Patiromer and spironolactone in resistant hypertension and advanced CKD: analysis of the randomized AMBER trial

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Key Points

- In the AMBER trial, patiromer enabled more persistent spironolactone use in patients with resistant hypertension and advanced CKD.
- Efficacy of patiromer was comparable in prespecified subgroups with eGFR 25–<30 and 30–45 ml/min/1.73m².
- Safety of patiromer was consistent between eGFR subgroups and prior reports, with no new safety signals even in the 25–<30 eGFR subgroup.

Abstract

**Background:** Mineralocorticoid receptor antagonists reduce mortality in patients with heart failure with reduced ejection fraction and have become a standard of care in those with resistant hypertension (rHTN). Yet their use is limited among patients with chronic kidney disease (CKD), primarily due to hyperkalemia.

**Methods:** AMBER was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study which reported that the use of the potassium-binding drug patiromer allowed a more persistent use of spironolactone in patients with CKD and rHTN. In this report, we compare the safety and efficacy of patiromer in advanced CKD as a prespecified analysis.

**Results:** Of the 295 patients randomized, 66 fell into the estimated glomerular filtration rate (eGFR) 25–<30 subgroup. In this subgroup, persistent use of spironolactone was seen in 19/34 (56%) in the placebo group and 27/32 (84%) in the patiromer group (absolute difference 29%, \( P=0.016 \)). In the eGFR 30–45 subgroup, persistent use of spironolactone was seen in 79/114 (69%) in the placebo group and 99/115 (86%) in the patiromer group (absolute difference 17%, \( P=0.003 \)). There was no significant
interaction between eGFR subgroups ($P=0.46$). Systolic blood pressure (BP) reduction with spironolactone in the eGFR 25–<30 subgroup was 6–7 mmHg; in the eGFR 30–45 subgroup, it was 12–13 mmHg. There was no significant interaction between eGFR subgroups on BP reduction ($P=0.79$). Similar proportions of patients reported adverse events (59% in the eGFR 25–<30 subgroup; 53% in the eGFR 30–45 subgroup).

**Conclusion:** Patiromer facilitates the use of spironolactone among patients with rHTN, and its efficacy and safety are comparable in those with eGFR 25–<30 and 30–45 mL/min/1.73m$^2$. 
**Introduction**

The prevalence of apparent resistant hypertension (rHTN) is approximately 10–15% in the treated hypertensive population (1). The prevalence of rHTN is substantially higher in patients with lower estimated glomerular filtration rate (eGFR) and higher degrees of albuminuria (2). The spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug–rHTN (PATHWAY-2) study demonstrated that among patients with rHTN optimized on a 3-drug regimen that included an angiotensin-converting enzyme (ACE) inhibitor, a calcium-channel blocker, and a diuretic, compared to adding an α- or β-blocker, spironolactone elicited a greater blood pressure (BP) reduction (3). However, in this trial, patients with eGFR <45 mL/min/1.73m² were excluded and the average eGFR of the randomized patients was 91 mL/min/1.73m². The US Guidelines recommend adding a mineralocorticoid receptor antagonist (MRA) to patients with rHTN. However, caution is advised for patients with eGFR <30 mL/min/1.73m² (4). The European Guidelines recommend adding an MRA to patients with rHTN as long as eGFR is >45 mL/min/1.73m² and plasma potassium (K⁺) is ≤4.5 mEq/L (5).

In addition to controlling BP, MRA therapy reduces mortality and hospitalization in patients with heart failure (HF) and comorbid chronic kidney disease (CKD) (6). The US Heart Failure Guidelines recommend MRA use in patients with comorbid HF down to eGFR of 30 mL/min/1.73m² (6). The ESC Heart Failure Guidelines recommend using MRAs with caution or seeking specialist advice for their use in patients with eGFR <30 mL/min/1.73m² (7), whereas the ACC/AHA/HFSA Guidelines note that MRAs may be harmful in patients with eGFR <30 mL/min/1.73m² (6). Finally, a 2017 Kidney Disease
Improving Global Outcomes (KDIGO) Controversies Conference noted that data were insufficient to recommend the use of MRA to treat rHTN in patients with CKD (8). Notably, this conference was held prior to the publication of AMBER (9). Furthermore, among patients with CKD, compared to placebo, a 2019 meta-analysis showed that the risk for hyperkalemia was increased by approximately 2.6-fold (10). Two consensus statements from the ESC (7,11) suggest the use of novel K\(^+\) binders to facilitate MRA use in patients with HF and concomitant CKD. Yet, the utilization of K\(^+\) binders in this population remains low. In fact, in patients with HF with reduced ejection fraction, it was noted that only 33\% of eligible patients received an MRA in a large registry from the United States (12). In a study from the Americas, Europe, Australia, and Asia, encompassing 1555 patients from 76 practices, 95\% of the patients with treatment–rHTN were prescribed a diuretic, whereas only 36\% received MRA (13). The use of MRA in high-risk patients with CKD, diabetes, and HF also remains low (6.6\%) (14) and fewer than 1\% of the patients with hypertension and CKD are prescribed an MRA (15).

