Effect of Patiromer on Serum Potassium Level in Patients With Hyperkalemia and Diabetic Kidney Disease
The AMETHYST-DN Randomized Clinical Trial

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IMPORTANCE Hyperkalemia is a potentially life-threatening condition predominantly seen in patients treated with renin-angiotensin-aldosterone system (RAAS) inhibitors with stage 3 or greater chronic kidney disease (CKD) who may also have diabetes, heart failure, or both.

OBJECTIVES To select starting doses for a phase 3 study and to evaluate the long-term safety and efficacy of a potassium-binding polymer, patiromer, in outpatients with hyperkalemia.

DESIGN, SETTING, AND PARTICIPANTS Phase 2, multicenter, open-label, dose-ranging, randomized clinical trial (AMETHYST-DN), conducted at 48 sites in Europe from June 2011 to June 2013 evaluating patiromer in 306 outpatients with type 2 diabetes (estimated glomerular filtration rate, 15 to <60 mL/min/1.73 m² and serum potassium level >5.0 mEq/L). All patients received RAAS inhibitors prior to and during study treatment.

INTERVENTIONS Patients were stratified by baseline serum potassium level into mild or moderate hyperkalemia groups and received 1 of 3 randomized starting doses of patiromer (4.2 g [n = 74], 8.4 g [n = 74], or 12.6 g [n = 74] twice daily [mild hyperkalemia] or 8.4 g [n = 26], 12.6 g [n = 28], or 16.8 g [n = 30] twice daily [moderate hyperkalemia]). Patiromer was titrated to achieve and maintain serum potassium level 5.0 mEq/L or lower.

MAIN OUTCOMES AND MEASURES The primary efficacy end point was mean change in serum potassium level from baseline to week 4 or prior to initiation of dose titration. The primary safety end point was adverse events through 52 weeks. Secondary efficacy end points included mean change in serum potassium level through 52 weeks.

RESULTS A total of 306 patients were randomized. The least squares mean reduction from baseline in serum potassium level at week 4 or time of first dose titration in patients with mild hyperkalemia was 0.35 (95% CI, 0.22-0.48) mEq/L for the 4.2 g twice daily starting-dose group, 0.51 (95% CI, 0.38-0.64) mEq/L for the 8.4 g twice daily starting-dose group, and 0.55 (95% CI, 0.42-0.68) mEq/L for the 12.6 g twice daily starting-dose group. In those with moderate hyperkalemia, the reduction was 0.87 (95% CI, 0.60-1.14) mEq/L for the 8.4 g twice daily starting-dose group, 0.97 (95% CI, 0.70-1.23) mEq/L for the 12.6 g twice daily starting-dose group, and 0.92 (95% CI, 0.67-1.17) mEq/L for the 16.8 g twice daily starting-dose group (P < .001 for all changes vs baseline by hyperkalemia starting-dose groups within strata). From week 4 through week 52, statistically significant mean decreases in serum potassium levels were observed at each monthly point in patients with mild and moderate hyperkalemia. Over the 52 weeks, hypomagnesemia (7.2%) was the most common treatment-related adverse event, mild to moderate constipation (6.3%) was the most common gastrointestinal adverse event, and hypokalemia (<3.5 mEq/L) occurred in 5.6% of patients.

CONCLUSIONS AND RELEVANCE Among patients with hyperkalemia and diabetic kidney disease, patiromer starting doses of 4.2 to 16.8 g twice daily resulted in statistically significant decreases in serum potassium level after 4 weeks of treatment, lasting through 52 weeks.

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Hyperkalemia is a potentially life-threatening condition.\textsuperscript{1,2} Patients at the highest risk for hyperkalemia are those taking renin-angiotensin-aldosterone system (RAAS) inhibitors with stage 3 or greater chronic kidney disease (CKD) who also have diabetes mellitus, heart failure, or both.\textsuperscript{3,8} Owing to the limited utility of current options to manage hyperkalemia, particularly over the long term, clinicians frequently must either avoid using RAAS inhibitors or use them at lower than recommended doses.\textsuperscript{9-11}

