Patiromer versus placebo to enable spironolactone use in the treatment of patients with resistant hypertension and chronic kidney disease (AMBER): a randomised, double-blind, placebo-controlled trial

Department of Medicine, Division of Nephrology, Indiana University School of Medicine, Indianapolis, IN, USA (Prof Rajiv Agarwal, MD)
University of Lorraine, Inserm 1433 CIC-P CHRU de Nancy, Inserm U1116 and FCRIN INI-CRCT, Nancy, France (Prof Patrick Rossignol, MD)
Medical Affairs (Alain Romero, PhD)**; Clinical Development** (Dahlia Garza, MD, Martha R. Mayo, PharmD; Suzette Warren)**; Biometrics** (Jia Ma, MD)**, Relypsa, Inc., a Vifor Pharma Group Company, Redwood City, CA, USA**
Calhoun Cardiology Center, University of Connecticut School of Medicine, Farmington, CT, USA (Prof William B. White, MD)
Institute of Cardiovascular Sciences University College London (UCL) and National Institute for Health Research (NIHR) UCL/UCL Hospitals Biomedical Research Centre, London, UK (Prof Bryan Williams, MD).

Correspondence to:
Dr. Rajiv Agarwal
Department of Medicine, Division of Nephrology
Indiana University, and RLR VA Medical Center
Indianapolis, IN 46202 (USA)
ragarwal@iu.edu

Short title: Patiromer to Enable Spironolactone in Resistant Hypertension and CKD

Keywords: Chronic kidney disease; Hyperkalaemia; Patiromer; Resistant hypertension; Spironolactone

Counts:

Words (manuscript text only): 4364/4500 max (introduction through discussion)

References: 20/30 max

Summary: 300/300 max (not counting funding statement)

Summary

Background

Spironolactone is effective at reducing blood pressure (BP) in patients with uncontrolled resistant hypertension (RHTN); however, its use in patients with chronic kidney disease (CKD) may be limited by hyperkalaemia. We evaluated use of the potassium binder patiromer to allow more persistent use of spironolactone in patients with CKD and RHTN.

Methods

This multicentre, randomised, double-blind, placebo-controlled study recruited outpatients with CKD (estimated GFR 25-≤45 mL/min/1.73 m^2) and uncontrolled RHTN and randomly assigned them (1:1) to receive either placebo or patiromer, and spironolactone 25 mg once daily. Dose titrations were permitted after 1 week (patiromer) and 3 weeks (spironolactone). The primary endpoint was the between-group difference at week 12 in the proportion of patients on spironolactone. The secondary efficacy endpoint was the between-group least squares mean (LSM) difference in unattended systolic automated office BP to week 12.

Findings

We randomised 295 patients who received at least one dose of spironolactone plus either placebo (n=148) or patiromer (n=147). Baseline mean (SD) systolic BP (mmHg) was 144.9 (7.0) and 143.3 (6.5) and mean (SD) serum potassium (mmol/L) was 4.69 (0.37) and 4.74 (0.36), for the placebo and patiromer groups respectively. At 12 weeks,

98 (66.2%) placebo- and 126 (85.7%) patiromer-treated patients remained on spironolactone (between-group difference, 19.5% [95% CI, 10.0, 29.0]; p<0.0001). LSM (95% CI) changes from baseline in systolic BP (mmHg) were -10.8 (-13.2, -8.3) and -11.7 (-14.1, -9.3) in the placebo and patiromer groups, respectively (both p<0.0001); LSM (95% CI) difference between groups was -1.0 mmHg (-4.4, 2.4), p=0.58. Adverse events, mostly mild or moderate in severity, occurred in 53% of placebo- and 56% of patiromer-treated patients.

Interpretation

In patients with RHTN and CKD, patiromer enabled more patients to continue treatment with spironolactone with less hyperkalaemia. Changes from baseline in BP over 12 weeks were comparable between treatment groups.

Funding

Relypsa, Inc., a Vifor Pharma Group Company.

Clinicaltrials.gov identifier NCT03071263.