The AMBER trial showed that among patients with rHTN and eGFR between 25 and 45 mL/min/1.73m\(^2\), patiromer, compared to placebo, enabled a more persistent use of spironolactone (9). Patiromer enabled a greater dose of spironolactone and reduced the risk of hyperkalemia by nearly 50\%. Here we report the prespecified subgroup analysis of AMBER primary and secondary endpoints by eGFR subgroups (eGFR 25–<30 mL/min/1.73m\(^2\) [eGFR 25–<30 subgroup] and 30–45 mL/min/1.73m\(^2\) [eGFR 30–45 subgroup]).
**Materials and Methods**

*Study Design and Participants*

AMBER was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study (ClinicalTrials.gov NCT03071263) to evaluate whether patiromer would allow more persistent use of spironolactone in patients with CKD and rHTN. The study design and primary outcomes have previously been published (9,16). AMBER was conducted in accordance with current standards, conforms with the principles outlined in the Declaration of Helsinki, and the study protocol was approved by the institutional review board or independent ethics committee for each institution before study initiation. All patients provided written informed consent before participating in the study.

Eligible patients were aged ≥18 years and had an eGFR between 25 and 45 mL/min/1.73m², with serum K⁺ (sK⁺) between 4.3 and 5.1 mEq/L. All patients had rHTN during screening, defined as unattended systolic automated office BP (AOBP) of 135–160 mmHg despite taking ≥3 antihypertensives, including a diuretic, and an ACE inhibitor or an angiotensin receptor blocker (unless not tolerated or contraindicated). Exclusion criteria included untreated secondary causes of hypertension (other than CKD), recent cardiovascular event (e.g., myocardial infarction, unstable angina, hospitalization for HF), and clinically significant ventricular arrhythmia or atrial fibrillation with heart rate >100 beats per minute.

AMBER had a screening/run-in period (up to 4 weeks), a double-blind treatment period (12 weeks), and a follow-up visit 2 weeks after the week 12 visit or early
termination. The screening period (4 visits separated by 4 to 10 days) ensured that patients were on stable doses of medication, had confirmed treatment–rHTN, and met all inclusion criteria. Eligible patients were randomly assigned (1:1) via interactive web response system at the final screening visit to receive patiromer or matching placebo, in addition to open-label spironolactone once daily (QD) and their baseline antihypertensive medications, starting on day 1 of randomized treatment. Visits during the double-blind treatment period were weekly (weeks 1–4) and then biweekly (weeks 6–12), at which time AOBP, body weight, blood samples for serum chemistry and spironolactone level (including metabolites) assessments, and adverse events (AEs) were collected.

At each visit after the initial screening visit, unattended AOBP measurements were recorded for each patient, as described (9). Investigators were instructed to keep baseline antihypertensive medications constant except for AE-related reasons where changes to baseline medications could be justified.

Treatments

Open-label oral spironolactone was started at 25 mg QD and increased to 50 mg QD at week 3 in patients with sK⁺ ≤5.1 mEq/L if systolic AOBP remained ≥120 mmHg. Patients initiated study drug (similarly marked packets of patiromer [Relypsa, Inc., a Vifor Pharma Group Company, Redwood City, CA] or placebo), taken QD with food at least 3 hours before or 3 hours after other medications (including spironolactone). The starting dose of patiromer was 8.4 g QD. Study drug dosing adjustments were made at intervals of ≥1 week to address hyperkalemia or hypokalemia: upward adjustment to
16.8 g QD, and then 25.2 g QD for local laboratory sK$^+$ >5.1 mEq/L; and downward adjustment for sK$^+$ <4.0 mEq/L. A titration algorithm was also used to reduce or discontinue the dose of spironolactone if decreases in eGFR or hypotension were observed (16).