Patiromer for oral suspension is an orally administered drug being investigated for the treatment of hyperkalemia. The active moiety, patiromer, is a nonabsorbed polymer that binds potassium throughout the gastrointestinal tract, thus increasing fecal excretion of potassium and lowering serum potassium levels.\textsuperscript{12} Patiromer consists of smooth, spherical beads approximately 100 μm in diameter that do not swell appreciably in liquids.\textsuperscript{13} Prior patiromer clinical trials have demonstrated the drug’s utility in treating hyperkalemia in at-risk populations for periods ranging from a few days to up to 12 weeks.\textsuperscript{12,14} PEARL-HF (N = 105) demonstrated the efficacy and safety of patiromer (15 g twice daily, equivalent to 12.6 g twice daily using the updated dosing nomenclature) in preventing the development of hyperkalemia over 4 weeks in normokalemic patients with heart failure, with or without kidney disease, who were started on spironolactone therapy.\textsuperscript{15} OPAL-HK (N = 243) showed the efficacy and safety of patiromer starting doses, 4.2 or 8.4 g twice daily, in treating mild or moderate-to-severe hyperkalemia, respectively, over 4 weeks in patients with CKD maintained while receiving RAAS inhibitors.\textsuperscript{12} OPAL-HK further demonstrated that when patiromer treatment was stopped at the end of the active treatment period, hyperkalemia rapidly recurred over 8 weeks, indicating the need for persistent treatment to maintain normokalemia.\textsuperscript{12} We present a study evaluating the effects of a range of starting doses of patiromer on serum potassium levels after 4 weeks in outpatients with hyperkalemia as well as patiromer safety and efficacy over a 52-week period.

## Methods

### Study Objectives

The AMETHYST-DN phase 2 multicenter, open-label, dose-ranging randomized clinical trial was conducted to inform dose selection for a phase 3 study using data from patients evaluated through 4 weeks, as well as to evaluate the 52-week safety and efficacy of patiromer in patients with diabetes and CKD receiving therapy with an angiotensin-converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB), or both, with or without spironolactone.

### Study Oversight

The study was conducted at 48 sites in 5 European countries. The protocol was approved by local or national independent ethics committees at each study site and performed in accordance with the International Conference on Harmonisation E6 Guideline for Good Clinical Practice, the Declaration of Helsinki principles, and local or national independent ethics committee requirements (study protocol available in Supplement 1).

The study was conducted in accordance with the European Union Clinical Trials Directive 2001/20/EC (European Union common technical document) for sites in the European Union. All patients provided written informed consent before any study-specific procedures were performed.

### Participants

The first patient was enrolled in June 2011 and the last patient completed the study in June 2013. Patients aged 30 to 80 years were eligible if they had type 2 diabetes and CKD, with or without hypertension. Based on data suggesting differences in hyperkalemia by race,\textsuperscript{16-18} information on race/ethnicity was collected by patient self-report from a selection of fixed categories. Chronic kidney disease was defined as an estimated glomerular filtration rate of 15 mL/min/1.73 m\textsuperscript{2} to less than 60 mL/min/1.73 m\textsuperscript{2} at screening (calculated using either the Chronic Kidney Disease Epidemiology Collaboration equation\textsuperscript{19} or the Modification of Diet in Renal Disease Study equation). All patients had been receiving an ACE inhibitor, ARB, or both for at least 28 days prior to screening.

### Study Design

The open-label study consisted of a screening visit, a run-in period of up to 4 weeks’ duration, an 8-week treatment phase followed by a long-term maintenance phase of up to 44 weeks’ duration (up to 52 weeks of total treatment), and a posttreatment follow-up period of up to 4 weeks’ duration (eFigure 1 in Supplement 2). Patients with serum potassium levels of 4.3 to 5.0 mEq/L (ie, normokalemia) at the screening visit and who had uncontrolled blood pressure (average sitting systolic blood pressure >130 to ≤180 mm Hg and diastolic blood pressure >80 to ≤110 mm Hg) were entered into the run-in period and randomly assigned in a 3:1 ratio into cohort 1 or cohort 2. A run-in period was conducted to identify patients without hyperkalemia who could potentially benefit from initiation or optimization of RAAS therapy. At the start of the run-in, patients in cohort 1 discontinued use of ACE inhibitor therapy, ARB therapy, or both and started losartan (100 mg/d), with the addition of spironolactone (25 mg/d) at the week 2 run-in visit if a blood pressure target of 130/80 mm Hg was not attained. Patients in cohort 2 remained taking prescribed ACE inhibitor, ARBs, or both and started spironolactone (25 mg/d). In both cohort 1 and cohort 2, the dose of spironolactone could be increased to 50 mg/d if needed for blood pressure control. Patients who developed hyperkalemia at any time during the 4-week run-in were eligible to be randomized into the treatment phase.