Research in context

Evidence before the study

Resistant hypertension (RHTN), i.e., blood pressure (BP) remaining above goal despite treatment with optimally tolerated doses of three antihypertensive agents from different classes, including a diuretic, is a significant medical problem. Assessed by 24-hour ambulatory BP monitoring, the prevalence of RHTN was found to be 8% in one large cohort, but in most cohorts of patients with chronic kidney disease (CKD) the prevalence of RHTN is several-fold higher. A previous study of patients with RHTN showed that spironolactone was superior to other treatment options, i.e., a beta-blocker or alpha-blocker, in improving BP control. Consequently, spironolactone (25-50 mg daily) is now recommended for the treatment of RHTN by international guidelines. However, guidelines acknowledge a lack of data on the safety and efficacy of spironolactone in patients with advanced CKD and RHTN. We searched PubMed for randomised clinical trials that were published in English between 1 Jan 1965 and 1 Jan 2017 with the search terms “resistant hypertension”, “chronic kidney disease”, and “spironolactone”. At the time of initiation of our study, to our knowledge, only one small randomised clinical trial (41 patients) of spironolactone vs placebo for the treatment of RHTN in advanced CKD had been reported but was underpowered.

Added value of this study

In this 12-week, randomised, double-blind, placebo-controlled trial of patients with CKD (eGFR 25 to ≤45 mL/min/1.73 m^2), once daily oral administration of patiromer was generally well tolerated and significantly increased the proportion of patients who

remained on spironolactone. Patiromer use was associated with a significantly reduced risk for hyperkalaemia during spironolactone therapy.

Implications of all the available evidence

Patients with advanced CKD have high rates of poor BP control, premature cardiovascular disease and end-stage kidney disease. There is a clear unmet medical need for safe and effective therapies to better control BP, especially in patients with RHTN. Results from the AMBER study suggest that patiromer enables the use of spironolactone, which effectively lowers systolic BP in patients with RHTN and CKD. Further clinical studies of patiromer to enable spironolactone use to reduce cardiovascular events and end-stage kidney disease are warranted.

Introduction

Resistant hypertension (RHTN) is defined as uncontrolled blood pressure (BP) while taking ≥3 classes of antihypertensive medication or taking ≥4 classes of antihypertensive medication regardless of BP level.[1,2] The prevalence of true RHTN evaluated by 24h ambulatory BP monitoring in a meta-analysis of 12 studies was found to be 10.25% (95% CI 7.65 to 13.19%),[3] suggesting that it affects over 100 million people globally. Recent studies suggest that excessive sodium retention is the principle mechanism underpinning RHTN.[4] This may explain why chronic kidney disease (CKD) is more commonly associated with RHTN. In an Italian cohort of patients with CKD, the prevalence was 22.9%, nearly three times that in the general population.[5]

CKD affects approximately 8-16% of the adult population,[6] and among those with CKD, the worldwide prevalence of apparent treatment-RHTN is between 2-4 times higher than that seen in a population without CKD.[7] About 1 in 4 patients with CKD has apparent treatment-RHTN.[7] Treatment-RHTN is associated with nearly a 2 fold risk of cardiovascular events and 2.7 fold risk for end-stage kidney disease compared to those with controlled hypertension.[5] Given this high prevalence of RHTN in CKD, there is an urgent unmet need to develop new therapies to treat this condition.

Consistent with the observation that RHTN appears to be a sodium retaining state,[4] in the PATHWAY-2 study, further diuretic therapy via add-on therapy with spironolactone was shown to be significantly more effective at lowering BP in RHTN than bisoprolol, doxazosin, or placebo.[8] This was consistent with findings in a meta-analysis of smaller studies suggesting that spironolactone was an effective treatment for RHTN.[9]

Despite the high frequency of RHTN in patients with CKD, the studies noted above evaluating spironolactone excluded patients with significant CKD due to the risk of spironolactone-induced hyperkalaemia. In a meta-analysis, the addition of spironolactone to an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) doubled the risk of hyperkalaemia in patients with mild to moderate CKD, which was dependent on baseline estimated glomerular filtration rate (eGFR), serum potassium (K^+) level, drug dose, and concomitant medications.[10] Thus, the risk of hyperkalaemia has limited the use of potentially the most effective treatment (i.e., spironolactone) for RHTN in patients with CKD.