**Endpoints and Statistical Analysis**

This prespecified analysis evaluated AMBER primary and secondary endpoints by eGFR subgroups (eGFR 25–<30 subgroup and eGFR 30–45 subgroup). The primary endpoint was the difference between treatment groups in the proportion of patients remaining on spironolactone at week 12. The secondary efficacy endpoint was the difference between treatment groups in the change in systolic AOBP from baseline to week 12 (or to the last available measurement before addition of any new antihypertensive medications or increase in any of the baseline antihypertensive medications). *Post-hoc* analyses by baseline eGFR included the following: differences in cumulative spironolactone dose, Kaplan-Meier estimated time to discontinuation of spironolactone, percent of patients receiving spironolactone 50 mg QD, daily dose of patiromer, rate of spironolactone discontinuation due to hyperkalemia, Kaplan-Meier estimate of the time to sK$^+$ ≥5.5 mEq/L, and sK$^+$ over time. Safety was assessed by vital signs, reports of AEs, change in eGFR from baseline, and changes in laboratory parameters (including NT-proBNP levels and urine albumin/creatinine ratio). Laboratory assessments included serum calcium (normal range 8.5–10.5 mg/dL) and magnesium (normal range 1.8–2.4 mg/dL) levels over time, and the number of patients with prespecified sK$^+$ <3.8 mEq/L and <3.5 mEq/L, serum calcium >10.5 mg/dL, and serum
magnesium <1.4 mg/dL and <1.2 mg/dL. Efficacy endpoints and safety were assessed in all randomized patients; all randomized patients received at least one dose of spironolactone and at least one dose of blinded study medication (patiromer or placebo). All laboratory results are based on central laboratory data.

Analysis of the primary endpoint, between-group differences in the proportion of patients remaining on spironolactone at week 12, used the Cochran-Mantel-Haenszel test stratified by baseline K⁺ category (4.3 to <4.7 versus 4.7 to 5.1 mEq/L) and presence/absence of diabetes mellitus. The secondary endpoint was analyzed using an analysis of covariance (ANCOVA) model, with baseline systolic AOBP as covariate, and the same categorical factors as for the primary endpoint. Time to discontinuation of spironolactone and time to hyperkalemia (sK⁺ ≥5.5 mEq/L) were analyzed using Kaplan-Meier methods, and average daily and cumulative dose of spironolactone analyzed using ANCOVA methods. Safety parameters were summarized descriptively. Statistical analyses were performed on SAS software, version 9.4.

Results

Patient Disposition and Baseline Characteristics

In AMBER, 295 patients were randomized to double-blind treatment with either placebo plus spironolactone (n=148) or patiromer plus spironolactone (n=147) in addition to their current treatment regimen of antihypertensive medications. Of these, 66 (22%) patients were in the eGFR 25–<30 subgroup (34 randomized to placebo and 32 randomized to patiromer) and 229 (78%) patients were in the eGFR 30–45 subgroup (114 randomized to placebo and 115 randomized to patiromer).
In the eGFR 25–<30 subgroup, 32 (94%) patients randomized to placebo and 32 (100%) patients randomized to patiromer completed the study (109 [96%] and 112 [97%] patients in the eGFR 30–45 subgroup, respectively; Supplemental Figure 1). The most common reason for study drug discontinuation was meeting a protocol-specified withdrawal criterion for high sK\(^+\). In the eGFR 25–<30 subgroup, study drug discontinuation due to hyperkalemia occurred in 9 (26%) patients on placebo and 2 (6%) patients on patiromer; the discontinuation rates were 25 (22%) in placebo and 8 (7%) on patiromer in the eGFR 30–45 subgroup. In the eGFR 25–<30 and eGFR 30–45 subgroups, respectively, 5% and 1% discontinued due to protocol-defined symptomatic hypotension and 3% and 2% discontinued due to protocol-defined decline in eGFR (Supplemental Table 1).

Baseline demographics and disease characteristics were generally similar in both eGFR subgroups (Table 1). In the eGFR 25–<30 and eGFR 30–45 subgroups, respectively, 100% and 97.8% were white, 39% and 52% had diabetes, 44% and 45% had a history of HF, and mean baseline sK\(^+\) was 4.78 mEq/L and 4.70 mEq/L.