During the initial study enrollment, many patients who otherwise met the eligibility criteria were excluded from participation because they were hyperkalemic. The protocol was therefore amended to add a third cohort to allow inclusion of eligible patients with preexisting hyperkalemia. For cohort 3, eligible patients with serum potassium levels greater than 5.0 to less than 6.0 mEq/L at screening continued the use of prescribed ACE inhibitor, ARBs, or both, skipped the run-in, and were randomized directly into the treatment phase. After the
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Original Investigation Research

protocol amendment, all eligible patients without hyperkalemia entered cohort 1 only, while enrollment into cohort 2 was discontinued.

Eligible patients from all 3 cohorts were stratified by baseline serum potassium level (stratum 1: >5.0-5.5 mEq/L [mild hyperkalemia]; stratum 2: >5.5-6.0 mEq/L [moderate hyperkalemia]) and randomly assigned in a 1:1:1 ratio to 1 of 3 patiromer starting doses per stratum (mild hyperkalemia: 4.2 g, 8.4 g, or 12.6 g twice daily [8.4 g/d, 16.8 g/d, 25.2 g/d]; moderate hyperkalemia: 8.4 g, 12.6 g, or 16.8 g twice daily [16.8 g/d, 25.2 g/d, 33.6 g/d]). A validated interactive web response system was used to assign patients to cohorts and starting doses using computer-generated randomization lists stratified by cohort, with a block size of 3.

After the baseline visit (day 1), patients returned for an assessment at day 3 (48 hours after the first patiromer dose), week 1, and weekly thereafter during the 8-week treatment phase. During the 44-week maintenance phase, patients were seen monthly, unless more frequent monitoring was required per protocol. The patiromer dose could be titrated upward or downward in a stepwise fashion to the individualized effective dose to maintain control of serum potassium level (eFigure 2A-D in Supplement 2). All patients (those who completed the entire 52-week treatment and those who withdrew early from the study) continued into the posttreatment follow-up period.

Non–RAAS inhibitor antihypertensive drug changes were allowed throughout the study if additional blood pressure reduction was required to achieve target levels (<130/80 mm Hg).

At the beginning of the follow-up period, patiromer was stopped, as were all RAAS inhibitor medications for patients with potassium levels greater than 5.0 mEq/L; these patients were followed up for 2 visits within 7 days of completing treatment or from early termination of study participation (day 3 and week 1 posttreatment). Patients with serum potassium levels of 5.0 mEq/L or less stopped patiromer but continued receiving RAAS inhibitor medications; these patients were followed up for 4 weeks (day 3 and weekly visits through week 4 posttreatment).

On study visit days, patients were instructed to take the morning patiromer dose before the visit. Blood was drawn for measurement of serum potassium level at approximately the same time on the morning of each study visit and tested by both local and central laboratories. Local laboratory measurements were used for assessments of serum potassium inclusion criteria and for testing related to the clinical care of patients. Central laboratory measurements were used for assessments of baseline values and efficacy and safety analyses. Adverse events and other safety data were obtained at each visit. Patients were counseled at each visit to restrict their intake of high-potassium foods (>250 mg/100 g) and to maintain a low-potassium diet (potassium intake of ≤3 g/d).²⁰

Study End Points
The primary efficacy end point was the mean change in central laboratory serum potassium level from baseline to week 4 or prior to the initiation of dose titration. The primary safety end point was the frequency and severity of adverse events through the end of the maintenance phase at week 52. Secondary efficacy end points included mean changes in serum potassium level from baseline to other postbaseline visits. Baseline was the last available measurement taken prior to the start of administration of patiromer. Adverse events, laboratory assessments, electrocardiograms, and vital signs were summarized descriptively for the entire study period. Analysis of the primary and secondary efficacy end points and safety was based on the intention-to-treat population, which included all patients who were randomized and received a dose of patiromer.