Recently, oral K^+ binding agents with improved efficacy and tolerability have been developed to lower serum K^+. Patiromer is a sodium-free, non-absorbed, K^+-binding polymer which is approved in the U.S., Europe, and other countries for lowering serum K^+ in patients with hyperkalaemia.[11,12] Previously, patiromer enabled spironolactone and prevented hyperkalaemia in heart failure patients with eGFR <60 mL/min/1.73 m^2 or a history of hyperkalaemia that previously led to discontinuation of drugs blocking the renin-angiotensin-aldosterone system (RAAS).[13] These findings in a heart failure population supported the development of a randomised controlled trial (RCT) to evaluate the use of patiromer as an adjunctive therapy to spironolactone in patients with RHTN and CKD, to reduce the risk of developing hyperkalaemia and thereby facilitate the use of spironolactone, in addition to triple BP-lowering therapy, to improve BP control in these patients.

In AMBER (**A** Rando**M**ized, Double-Blind, Placebo-controlled, Parallel Group Study of Patiromer for the Enablement of Spironolactone Use for **B**lood Pr**E**ssure Control in

Patients with **R**esistant Hypertension and Chronic Kidney Disease: Evaluation of Safety and Efficacy), we therefore aimed to test the safety and efficacy of patiromer administered once daily for 12 weeks to allow the persistent use of spironolactone initiated for the treatment of RHTN in patients with CKD.

Methods

Study design and participants

The AMBER trial design (ClinicalTrials.gov identifier NCT03071263) has previously been published.[14] This phase 2 multicentre, randomised, double-blind, placebo controlled, parallel group study of patiromer for the enablement of spironolactone use for BP control in patients with RHTN and CKD enrolled participants from 62 outpatient centres in 10 countries (see **Supplemental Appendix**). Patients were typically recruited from within the investigators' practices. Patients eligible for inclusion were aged ≥18 years with an eGFR of 25–45 mL/min/1.73 m^2, serum K^+ between 4.3 and 5.1 mmol/L, and RHTN. RHTN was defined as unattended systolic automated office blood pressure (AOBP) of 135–160 mmHg during screening despite taking ≥3 antihypertensives, including a diuretic, and ACEI or an ARB (unless not tolerated or contraindicated). Patients with untreated secondary causes of hypertension were excluded; full details of the inclusion and exclusion criteria were previously published.[14] The study consisted of a run-in period (up to 4 weeks), double-blind treatment period (12 weeks) and follow-up visit 2 weeks after the week 12 visit or early termination.

The study protocol was approved by the institutional review board or the independent ethics committee for each institution before study initiation, and all patients provided written informed consent before participating in the study.

Randomisation and masking

Patients meeting all eligibility criteria at the final screening visit were stratified by the local K^+ measurement (4.3 to <4.7 vs. 4.7 to 5.1 mmol/L) and history of diabetes. By use of an interactive web response system, eligible patients were stratified and randomly assigned (1:1) to receive patiromer 8.4 g once daily or matching placebo in addition to open-label spironolactone 25 mg once daily and their baseline BP medications at the final screening visit. The blinded study drug was provided in packets as a powder for oral suspension, with each packet containing patiromer (4.2 g) or microcrystalline cellulose placebo. All randomised patients were instructed to take spironolactone, assigned study drug (2 packets of either patiromer or placebo), and their antihypertensive medications starting on day 1 of randomised treatment. Participants, the study team that administered treatments and measured BP, and the investigators were all masked to participants' assigned treatment groups. Treatments were supplied in identical numbered packets that showed no identification of the treatment. In order to maintain masking, study drug was provided to the patient by a blinded study team member whose only role was to handle the study drug.

Procedures

The screening period consisted of 4 visits (S1, S2, S3, and S4), each separated by 4 to 10 days, and was designed to ensure that patients were on stable doses of medication, had true treatment-RHTN, and met all inclusion criteria. Visits during the double-blind treatment period were weekly (weeks 1–4) and then biweekly (weeks 6–12).

The following data were collected or assessed at each visit: BP (detailed below), body weight, blood samples for serum chemistry assessments, and adverse events. At weeks 1, 4, 8, and 12, medication adherence was evaluated via the measurement of spironolactone in plasma (validated liquid chromatography-tandem mass spectrometry [minimal level of detection: 1ng/mL]) and qualitative assessment of associated chromatograms for peaks corresponding to spironolactone metabolites 7α-thiomethylspironolactone and canrenone. A single 24-hour urine collection was performed beginning at least 24 hours prior to the baseline visit, which was used to determine urine sodium, K^+, and albumin to creatinine ratio (ACR). Spot urine was collected for measuring ACR at baseline and weeks 4, 8, and 12. Baseline spot urine samples were from 2 first morning voids, collected 1 and 2 days prior to the baseline visit. At weeks 4, 8, and 12, samples were from 3 first morning voids collected on the day of the visit and on 1 and 2 days prior to the visit.