**Efficacy**

There was no significant interaction between eGFR subgroups (P=0.46) for the primary endpoint. In the eGFR 25–<30 subgroup, 55.9% of patients receiving placebo remained on spironolactone at week 12 (Figure 1) compared with 84.4% of patients receiving patiromer (between-group difference=28.5%, 95% confidence interval [CI] 7.6–49.4; P=0.016). In the eGFR 30–45 subgroup, 69.3% of patients receiving placebo remained on spironolactone at week 12, compared with 86.1% of patients receiving
patiromer (between-group difference=16.8%, 95% CI 6.2−27.4; \(P=0.003\)). Kaplan-Meier estimates of the time to early discontinuation of spironolactone are shown in Figure 2. In the eGFR 25–30 subgroup, treatment-group separation in time to discontinuation of spironolactone began as early as 2 weeks, whereas it was not until 6 weeks that this occurred in the eGFR 30–45 subgroup.

The cumulative dose of spironolactone over 12 weeks is shown in Supplemental Table 2. The least squares (LS) mean (standard error [SE]) difference between treatment groups (patiromer minus placebo) in cumulative spironolactone dose was 732.4 (274.3) mg in the eGFR 25–30 subgroup and 273.8 (139.7) mg in the eGFR 30–45 subgroup. In the eGFR 25–30 subgroup, 41% in the placebo group and 72% in the patiromer group were receiving the 50 mg QD dose of spironolactone at week 12 (54% and 69% in the eGFR 30–45 subgroup, respectively). The LS mean (SE) difference in average daily dose of spironolactone (patiromer minus placebo) was 4.3 (1.9) mg in the eGFR 25–30 subgroup and 1.7 (1.1) mg in the eGFR 30–45 subgroup. Median (Q1, Q3) daily doses of patiromer were 11.2 (8.4, 16.1) g/day and 9.8 (8.4, 15.9) g/day in the eGFR 25–30 and 30–45 subgroups, respectively.

In the eGFR 25–30 subgroup, sK\(^+\) ≥5.5 mEq/L occurred in 18 (53%) patients receiving placebo and in 11 (34%) patients receiving patiromer. In the eGFR 30–45 subgroup, sK\(^+\) ≥5.5 mEq/L occurred in 77 (68%) patients receiving placebo and in 41 (36%) patients receiving patiromer. The Kaplan-Meier estimates of the time to first sK\(^+\) ≥5.5 mEq/L are shown in Figure 3. The separation between the treatment groups in the occurrence of first sK\(^+\) ≥5.5 mEq/L occurred earlier in those in the eGFR 25–30 subgroup, evident after week 1. In those in the eGFR 30–45 subgroup separation
between treatment groups was evident after week 3. Mean sK⁺ over time through week 12 by eGFR subgroup is shown in Supplemental Figure 2.

In the eGFR 25–<30 subgroup, the LS mean (SE) systolic AOBP reductions from baseline to week 12 are shown in Figure 4 (P<0.02 versus baseline for both treatment groups; P=0.94 for difference between treatment groups). In the eGFR 30–45 subgroup, systolic AOBP reductions were also statistically significant versus baseline for both treatment groups (P<0.0001; P=0.60 for difference between treatment groups). There was no significant interaction between eGFR subgroups (P=0.79) for systolic AOBP change from baseline. Additions to antihypertensive medications before week 12 occurred in 4 placebo patients (all 4 in the eGFR 30–45 subgroup) and no patiromer patients. No additions in antihypertensive medications were reported to be due to new edematous states.

Safety

Overall similar numbers of patients reported AEs (Table 2): 19 (56%) and 20 (63%) patients, respectively, randomized to placebo and patiromer in the eGFR 25–<30 subgroup (60 [53%] and 62 [54%] patients, respectively, in the eGFR 30–45 subgroup). AEs were generally mild to moderate in severity. The most frequently occurring class of AEs in both subgroups was gastrointestinal (GI) disorders, occurring in 5 (15%) and 9 (28%) patients in the eGFR 25–<30 subgroup who had been randomized to placebo and patiromer, respectively (in 19 [17%] and 15 [13%], respectively, of those in the eGFR 30–45 subgroup). Diarrhea was the only individual AE within the GI class that occurred in 4 or more patients in the eGFR 25–<30 subgroup (both treatment groups
combined), and was reported in 3 (9%) and 5 (16%) placebo- and patiromer-treated patients, respectively (in 5 [4.4%] and 4 [3.5%], respectively, in the eGFR 30–45 subgroup).