Prior to database lock and after the last patient’s follow-up visits were completed, a safety review board was convened to independently review all deaths occurring within the study. Adjudication was performed for cause of death and whether the death was related to hypokalemia or hyperkalemia.²¹

Sample Size Calculations and Statistics
A sample size of 42 patients for each patiromer starting-dose group provided 90% power to detect an effect size of 0.5 (assuming a mean change of 0.3 [SD, 0.6] mEq/L), for the mean change in serum potassium level from baseline to week 4 or prior to the initiation of dose titration of patiromer. The effect size is based on the variability in serum potassium levels observed in a phase 2 hyperkalemia prevention study,²² as well as consideration of a clinically meaningful difference for the mean change in serum potassium levels in a hyperkalemia treatment study, as estimated by the authors responsible for the study concept and design. The test was based on a 2-sided, 1-sample paired t test and a significance level of α = .05. Approximately 50 patients were to be randomized to each starting dose (300 total), assuming a 15% nonevaluable rate.

A parallel-lines analysis of covariance model, with treatment factor and baseline serum potassium level as the covariate, was used for the analysis of the primary efficacy measure within each stratum. For patients who required dose titration or who discontinued before week 4, the primary efficacy end point was the last observed data prior to titration or discontinuation. For the prespecified secondary end points, the mean changes in serum potassium level from baseline to postbaseline visits were analyzed according to observed data at the time point of interest using t tests. No adjustment of type I error for multiple comparisons was applied because the purpose of the study was to determine a starting dose and not to assess superiority between 2 or more treatment groups. In a post hoc analysis, changes in serum potassium levels at postbaseline time points through week 52 were estimated for each stratum using a mixed-effects repeated-measures model with central laboratory serum potassium value as the dependent variable, time point and starting dose as fixed-effect predictors, baseline central laboratory serum potassium value as a continuous covariate, and patient as a random effect. An unstructured correlation matrix was fit.

All analyses were conducted using SAS version 9.3 (SAS Institute Inc). A prespecified interim analysis was conducted to support dose selection for the phase 3 patiromer trial. The statistical analysis plan is available in Supplement 1.
Results

A total of 324 patients were enrolled; 222 patients entered stratum 1 (mild hyperkalemia) and 84 entered stratum 2 (moderate hyperkalemia), for a total of 306 randomized patients (Figure 1). Disposition by cohort is shown in eFigures 3A and 3B in Supplement 2; 77% of patients entering run-in became hyperkalemic; the median time to hyperkalemia after initiation of RAAS inhibitor therapy was 15 days (95% CI, 14-22 days) (see eFigure 4 in Supplement 2 for additional details on the stability of potassium values during the run-in). Two patients with mild hyperkalemia did not receive patiromer and therefore were not included in the efficacy or safety analyses. Of the 304 patients evaluated at week 4 or time of first dose titration, 300 were analyzed for the primary efficacy end point. One patient each with mild hyperkalemia in the patiromer 8.4 g/d and 25.2 g/d groups and 1 patient with moderate hyperkalemia in the patiromer 25.2 g/d group were excluded from the analysis because of missing baseline values. A patient with mild hyperkalemia in the patiromer 33.6 g/d group was excluded because of a lack of available central laboratory results. Disposition for the entire study is presented in Figure 1.

Mean baseline age of the study population was 66.3 years; 63.2% were men and 100% were white (Table 1). All patients had hypertension and type 2 diabetes; 65% had stage 3 CKD and 22% had stage 4 CKD; 35% had heart failure. Median ratio of albumin to creatinine was 300 (interquartile range, 50-1490) mg/L. Mean serum potassium level at baseline was 5.3 mEq/L. For patients who were hyperkalemic at screening, serum potassium level was confirmed by a second value; mean data for each value are shown in eTable 1 in Supplement 2. Baseline characteristics by starting-dose group were generally balanced within each stratum (Table 1). Baseline characteristics for patients who prematurely discontinued and for those who completed the study are shown in eTable 2 in Supplement 2. As described in the methods, all patients received RAAS inhibitor medications during the treatment and maintenance phases of the study.

Efficacy

The least squares mean reduction from baseline in serum potassium level at week 4 or at the time of first dose titration in patients with mild hyperkalemia was 0.35 (95% CI, 0.22-0.48) mEq/L for the 8.4 g/d group, 0.51 (95% CI, 0.38-0.64) mEq/L for the 16.8 g/d group, and 0.55 (95% CI, 0.42-0.68) mEq/L for the 25.2 g/d group. In those with moderate hyperkalemia, the least squares mean reduction from baseline in serum potassium level at week 4 or at the time of first dose titration was 0.87 (95% CI, 0.60-1.14) mEq/L for the 16.8 g/d group, 0.97 (95% CI, 0.70-1.23) mEq/L for the 25.2 g/d group, and 0.92 (0.67-1.17) mEq/L for the 33.6 g/d group (P < .001 for all changes compared with baseline by hyperkalemia strata and by starting-dose groups within strata) (Figure 2). Change from baseline at week 8 (end of treatment phase) is also shown in Figure 2. Based in part on the prespecified interim analysis of the primary efficacy end point (see Supplement 1 for details) the lowest starting doses were chosen for patients with mild hyperkalemia (8.4 g/d) and those with moderate hyperkalemia (16.8 g/d) for the phase 3 patiromer trial.