Blood Pressure Measurement

At each visit after the initial screening visit, office BP measurements were recorded for each patient. BP was measured using an oscillometric BP monitoring device (IntelliSense® HEM-907; Omron Healthcare Inc., Kyoto, Japan). The device was

programmed to allow a 5-min rest period before initiating the sequence of triplicate measurements, with a 1-min interval between each measurement. No observer was present in the room for these automated measurements. Patients were provided with an home blood pressure (HBP) monitor (Tel-O-Graph®, I.E.M. GmbH, Stolberg, Germany) at the first visit, trained in its use, and instructed to measure HBP in triplicate twice daily after 5 minutes of seated rest at the same times each day (e.g., 8:00 am and 8:00 pm). Patients also brought their HBP monitor to each office visit, and used it to measure BP immediately following the measurement of AOBP.

Drug Treatments

Open-label oral spironolactone was started at 25 mg once daily, and increased to 50 mg once daily at week 3 in patients with systolic AOBP ≥120 mmHg and K^+ ≤5.1 mmol/L. The spironolactone dosing algorithm was previously published.[14] Patients with systolic AOBP ≤120 mmHg and serum K^+ > 5.1 mmol/L at week 3 continued on the 25 mg spironolactone dose until the first subsequent visit at which serum K^+ was ≤5.1 mmol/L (and systolic AOBP was ≥120 mmHg), at which time the spironolactone dose was increased to 50 mg. Patients with systolic AOBP <120 mmHg at week 3 continued on the 25-mg dose. At any visit, if a patient experienced hypotensive symptoms, with systolic AOBP <120 mmHg, or if systolic AOBP was <100 mmHg even in the absence of symptoms, the spironolactone dose could be reduced to 25 mg every other day or discontinued at the investigator's discretion. For decreases in eGFR of 30–50%, the spironolactone dose was decreased and eGFR was monitored weekly; spironolactone was discontinued if eGFR did not return to within 30% of baseline within 4 weeks. For eGFR decreases >50%, spironolactone was discontinued and eGFR was monitored

weekly until returning to within 15% of baseline and monitored biweekly thereafter until end of study. If spironolactone was discontinued, double-blind study drug (patiromer or placebo) was discontinued at the same time. Concomitant antihypertensive medications were to be kept at stable doses during the study.

Patients initiated study drug (patiromer [Relypsa, Inc., a Vifor Pharma Group Company, Redwood City, CA] or matching placebo) with 2 packets daily taken with food at least 3 hours before or 3 hours after other medications, including spironolactone. Dosing adjustments were made at intervals of ≥1 week in 2-packet/day increments or decrements, upward for local serum K^+ >5.1 mmol/L, and downward for serum K^+ <4.0 mmol/L.[14] The maximum daily dosage was 6 packets; the minimum was 0 packets. There were 3 protocol-specified criteria for treatment withdrawal due to high serum K^+: 1) K^+ ≥5.5 mmol/L and <6.0 mmol/L, and on maximum dose of patiromer/placebo, and repeat K^+ level within 1 day was still ≥5.5 mmol/L, 2) K^+ ≥5.5 and <6.0 mmol/L, not on maximum dose but after dose was increased by 2 packets, repeat K^+ within 3 days was still ≥5.5 mmol/L, and 3) K^+ ≥6.0 mmol/L and repeat K^+ within 1 day was still ≥ 6.0 mmol/L. Patients who discontinued patiromer/placebo were required to discontinue spironolactone at the same time. Patients who discontinued spironolactone and patiromer/placebo for any reason remained in the study and were treated with standard medical care based on the investigator's clinical judgment. Dietary counselling was provided at each visit in accordance with the standard practices of the investigator. Patients were instructed not to change dietary intake of potassium containing foods during the study.

Endpoints

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). Other prespecified endpoints included between-group differences in cumulative dose and duration of exposure to spironolactone, time to discontinuation of spironolactone, time to and proportion of patients with serum K^+ ≥5.5 mmol/L, change in albuminuria (urine ACR) from baseline to week 12, and patient-reported outcomes as measured by the EuroQol Group 5-domain 5-level (EQ-5D-5L) questionnaire. Change in 7-day systolic HBP over time was evaluated as a prespecified exploratory endpoint. Safety was assessed by vital signs, reports of adverse events, and changes in laboratory parameters.