Incidence of baseline or any post-baseline $sK^+$ measurement <3.8 mEq/L through week 12 is reported by eGFR subgroup in Supplemental Table 3; 1 patient in the eGFR 30–45 subgroup receiving patiromer had a post-baseline $sK^+$ measurement between 3.0 and <3.5 mEq/L through week 12. In the eGFR 25–<30 subgroup, none had $sK^+$ <3.5 mEq/L. No patients in either subgroup had $sK^+$ <3.0 mEq/L.

In the eGFR 25–<30 subgroup, one serious AE occurred in a patient receiving placebo (hypersensitivity; considered by the investigator to be unrelated to spironolactone or placebo). In the eGFR 30–45 subgroup, one serious AE occurred in each of 4 patients; 3 receiving placebo (renal failure, renal colic, and aortic rupture [the AE leading to death]), and 1 receiving patiromer (humerus fracture).

Mean changes in eGFR and urine albumin/creatinine ratio are shown in Supplemental Table 4. The changes from baseline were generally similar by eGFR subgroup. AEs indicative of worsening renal function are described in Supplemental Appendix A.

Mean serum calcium and magnesium levels in both eGFR subgroups remained within the normal range in both treatment groups during the study (Supplemental Table 5 and Supplemental Appendix B) and the results were not modified by eGFR subgroup.
Discussion

Spironolactone reduces morbidity and mortality in patients with HF with reduced ejection fraction (6,7,17) and is a standard of care among patients with rHTN (3,5,18). However, the use of spironolactone is low in those with congestive HF (12) and treatment–rHTN (13) patients with CKD and/or diabetes (14) and is rarely prescribed to patients with CKD and hypertension (15). In part, low spironolactone utilization may be because of fear of provoking hyperkalemia. Data from the Swedish Heart Failure Registry have indicated that renin-angiotensin-aldosterone system (RAAS) inhibitors are beneficial in reducing mortality even in patients with stage 4 CKD (19). However, once hyperkalemia occurs, clinical experience shows that RAAS inhibitors are promptly discontinued, potentially removing any protective effect of these drugs (20). The AMBER study demonstrated that the use of the K\(^+\)-binding drug patiromer enables the persistent use of spironolactone in patients with CKD and rHTN (9).

In this analysis, results were similar across CKD subgroups with respect to efficacy in patients with rHTN. However, in the eGFR 25–<30 subgroup, separation between treatment group curves for discontinuation of spironolactone began as early as 2 weeks, whereas it was not until 6 weeks that this occurred in the eGFR 30–45 subgroup. Spironolactone, regardless of use of placebo or patiromer, provoked a reduction from baseline in systolic BP that was statistically significant. The reduction from baseline in the eGFR 30–45 subgroup was between 12–13 mmHg, while in the eGFR 25–<30 subgroup it was about 6 mmHg. There was no evidence of an interaction between baseline eGFR subgroups for either the primary or secondary endpoint. Patiromer’s safety profile was generally consistent between CKD subgroups and with
previous reports (21,22), and this analysis of the AMBER data shows no obvious signal of harm even among patients with eGFR <30 mL/min/1.73m$^2$.

As patiromer exchanges potassium for calcium, this may be an important consideration in patients with advanced CKD. Prior studies, in healthy adults, have suggested that only a small fraction of the calcium released from patiromer is available for absorption (73 mg/day at the highest approved doses of patiromer [25.2 g]) (23). Some of the released calcium from patiromer also may bind to phosphate and thus reduce serum phosphate levels as demonstrated in prior studies (23,24). In patients with advanced CKD, physicians should consider the risks of a potential small increase in calcium absorption compared with the potential benefits of continuing spironolactone.

Inclusion of CKD patients with eGFR 25–<30 is a strength of our study as stage 4 CKD patients are systematically excluded from randomized controlled trials (25) and in our study the retention rate of these patients in a multicenter trial was very high. Our analysis shows that even in the eGFR 25–<30 subgroup, spironolactone can reduce systolic AOBP by 6 mmHg, similar to what has been observed by renal denervation trials in ovine models of CKD (26). Inclusion of patients with eGFR 25–<30 with rHTN is uncommon and our data demonstrating the safety and efficacy of patiromer with spironolactone is important in this group of patients.