Results for the prespecified analysis (observed cases) of mean serum potassium level over the entire study, including posttreatment follow-up, are shown in eFigures 6 and 7 in Supplement 2. Results of a post hoc, mixed-model, repeated-measures analysis that included all available potassium measurements are shown in Figure 3 and were consistent with the prespecified analysis. Significant (P < .001) reductions in mean serum potassium level were seen at the first postbaseline assessment, approximately 48 hours after patiromer initiation, in both stratum 1 (mild hyperkalemia) and stratum 2 (moderate hyperkalemia). From baseline least squares means of 5.2 mEq/L (stratum 1) and 5.7 mEq/L (stratum 2), mean serum potassium levels below 5.0 mEq/L were seen by 48 hours (stratum 1) and week 1 (stratum 2). eFigures 6 and 7 in Supplement 2 show the time to normal serum potassium level, by stratum, in the 8-week treatment phase.

From week 4 through week 52, significant (P < .001) mean decreases from baseline in serum potassium levels were observed at each monthly time point in patients with mild and moderate hyperkalemia (Figure 3). Similar results were seen by starting-dose group within each stratum and by cohort (eFigures 8-10 in Supplement 2). The majority of patients who entered the maintenance phase had serum potassium levels within the target range (3.8-5.0 mEq/L). The proportion of patients with potassium levels within target range at each scheduled visit of the maintenance phase through week 52 ranged from 83.1% to 92.7% in patients with mild hyperkalemia (n = 180) and from 77.4% to 95.1% in patients with moderate hyperkalemia (n = 66).

Patients discontinuing patiromer (either prematurely or at the end of the maintenance phase [week 52]) were to be followed up for up to 28 days to assess changes in serum potassium levels and potential safety concerns in this withdrawal period. A total of 238 patients (172 with mild hyperkalemia and 66 with moderate hyperkalemia at baseline) entered the posttreatment follow-up. Significant (P < .001) increases in least squares mean serum potassium levels were seen by day 3 posttreatment in patients with mild hyperkalemia (0.25 [95% CI, 0.19-0.31] mEq/L) (n = 63) and moderate hyperkalemia (0.33 [95% CI, 0.20-0.46] mEq/L) (n = 58). Twenty-eight days following the cessation of patiromer treatment, the least squares mean increase in serum potassium level was 0.39 (95% CI, 0.32-0.46) mEq/L in patients with mild hyperkalemia (n = 126) and 0.48 (95% CI, 0.31-0.62) mEq/L in those with moderate hyperkalemia (n = 47) (P < .001 for both strata).

Patiromer Dosing During the Treatment Phase

Mean daily doses at week 4 and week 4 through 8, respectively, were 18.5 (SD, 7.9) g/d and 19.6 (SD, 9.3) g/d in patients with mild hyperkalemia and 26.9 (SD, 8.3) g/d and 28.0 (SD, 12.4) g/d in patients with moderate hyperkalemia. In both strata, the majority of patients in all starting-dose groups had either no titrations or 1 titration during the treatment phase, with a dose increase being more common than...
Figure 1. Patient Disposition by Assigned Strata (Mild or Moderate Hyperkalemia) and Starting Dose Over 52 Weeks

535 Patients screened

211 Excluded
98 Noneligible eGFR\textsuperscript{a}
52 Noneligible serum potassium level
43 Noneligible ACR\textsuperscript{a}
8 Withdraw consent
3 Did not meet other eligibility criteria
3 Other

324 Enrolled

4-Week run-in period
79 With serum potassium 4.3 to 5.0 mEq/L (normokalemic) and uncontrolled blood pressure\textsuperscript{b}
76 Randomized to cohort 1 (discontinued RAAS inhibitor and started losartan plus spironolactone after 2 wk if needed for blood pressure control)
3 Randomized to cohort 2 (continued current RAAS inhibitor and added spironolactone)
18 Excluded
17 Serum potassium ≤5.0 mEq/L
  1 Serum potassium 6.2 mEq/L