The study was overseen by an independent Data Safety and Monitoring Committee (see **Supplemental Appendix**).

Statistical analysis

It was estimated that a cohort of 280 patients would provide 90% power to detect a difference between treatment groups of ≥20% in the proportion of patients remaining on spironolactone at week 12 at an $\alpha = 0.05$. Assuming a dropout rate of 15%, the sample size also provides approximately 80% power to detect a 4 mmHg difference between treatment groups in change in systolic automated oscillometric blood pressure (AOBP)

286 from baseline to week 12 (or to the last available AOBP before addition of any new
287 antihypertensive medications or change in any of the baseline antihypertensive
288 medications).[14]
289 The efficacy endpoints and safety were assessed in all randomised patients; all
290 randomised patients received at least one dose of spironolactone and at least one dose
291 of blinded study medication (patiromer or placebo).
292 To evaluate the primary endpoint of between-group differences in the proportion of
293 patients remaining on spironolactone at week 12, the Cochran-Mantel-Haenszel test,
294 stratified by baseline K^+ category (4.3 to <4.7 vs. 4.7 to 5.1 mmol/L) and
295 presence/absence of diabetes mellitus was used. The secondary endpoint was
296 analysed using an analysis of covariance (ANCOVA) model, with baseline systolic
297 AOBP as a covariate and baseline serum K^+ and presence/absence of diabetes mellitus
298 as categorical factors. The primary and secondary endpoints were also evaluated in
299 prespecified subgroups: sex, age group (<65 vs ≥65 years), central serum K^+ (4.3-<4.7
300 /L vs 4.7-5.1 mmol/L), eGFR (<30 vs ≥30 mL/min/1.73m^2), presence of diabetes, history
301 of heart failure, and geographic region (Eastern/Central Europe vs all other countries).
302 Time to discontinuation of spironolactone and time to hyperkalaemia (serum K^+ ≥5.5
303 mmol/L) were analysed using Kaplan-Meier methods. Average daily and cumulative
304 dose of spironolactone, and change in ACR from baseline to week 12 were analysed
305 using ANCOVA methods. Safety parameters, EQ-5D-5L, and systolic HBP data were
306 analysed descriptively. Statistical analyses were performed on SAS software, version
307 9.4.
308

Role of the funding source

The study was sponsored by Relypsa, Inc. (Redwood City, CA, USA). The steering Committee designed the study in collaboration with the sponsor. Worldwide Clinical Trials, Ltd. (Morrisville, North Carolina) was responsible for site management and monitoring and data collection. The authors had full access to the data, which were analysed 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.

Results

Patient disposition

Between 13 February 2017, and 20 August 2018, 574 patients were screened (**Figure 1**). Of these, 295 met all inclusion and exclusion criteria and were randomly assigned to spironolactone in addition to double-blind treatment with either placebo (n=148) or patiromer (n=147). Overall, 141 (95%) patients in the placebo group and 144 (98%) patients in the patiromer group completed the study; the most common reasons for premature study discontinuation were adverse events (3 placebo patients, 1 patiromer patient) and consent withdrawal (3 placebo patients; 1 patiromer patient). Reasons for discontinuation of study drug are shown in **Supplemental Table 1**. The most common reason for study drug discontinuation was meeting a protocol-specified withdrawal criterion for high serum K^+, occurring in 34 (23%) patients on placebo and 10 (6.8%) patients on patiromer.

Baseline characteristics

Baseline demographics and disease characteristics were balanced between treatment groups (**Table 1**). The majority of patients were white (98%) and about half were men (52%); Baseline systolic AOBP and serum K^+ were well matched between groups. Thirty-four patients on placebo and 32 patients on patiromer had baseline eGFR <30 ml/min/1.73 m^2.