Limitations of AMBER are as follows: Power calculations were performed for the primary analysis as most trials do not have the power to detect interaction effects for subgroups; this is also true for the AMBER trial. The number of patients with stage 4 CKD in this study is small and therefore we can only appropriately comment on large differences in safety and efficacy based on CKD stage. Since we found none,
considering that this is prespecified subgroup analysis in the statistical analysis plan we can conclude that to the best of our ability the safety and efficacy of patiromer are comparable for early stage 4 CKD and late stage 3 CKD. Enabling spironolactone use with patiromer requires considerations related to managing drug-drug interactions and adds on another therapy to patients that are likely already on multiple medications. On the other hand, enabling steroidal MRA use with patiromer may improve heart and kidney risk but that will need evaluation in separate studies such as DIAMOND for CV outcomes (NCT03888066) and potentially other studies for kidney failure outcomes. The non-steroidal MRA, finerenone has not been tested in resistant hypertension and its BP lowering potential is minimal.

In conclusion, our analyses from AMBER show that patiromer enables the use of spironolactone independent of eGFR within the range studied in AMBER, and the safety and efficacy of patiromer is comparable in patients within this range of advanced CKD.
Disclosures

RA reports personal fees from Akebia, AstraZeneca, Bayer, Boehringer Ingelheim, Diamedica, Eli Lilly, Johnson & Johnson, Merck, Reata, Relypsa, Inc., a Vifor Pharma Group Company, Sanofi; has served as associate editor of the *American Journal of Nephrology*, *Nephrology Dialysis and Transplantation*; and an author on *UpToDate*; and received research grants from the US Veterans Administration and the National Institutes of Health; PR reports consulting for G3P and Idorsia; honoraria from Ablative Solutions, AstraZeneca, Bayer, Boehringer-Ingelheim, Corvidia, CVRx, Fresenius, Grunenthal, Novartis, NovoNordisk, Relypsa, Inc., a Vifor Pharma Group Company, Sequana Medical, Servier, Stealth Peptides, and Vifor Fresenius Medical Care Renal Pharma; and travel grants from AstraZeneca, Bayer, CVRx, Novartis, and Vifor Fresenius Medical Care Renal Pharma; Cofounder: CardioRenal; JB and SA report employment by Relypsa, Inc., a Vifor Pharma Group Company, and stock in Vifor Pharma; MRM reports previous employment by Relypsa, Inc., a Vifor Pharma Group Company, during the time of the study; BW reports honoraria for lectures on hypertension from Daichii Sankyo, Pfizer, Novartis, Servier, and Boehringer Ingelheim, and consulting for Novartis, Relypsa, Inc., a Vifor Pharma Group Company, and Vascular Dynamics Inc.; WBW has nothing to disclose.

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J Budden: Funding acquisition; Visualization; Writing - review and editing

M Mayo: Conceptualization; Funding acquisition; Methodology; Project administration; Resources; Supervision; Visualization; Writing - review and editing

S Arthur: Conceptualization; Data curation; Formal analysis; Methodology; Software; Supervision; Validation; Visualization; Writing - review and editing

B Williams: Conceptualization; Investigation; Methodology; Supervision; Visualization; Writing - review and editing

W White: Conceptualization; Investigation; Methodology; Supervision; Visualization; Writing - review and editing
All authors were involved in data interpretation, review and writing of the manuscript. The authors had full access to the data, which were analyzed by the sponsor. All authors were responsible for the interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

**Data Availability**

Individual patient data will be shared. A research proposal must be approved by an independent review panel and the study sponsor, and researchers must sign a data sharing agreement. Anonymized individual patient-level data will be provided in a secure access environment upon approval of a research proposal and a signed data sharing agreement. Data can be requested 12 months after the primary publication. Data will be available for a period of 2 years for requests. Proposals for access should be sent to datasharing@viforpharma.com. The AMBER (NCT03071263) study protocol and overall results are posted to the National Institutes of Health clinical trials website (https://clinicaltrials.gov/ct2/show/NCT03071263).

**Supplemental Materials**

Supplemental Appendix A. Adverse events indicative of worsening renal function.

Supplemental Appendix B. Serum calcium and magnesium levels above or below prespecified thresholds during the study.

Supplemental Table 1. Reasons for early discontinuation of study treatment by eGFR subgroup and treatment.

Supplemental Table 2. Cumulative spironolactone dose over 12 weeks by eGFR subgroup and treatment.

Supplemental Table 3. Prespecified laboratory values of interest by eGFR subgroup and treatment.
Supplemental Table 4. eGFR and urine albumin/creatinine ratio change from baseline at week 12.

Supplemental Table 5. Serum calcium and magnesium levels results over time and change from baseline.