Non run-in period
245 With serum potassium >5.0 to <6.0 mEq/L (cohort 3)
continued current RAAS inhibitor

306 Randomized and stratified by baseline serum potassium

Stratum 1
222 Mild hyperkalemia (serum potassium >5.0 to 5.5 mEq/L)
74 Randomized to receive 8.4 g/d patiromer
74 Received patiromer as randomized
73 Received patiromer as randomized
  1 Did not receive patiromer
18 Discontinued patiromer treatment
  6 Withdraw consent
  4 Adverse event
  3 Nonadherence
  1 Died
  1 High serum potassium
  1 Low serum potassium
  2 Other
56 Completed treatment
73 Included in primary analysis
  1 Excluded (week 4 results available but missing baseline data)
74 Included in primary analysis
  2 Excluded
  1 Did not receive patiromer
  1 No central laboratory results available before titration
73 Included in primary analysis

Stratum 2
84 Moderate hyperkalemia (serum potassium >5.5 to <6.0 mEq/L)
28 Randomized to receive 16.8 g/d patiromer
28 Received patiromer as randomized
26 Randomized to receive 25.2 g/d patiromer
26 Received patiromer as randomized
24 Discontinued patiromer treatment
  5 Withdraw consent
  7 Adverse event
  4 Nonadherence
  1 High serum potassium
  1 Low serum potassium
  3 Other
9 Discontinued patiromer treatment
  2 Withdraw consent
  2 Adverse event
  1 Nonadherence
  4 Died
  1 Abnormal renal function
  1 Other
21 Completed treatment
27 Included in primary analysis
  1 Excluded (week 4 results available but missing baseline data)

ACR indicates albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate.
\textsuperscript{a} Only if serum potassium level was eligible at screening visit 1.
a dose decrease. Overall, the mean number of titrations across the dose groups in each stratum was similar. Through week 4, in patients with mild hyperkalemia, 47.3% in the 8.4 g/d group, 58.9% in the 16.8 g/d group, and 65.8% in the 25.2 g/d group had no dose adjustments. In patients with moderate hyperkalemia, 53.8% in the 16.8 g/d group, 50.0% in the 25.2 g/d group, and 33.3% in the 33.6 g/d group had no dose adjustments. In patients with mild hyperkalemia,
35.1% in the 8.4 g/d group, 26.0% in the 16.8 g/d group, and 31.5% in the 25.2 g/d group had 1 dose adjustment. In patients with moderate hyperkalemia, 26.9% in the 16.8 g/d group, 32.1% in the 25.2 g/d group, and 36.7% in the 33.6 g/d group had 1 dose adjustment.

Mean daily doses at week 4 and weeks 4 through 8 were similar to the assigned starting dose in each dose group in both strata. Over the entire 52-week study, mean daily patiromer doses were similar to those at week 4 through week 8 (19.4 [SD, 9.1] g/d and 27.2 [SD, 10.8] g/d in patients with...
Abbreviation: CKD, chronic kidney disease.

At least 1 adverse event leading to patiromer discontinuation occurred in 28 patients (9.2%) overall (20 patients [9.1%] with mild hyperkalemia and 8 [9.5%] with moderate hyperkalemia). The most common adverse events leading to treatment discontinuation were worsening of CKD (8 patients [2.6%]) and hypokalemia (5 patients [1.6%]; none with serum potassium level <3.0 mEq/L). A single patient discontinued due to a hypertension-related adverse event (hypertensive crisis). This event was not related to patiromer, per the investigator. No patient discontinued patiromer because of hypomagnesemia.

Serious adverse events were reported for 44 patients (14.5%); none were attributed to patiromer by the investigator. The most common serious adverse event was worsening of CKD (6 patients [2.0%]) (eTable 4 in Supplement 2). Over 52 weeks, 15 patients (4.9%) died; 11 of the 15 deaths were assessed by the safety review board as related to cardiovascular causes (sudden cardiac death in 7 patients and acute myocardial infarction in 4 patients; 10 had a prior history of either atherosclerotic heart disease, heart failure, or both). No deaths were considered by study investigators to be related to patiromer, and none were considered by the safety review board to be related to hyperkalemia or hypokalemia. None of the patients who died had a last observed potassium value below the normal limit. Among 7 patients who experienced sudden cardiac death, none had serum magnesium levels less than 1.58 mg/dL, measured at the last observation (Supplement 2).

