1 (0.2)	0
Renal and urinary disorders	**5 (1)**	**(0)**
Worsening renal function	4 (1)	0
Acute kidney injury	1 (0.2)	0
Infections and infestations	**2 (0.5)**	**1 (0.5)**
Arteriosclerotic gangrene	0	1 (0.5)
Escherichia bacteremia	1 (0.2)	0
Gastrointestinal infection	1 (0.2)	0
Urinary tract infection	1 (0.2)	0
Vascular disorders	**2 (0.5)**	**1 (0.5)**
Diabetic vascular disorder[b]	0	1 (0.5)
Hypertensive crisis	1 (0.2)	0

Intermittent claudication	1 (0.2)	0
Blood and lymphatic system disorders	**1 (0.2)**	**0**
Anemia	1 (0.2)	0
Gastrointestinal disorders	**1 (0.2)**	**0**
Mesenteric artery thrombosis[b]	1 (0.2)	0
General disorders and administration site conditions	**1 (0.2)**	**0**
Sudden cardiac death[b]	1 (0.2)	0
Investigations	**1 (0.2)**	0
Anticoagulation drug level below therapeutic level	1 (0.2)	0
Metabolism and nutrition disorders	**1 (0.2)**	0
Gout	1 (0.2)	0

[a] No serious adverse events were considered related to treatment with patiromer.

[b] Adverse event led to death.

CKD, chronic kidney disease.

Supplemental Table 4. Mean (SD) serum calcium, phosphate and magnesium at baseline, Week 4 and change from baseline to Week 4 (safety population; N=632)

	Patients with Stage 3b–5 CKD (n=421)	**Patients with Stage 1–3a CKD (n=211)**
Mean (SD) serum Ca^{2+}, mg/dL		
Baseline[a]	9.21 (0.65)	9.51 (0.51)
Week 4[a]	9.23 (0.63)	9.55 (0.50)
Change from baseline to Week 4	−0.005 (0.55)	+0.043 (0.50)
Mean (SD) serum Mg^{2+}, mg/dL		
Baseline[a]	2.14 (0.31)	2.0 (0.24)
Week 4[a]	1.95 (0.27)	1.88 (0.27)
Change from baseline to Week 4	−0.19 (0.28)	−0.12 (0.21)
Mean (SD) phosphate, mg/dL		
Baseline[a]	3.97 (0.73)	3.58 (0.60)
Week 4[a]	3.76 (0.87)	3.48 (0.66)
Change from baseline to Week 4	−0.19 (0.80)	−0.11 (0.74)

[a]Not all patients had baseline or post-baseline measurements available.

Ca^{2+}, calcium; CKD, chronic kidney disease; Mg^{2+}, magnesium; SD, standard deviation.

Supplemental Table 5. Mean (SD) eGFR and spot urine ACR at baseline, Week 4 and change from baseline to Week 4 (safety population; N=632)

	Patients with Stage 3b–5 CKD (n=421)	**Patients with Stage 1–3a CKD (n=211)**
Mean (SD) eGFR, mL/min/1.73m^2		
Baseline[a]	27.9 (8.9)	58.1 (12.7)
Week 4[a]	31.0 (13.4)	59.4 (16.2)
Change from baseline to Week 4	+2.6 (10.0)	+0.9 (13.6)
Mean (SD) spot urine ACR (mg/g)		
Baseline[a]	1249.9 (1913.4)	599.8 (1235.9)
Week 4[a]	887.9 (1416.9)	634.9 (1375.1)
Change from baseline to Week 4	−213.6 (1118.65)	+4.4 (905.08)

[a]Not all patients had baseline or post-baseline measurements available.

ACR, albumin–creatinine ratio; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; SD, standard deviation.