Efficacy endpoints

The primary efficacy endpoint was met, with a significantly higher proportion of patients randomised to patiromer compared with placebo remaining on spironolactone

339 treatment at week 12 (between-group difference [95% confidence interval (CI)], 19.5%
340 [10.0, 29.0]; p<0.0001, **Table 2**). Consistent results were observed across prespecified
341 subgroups (**Supplemental Figure 1)**. The Kaplan-Meier estimate of the time to
342 discontinuation of spironolactone is shown in **Figure 2A**. During the 12-week study,
343 significantly more placebo patients than patiromer patients had serum K^+ ≥5.5 mmol/L
344 (p<0.0001). The Kaplan-Meier estimate of the time to serum K^+ ≥5.5 mmol/L is shown in
345 **Figure 2B**. **Supplemental Figure 2** shows mean serum K^+ over time in both treatment
346 groups and the cumulative number of patients discontinuing due to hyperkalaemia at
347 each timepoint.

348 The cumulative dose of spironolactone was higher by 384.7 mg (95% CI, 140.4,
349 629.0) with patiromer compared with placebo; p=0.002) (**Table 2**). The mean (standard
350 error [SE]) duration of spironolactone exposure was 68.6 (1.9) days in the placebo
351 group and 75.6 (1.6) days in the patiromer groups; the least squares (LS) mean (95%
352 CI) between group difference was 7.1 days (2.2, 12.0; p=0.0045). By week 12, 76
353 (51.4%) of placebo-treated and 102 (69.4%) of patiromer-treated patients were
354 receiving 50 mg of spironolactone. The median (Q1, Q3) daily dose of patiromer was
355 9.8 (8.4, 16.0) g.

356 There were significant reductions in unattended systolic AOBP from baseline to
357 week 12 in both treatment groups, with no significant difference between groups (**Table**
358 **2**). LS mean (SE) changes in systolic AOBP during the study are shown in **Figure 3**.
359 Systolic HBP results were consistent with systolic AOBP results (**Supplemental Figure**
360 **3**). Additions to antihypertensive medications before week 12 occurred in 4 patients (all

on placebo). Baseline doses of ACEI and ARB were not altered during the study (**Supplemental Table 2**).

Measurement of spironolactone serum concentration and/or detection of its metabolites demonstrated that at week 1, 271/292 (92.8%) patients (both placebo or patiromer groups combined) who should have been on the drug had detectable levels. At week 4, 258/269 (95.9%), week 8, 226/247 (91.5%) and at week 12, 202/222 (91.0%) had detectable levels of spironolactone or its metabolites.

To further understand the relationship between the time to discontinuation of spironolactone and the proportion of patients with presence of spironolactone (and/or its metabolites), we performed an exploratory analysis in patients who discontinued spironolactone and study drug (placebo and patiromer groups combined) before week 12 (n=71). At 1 week after the last spironolactone dose, 20/23 (87.0%) had detectable metabolites. At 2 weeks after the last spironolactone dose, 12/16 (75.0%), and at 3 weeks 4/11 (36.4%) had detectable metabolites.

Among the 254 patients for whom we had BP data at the time of discontinuation of spironolactone and 2 weeks later, the mean increment in systolic BP was 6 mmHg (95% CI, 4.2, 7.8). These patients had a persistent reduction from baseline in systolic BP that averaged 7.1 mmHg (95% CI, 5.5, 8.7). Thus, on average 54% of the systolic BP effect remained despite discontinuation of spironolactone 2 weeks earlier.

There was no difference between treatment groups in spot urine ACR over time (**Supplemental Table 3)**. EQ-5D-5L questionnaire scores increased by a mean (SE) 2.8 (1.0) in the placebo group and by 4.8 (0.8) in the patiromer group (**Supplemental Table 4).**

Safety

Adverse events are shown in **Table 3**. Most adverse events were mild or moderate in severity and there were few severe adverse events. The most frequently reported adverse events were gastrointestinal disorders in 24 (16.2%) patients in the placebo group and in 24 (16.3%) patients in the patiromer group. The most common individual adverse event within this class was diarrhoea, occurring in similar proportions of patients in each treatment group. No adverse events of diarrhoea were serious and none led to premature discontinuation of study drugs.