Reductions in systolic and diastolic blood pressure were observed in all starting-dose groups in both strata. Mean blood pressure at baseline was 153.5/83.6 mm Hg in patients with mild hyperkalemia and 153.8/81.9 mm Hg in patients with moderate hyperkalemia. Mean blood pressure decreases from baseline were seen as early as day 3 (9.1/4.5 mm Hg in patients with mild hyperkalemia and 8.0/4.0 mm Hg in patients with moderate hyperkalemia) (eTable 5 in Supplement 2). Reductions were observed at 4 weeks in both strata (11.2/6.8 mm Hg and 8.0/5.8 mm Hg, respectively), suggesting that there was minimal additional dose titration to maintain control of serum potassium levels after week 8. Across starting-dose groups and strata, adherence over the entire study ranged from 86.7% to 95.9%.

**Safety**

Over the 52 weeks, 69% of patients reported at least 1 treatment-emergent adverse event, with 20% reporting an adverse event considered by the investigator to be related to patiromer. The most frequently reported adverse events (≥5.0% of patients, regardless of stratum or starting-dose group) were worsening of CKD (9.2%), hypomagnesemia (8.6%), worsening of hypertension (7.9%), constipation (6.3%), and diarrhea (5.6%) (Table 2). Among treatment-related adverse events, the most frequently reported were hypomagnesemia (7.2%), constipation (4.6%), and diarrhea (2.7%). The adverse event of worsening of hypertension was considered related to patiromer in 1 patient (0.3%). No adverse events of worsening CKD were considered by study investigators to be related to study drug. Mean serum magnesium level remained in the normal range (1.5-2.4 mg/dL) throughout the 52-week treatment period and was relatively constant. Mean change from baseline to week 4 ranged from −0.10 to −0.20 mg/dL in patients with mild hyperkalemia and from −0.10 to −0.30 in patients with moderate hyperkalemia, with mean changes from baseline at subsequent visits in a similar range and independent of dose, including at week 52 (end of treatment) (eTable 3 in Supplement 2). No patient developed severe hypomagnesemia (<1.0 mEq/L), and no patient had cardiac arrhythmias or neuromuscular abnormalities that were temporally associated with hypomagnesemia (Supplement 2).

All cases of constipation were mild to moderate, and only 2 patients discontinued as a result of this event. Over the 52 weeks, hypokalemia (serum potassium <3.5 mEq/L) occurred in 17 patients (5.6%), with no patients developing a serum potassium level less than 3.0 mEq/L.
Potassium levels and control volume in patients with advanced CKD.1,2 Hyperkalemia develops in approximately 10% of outpatients within 1 year after initiation of RAAS inhibitor therapy.23 AMETHYST-DN was designed to assess the efficacy of patiromer in high-risk patients for development of hyperkalemia at 4 weeks as well as long-term safety.

Patiromer consistently maintained normal serum potassium levels over 52 weeks, with few patients requiring dose titration. Over this period, patiromer use demonstrated high adherence, low risk of hypokalemia, and minimal discontinuations because of adverse events. Treatment discontinuations were largely driven by withdrawal of consent, which may be attributable in part to study duration and frequency of study visits during the treatment period, both of which are potentially burdensome to patients.

We believe that patient selection was clinically relevant, because patients at greatest risk for hyperkalemia include those with diabetes and those with impaired renal function.24 Diuretics are frequently used to prevent the increase in serum potassium levels and control volume in patients with advanced CKD.1,2 However, because these agents can induce intravascular volume depletion, leading to a reduction in kidney function as well as increase the risk of diabetes and gout, they are not ideal agents for lowering serum potassium levels over the long term. Other approaches have included chronic sodium bicarbonate therapy with diuretics; however, this combination has other unintended consequences, such as metabolic alkalosis and sodium retention.