Supplemental Figure 1. Patient disposition by eGFR subgroups.

Supplemental Figure 2. Mean (SE) central laboratory serum potassium during active treatment in the A) eGFR 25–<30 subgroup, and B) eGFR 30–45 subgroup.
References


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<th>Characteristic</th>
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<th>eGFR 30–45 Subgroup</th>
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<td>3.7 (0.84)</td>
<td>3.8 (0.91)</td>
</tr>
<tr>
<td>Use of medications for diabetes, n (%)</td>
<td>9 (26.5)</td>
<td>13 (40.6)</td>
</tr>
</tbody>
</table>

AOBP, automated office blood pressure; eGFR, estimated glomerular filtration rate; SD, standard deviation; sK⁺, serum potassium.
Table 2. Adverse event summary by eGFR subgroups.

<table>
<thead>
<tr>
<th>AE, adverse event</th>
<th>eGFR 25–&lt;30 Subgroup</th>
<th>eGFR 30–45 Subgroup</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Spironolactone + Placebo (n=34)</td>
<td>Spironolactone + Patiromer (n=32)</td>
</tr>
<tr>
<td>AEs</td>
<td>19 (55.9)</td>
<td>20 (62.5)</td>
</tr>
<tr>
<td>Severe AEs</td>
<td>1 (2.9)</td>
<td>1 (3.1)</td>
</tr>
<tr>
<td>Serious AEs*</td>
<td>1 (2.9)</td>
<td>0</td>
</tr>
<tr>
<td>AE leading to study treatment discontinuation</td>
<td>5 (14.7)</td>
<td>4 (12.5)</td>
</tr>
<tr>
<td>AE leading to death</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Most common AEs†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3 (8.8)</td>
<td>5 (15.6)</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>2 (5.9)</td>
<td>4 (12.5)</td>
</tr>
<tr>
<td>Headache</td>
<td>3 (8.8)</td>
<td>2 (6.3)</td>
</tr>
<tr>
<td>Hyperkalemia or blood K⁺ increased</td>
<td>2 (5.9)</td>
<td>3 (9.4)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>1 (2.9)</td>
<td>3 (9.4)</td>
</tr>
</tbody>
</table>

AE, adverse event; eGFR, estimated glomerular filtration rate, K⁺, potassium.

*None were considered related to study drug in the opinion of the investigator. †AEs occurring in 4 or more patients in the combined treatment groups for the eGFR 25–<30 subgroup.

Data are n (%) of patients with at least one event; each patient is counted only once for each adverse event. Serum magnesium 1.2–1.4 mg/dL occurred in 1 placebo patient and 3 patiromer patients with eGFR 30–45 subgroup; no patients had serum magnesium <1.2 mg/dL.
Figure Legends

Figure 1. Percentage of patients who remained on spironolactone at week 12 by eGFR subgroup.

eGFR, estimated glomerular filtration rate.

Figure 2. Time to discontinuation of spironolactone in patients in the (A) eGFR 25–<30 subgroup and (B) eGFR 30–45 subgroup.

eGFR, estimated glomerular filtration rate; HK, hyperkalemia; PAT, patiromer; PBO, placebo; Spiro, spironolactone.

Discontinued patients = Number of patients who discontinued study treatment early for hyperkalemia or other reasons prior to or at a study visit.

Figure 3. Time to first sK⁺ value ≥5.5 mEq/L during treatment in patients in the (A) eGFR 25–<30 subgroup and (B) eGFR 30–45 subgroup.

eGFR, estimated glomerular filtration rate; PAT, patiromer; PBO, placebo; sK⁺, serum potassium; Spiro, spironolactone.

The Kaplan-Meier (product-limit) estimates are shown. The number of patients at risk at each time point is the number of patients on treatment and still without event at the end of the time point. The patients who completed 12 weeks of study treatment and had not had any event are censored at week 12.

Figure 4. LS mean (SE) systolic AOBP change from baseline to week 12 by eGFR subgroup.