Consistent with the efficacy endpoint, the most common individual adverse event was hyperkalaemia or blood potassium increased (none serious) (**Table 3**). Post-baseline, 4 (2.7%) patients in the placebo group and 6 (4.1%) patients in the patiromer group had serum K^+ <3.8 mmol/L; in one patient on patiromer, the serum K^+ value was <3.5 mmol/L but ≥3.0 mmol/L. There were 14 (9.5%) placebo and 17 (11.6%) patiromer patients with adverse events indicative of worsening kidney function or its equivalent. These included adverse events of renal failure, renal impairment, CKD, and nephropathy. In 6 (4.1%) placebo and 10 (6.8%) patiromer patients, these events led to spironolactone dose decrease. In 3 (2.0%) placebo and 2 (1.4%) patiromer patients, these events led to early discontinuation of spironolactone. Serious renal adverse events occurred in 2 (1.4%) placebo-treated patients (renal colic and renal failure [see **Supplemental Appendix**]) and in none of the patiromer-treated patients. One patient (placebo group) died due to a serious adverse event of aortic rupture (see **Supplemental Appendix**).

Mean (SE) eGFR decreased in both treatment groups during the study; by week 12, the decrease was 2.1 (0.6) mL/min/1.73m^2 in the placebo group and 1.4 (0.6) mL/min/1.73m^2 in the patiromer group. The eGFR increased after study drugs were stopped, with mean (SE) changes from baseline to follow-up of -1.3 (0.6) mL/min/1.73m^2 for placebo and -0.3 (0.8) mL/min/1.73m^2 for patiromer. Similarly, there were small increases in serum creatinine during the study **(Supplemental Table 5)**. Post-baseline, 26 (17.6%) of placebo-treated and 28 (19.0%) of patiromer-treated patients had declines in eGFR of more than 30%; 4 (2.7%) patients on placebo and 1 (0.7%) on patiromer had declines in eGFR of more than 50%. Among the patients with baseline eGFR <30 ml/min/1.73 m^2, none had declines in eGFR of more than 50% and none went on dialysis during the study.

Mean serum magnesium and calcium levels remained within the normal range in both treatment groups during the study (see **Supplemental Appendix** and **Supplemental Table 5**).

Discussion

Use of the K^+ binder patiromer enabled more persistent use of spironolactone in patients with uncontrolled RHTN and advanced CKD. This was accompanied by a lower rate of and fewer discontinuations of spironolactone due to hyperkalaemia, as well as a delay in the time to hyperkalaemia in patients treated with patiromer. Two out of 3 placebo-treated patients developed hyperkalaemia; this risk was reduced by half in the patiromer-treated patients. In addition, 69% of patiromer-treated patients compared with 51% of placebo-treated patients were able to up-titrate to 50 mg spironolactone during

the 12 week trial. Consequently, the mean cumulative dose of spironolactone administered during the AMBER study was significantly higher in the patiromer group than in the placebo group, by approximately 400 mg.

Spironolactone therapy added to a standard 3-drug antihypertensive regimen in patients with uncontrolled RHTN significantly reduced mean systolic AOBP; furthermore, adherence to spironolactone was demonstrated in >90% of the patients based on detectable plasma levels of spironolactone or its metabolites. Our study did not include a placebo for spironolactone control group, hence, we cannot definitively conclude that spironolactone reduced BP in our RHTN patients with CKD. However, BP reduction does seem likely based on two observations. First, the reductions in BP in AMBER were of similar magnitude to those observed in PATHWAY-2 (11-12 mm Hg)[8] and second, at study end when spironolactone was discontinued, there was a rebound increase in BP (6 mmHg) in just 2 weeks.

Of interest, despite patiromer enabling more prolonged use of spironolactone, there was no significant difference in BP between treatment groups at study end. In examining these results, we found that many patients (98 of 148) in the placebo group continued to be on spironolactone and that spironolactone metabolites were detectable long after discontinuation - among patients who discontinued spironolactone before week 12, spironolactone metabolites were still detectable in 36.4% of patients even 3 weeks later. Additionally, consistent with the long half-lives of spironolactone metabolites, approximately half of the systolic BP effect was still present, 2 weeks after discontinuation of spironolactone. Finally, as most discontinuations in the placebo group

occurred after 6 weeks of the study, it was likely that there was too little time to observe a difference in systolic AOBP between treatment groups.