Sodium polystyrene sulfonate is the only drug specifically indicated for the treatment of hyperkalemia in the United States.25 Use of this compound has been problematic because of concerns over questionable efficacy in removing potassium and poor gastrointestinal tolerability.26-27 Although rare, bowel necrosis has been reported and is associated with a relatively high mortality rate28-31 and has led to warnings in the prescribing information about this complication.25,32 In addition, given that sodium is the counter exchange ion, caution is advised when sodium polystyrene sulfonate is administered to patients who cannot tolerate even a small increase in sodium load (ie, those with severe congestive heart failure, severe hypertension, or marked edema).25

Patiromer, a novel potassium-binding polymer, uses calcium rather than sodium as the counter ion exchange, thus avoiding the risk of a sodium load in patients. No dose-related edema was observed in this trial, nor were any clinically relevant changes in serum calcium or phosphate levels detected after 52 weeks of treatment.

Reductions in mean systolic and diastolic blood pressure were observed in all starting-dose groups in both strata. Although there is no direct pharmacological mechanism to explain this magnitude of blood pressure reduction, a possible reason is that control of potassium allowed for continuation of RAAS inhibitor therapy, maximal dosing, or both. Additionally, better blood pressure control may reflect a combination of better patient adherence to antihypertensive medications as an effect of study participation, close monitoring by clinical sites, and effects of blood pressure medication adjustments. It is also acknowledged that this study was not designed to assess the effects of patiromer on blood pressure. Without a placebo control, these blood pressure changes are difficult to interpret and may represent, at least in part, regression to the mean. In spite of this decrease in mean blood pressure over time, adverse events of worsening hypertension were reported in 7.9% of patients. None appeared to be associated with a persistent serum potassium level less than 4.0 mEq/L but were generally ascribed to worsening of the underlying CKD.

Worsening of CKD was the most frequently reported adverse event during the trial and the most common adverse event leading to discontinuation. However, most of these adverse events occurred during the long-term maintenance phase, suggesting that the progression of underlying CKD may have been contributory. Consistent with this finding, the proportion of patients with more severe CKD (ie, stages 4-5) at baseline was higher among those who discontinued the study (32.3%) than among those who completed the study (19.9%) (eTable 2 in Supplement 2). One possible explanation for the higher rate of discontinuation among patients with advanced CKD is that continuation of RAAS inhibitor therapy will reduce GFR by as much as 20%
to 30% from baseline if blood pressure is lowered. However, in long-term outcome studies in CKD stage 3, RAAS inhibitor therapy has slowed CKD progression.33,34

Study limitations include the lack of blinding, which may have affected data recording and reporting through observer bias allowing for underreporting of adverse events; and the lack of a comparator, which raises the possibility of regression to the mean contributing to apparent reductions in serum potassium level. However, the stability of multiple screening measures for serum potassium level in cohort 3, the increase in serum potassium level after initiation of RAAS inhibitor therapy in cohorts 1 and 2, and the increase in potassium level during the follow-up period after discontinuation of patiromer argue against regression to the mean. Alternatives to this design were considered, but the study investigators did not think it clinically appropriate to use a placebo control in this long-term trial as this would subject study participants to the potentially life-threatening risks of hyperkalemia. The chronic use of polystyrene sulfonate compounds as blinded, active-control agents would have been difficult, given their poor gastrointestinal tolerability and unpleasant taste.35 The efficacy of patiromer was demonstrated in previously reported placebo-controlled trials (PEARL-HF and OPAL-HK),12-15 and the need for persistent therapy with the drug was evidenced by recurrent hyperkalemia on cessation of treatment.12 This study was designed to find an appropriate dose for a phase 3 trial. Additionally, it was designed to assess the long-term safety of varying doses.

Based on the findings of this study, a phase 3 study was performed in which patiromer demonstrated consistent efficacy as shown in our study.12 The consistency of results across the secondary end points supports the conclusions regarding long-term efficacy. The 52-week data support the finding of OPAL-HK, demonstrating that long-term management of serum potassium level is needed in patients with CKD taking RAAS inhibitors to reduce recurrence of hyperkalemia. Whether control of hyperkalemia and continued use of RAAS inhibitors (including dual RAAS inhibition) in stages 4 and 5 CKD will improve long-term outcomes remains to be established.

Conclusions

Among patients with hyperkalemia and diabetic kidney disease, patiromer starting doses of 4.2 to 16.8 g twice daily (8.4-33.6 g/d) resulted in statistically significant decreases in serum potassium levels after 4 weeks of treatment, lasting through 52 weeks.

ARTICLE INFORMATION

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REFERENCES


8. McMurray JJ, Adamopoulos S, Anker SD, et al; Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology: ESC Committee for Practice Guidelines. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology: Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2012;14(8):803-869.