AOBP, automated office blood pressure; eGFR, estimated glomerular filtration rate; LS, least squares; PAT, patiromer; PBO, placebo; SE, standard error; Spiro, spironolactone.
Figure 1

**eGFR 25–<30 Subgroup**

- Placebo: 19/34 (55.9%)
- Patiromer: 27/32 (84.4%)

**eGFR 30–45 Subgroup**

- Placebo: 79/114 (69.3%)
- Patiromer: 99/115 (86.1%)

**P=0.46 for interaction between subgroups**

Difference in proportions:

- Placebo vs Patiromer: 28.5% (P=0.016)
- Placebo vs Patiromer: 16.8% (P=0.003)
Figure 2

**A) eGFR 25–<30 Subgroup**

Circles indicate censored observations

- **Spiro + PBO**
  - Study Week: 114, 112, 110, 108, 103, 98, 89, 85, 79
  - No. at risk: 32, 32, 32, 31, 30, 28, 27

- **Spiro + PAT**
  - Study Week: 115, 114, 111, 109, 104, 103, 103, 99, 99
  - No. at risk: 32, 32, 32, 31, 30, 28, 27

**Discontinued due to HK**

- **Spiro + PBO**
  - Study Week: 0, 0, 2, 3, 4, 4, 6, 8, 9
  - No. at risk: 34, 34, 32, 28, 27, 26, 24, 21, 19

- **Spiro + PAT**
  - Study Week: 0, 0, 0, 0, 0, 0, 2, 2
  - No. at risk: 2, 2, 3

**Discontinued due to other reasons**

- **Spiro + PBO**
  - Study Week: 0, 0, 2, 3, 4, 4, 5, 6
  - No. at risk: 114, 112, 110, 108, 103, 98, 89, 85, 79

- **Spiro + PAT**
  - Study Week: 0, 0, 2, 3, 4, 5, 7, 7, 7
  - No. at risk: 115, 114, 111, 109, 104, 103, 103, 99, 99

**B) eGFR 30–45 Subgroup**

Circles indicate censored observations

- **Spiro + PBO**
  - Study Week: 0, 1, 2, 5, 8, 10, 18, 21, 25
  - No. at risk: 114, 112, 110, 108, 103, 98, 89, 85, 79

- **Spiro + PAT**
  - Study Week: 0, 1, 2, 5, 7, 7, 7, 8
  - No. at risk: 115, 114, 111, 109, 104, 103, 103, 99, 99

**Discontinued due to HK**

- **Spiro + PBO**
  - Study Week: 0, 0, 2, 3, 4, 4, 2, 2
  - No. at risk: 34, 34, 32, 28, 27, 26, 24, 21, 19

- **Spiro + PAT**
  - Study Week: 0, 0, 2, 3, 4, 5, 7, 7, 7
  - No. at risk: 2, 2, 3

**Discontinued due to other reasons**

- **Spiro + PBO**
  - Study Week: 0, 0, 1, 1, 1, 2, 4, 7, 8
  - No. at risk: 114, 112, 110, 108, 103, 98, 89, 85, 79

- **Spiro + PAT**
  - Study Week: 0, 0, 1, 2, 5, 7, 7, 7, 8
  - No. at risk: 2, 2, 3
### Figure 3

**A)** eGFR 25–<30 Subgroup

<table>
<thead>
<tr>
<th>Study Week</th>
<th>No. at risk</th>
<th>Spiro + PBO</th>
<th>Spiro + PAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>34</td>
<td>32</td>
<td>32</td>
</tr>
<tr>
<td>1</td>
<td>32</td>
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<td>30</td>
</tr>
<tr>
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<td>24</td>
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</tr>
<tr>
<td>4</td>
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</tr>
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<tr>
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<tr>
<td>12</td>
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<td>4</td>
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</tr>
</tbody>
</table>

**B)** eGFR 30–45 Subgroup

<table>
<thead>
<tr>
<th>Study Week</th>
<th>No. at risk</th>
<th>Spiro + PBO</th>
<th>Spiro + PAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>114</td>
<td>115</td>
<td>115</td>
</tr>
<tr>
<td>1</td>
<td>104</td>
<td>108</td>
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<td>69</td>
</tr>
<tr>
<td>8</td>
<td>14</td>
<td>24</td>
<td>24</td>
</tr>
</tbody>
</table>

Circles indicate censored observations.
eGFR 25–<30 Subgroup

-6.2 mmHg

P=0.014

Spiro + PBO
n=32/148

Spiro + PAT
n=32/147

eGFR 30–45 Subgroup

-11.9 mmHg

P<0.0001

Spiro + PBO
n=109/148

Spiro + PAT
n=112/147

LS mean (95% CI) difference between groups:

-0.3 (−7.2, 6.6)

P=0.94

LS mean (95% CI) difference between groups:

-1.0 (−4.9, 2.9)

P=0.60

P=0.79 for interaction between subgroups