The AMBER trial results strengthen the available evidence that patiromer can enable the persistent use of spironolactone. Among normokalemic heart failure patients with CKD or a history of hyperkalaemia, patiromer use resulted in fewer discontinuations of drugs blocking the RAAS.[13] In addition, exploratory analyses in patients with CKD and hyperkalaemia receiving RAAS inhibitors (RAASi), suggest that patiromer safely enables the use of RAASi.[15] The AMBER study also provides new evidence of patiromer's tolerability relative to placebo. At a median daily dose of 9.8 g patiromer, the rates of overall adverse events, as well as gastrointestinal adverse events, were comparable to that in the placebo group. The safety profile of patiromer in AMBER was consistent with previous reports in hyperkalaemic patient populations with or without CKD, diabetes, or hypertension.[15-17]

Our study has a number of strengths. It was the first adequately powered RCT of enablement of spironolactone treatment of RHTN in patients with advanced CKD, a vulnerable population at high risk for cardiovascular events. By design, the study's exclusion criteria were limited to ensure that the results would be relevant to a broad population of patients with CKD. For example, 48% of patients were women, 50% of patients had diabetes mellitus, and 45% had heart failure. We undertook careful standardised measurement of unattended systolic AOBP for the key secondary outcome measure of BP lowering with spironolactone treatment, similar to what has been recommended in recent hypertension guidelines.[18] The screening period was 4 weeks, during which multiple BP measurements were taken, and was designed to

exclude patients with white-coat hypertension. While the use of unattended AOBP in itself does not entirely exclude white-coat hypertension,[19] among patients with CKD, unattended AOBP is similar to 24-hour ambulatory BP monitoring in its ability to predict echocardiographic left ventricular hypertrophy.[20] Finally, we evaluated adherence to spironolactone by measuring spironolactone or its metabolites at frequent intervals and demonstrated excellent adherence with the drug.

Our study also has some limitations. While we actively recruited patients from sites in South Africa and the US, the patients enrolled in the study were predominantly white, and our results may not extend to other racial/ethnic populations. Twelve weeks may not have been long enough to assess differences between treatments in AOBP arising from the more persistent use of spironolactone. However, given that patiromer did allow more persistent use of spironolactone due to the prevention of hyperkalaemia, it is possible that over the longer term, clinically relevant BP differences between groups may have emerged.

In conclusion, AMBER demonstrated that in patients with RTHN and advanced CKD, concomitant use of patiromer enabled more persistent use of spironolactone by reducing the risk of hyperkalaemia. It was also shown that spironolactone lowered BP in patients with RTHN and advanced CKD by a comparable magnitude to that seen in prior placebo-controlled RCTs in patients with less advanced CKD.[8] Persistent spironolactone enablement with patiromer in this population of patients with advanced CKD has clinical relevance in the treatment of RHTN.

Contributors

RA, DG, MRM, AR, WBW, PR, BW designed the study, SW collected data, and JM analysed the data. RA wrote the first draft of the manuscript. All authors were involved in data interpretation, review and writing of the manuscript.

Declaration of interests

RA reports personal fees from Abbvie, Akebia, Amgen, AstraZeneca, Bayer, Birdrock Bio, Boehringer Ingelheim, Celgene, Daiichi Sankyo, Eli Lilly, GlaxoSmithKline, Ironwood Pharmaceuticals, Johnson & Johnson, Merck, Novartis, Opko, Otsuka, Reata, Relypsa, Sandoz, Sanofi, Takeda, ZS Pharma; 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 Idorsia; honoraria from AstraZeneca, Bayer, CVRx, Fresenius, Grunenthal, Novartis, NovoNordisk, Relypsa, 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.

DG, **MRM**, **SW**, **JM**, and **AR** report employment by Relypsa, Inc., a Vifor Pharma Group Company, and stock in Vifor Pharma.

WBW reports serving as a consultant to Relypsa, Inc., a Vifor Pharma Group Company (AMBER Steering Committee).

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.

Data sharing

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. Anonymised individual patient level data will be provided in a secure access environment upon approval of a research proposal and a signed data sharing agreement. Time frame: Data can be requested 24 months after the primary publication. Data will be available for a period of 3 years for requests. Proposals for access should be sent to datasharing@viforpharma.com. The AMBER NCT03071263 study protocol and overall results will be posted to the NIH clinical trials website https://clinicaltrials.gov/ct2/show/NCT03071263 by Q4/2019.

Acknowledgments

This study was sponsored and funded by Relypsa, Inc., a Vifor Pharma Group Company. The authors acknowledge the support of the National Institute for Health Research Clinical Research Network (NIHR CRN). Susan Arthur (Relypsa, Inc.) contributed to critical data analyses and data interpretation. We would like to thank Lisa Savitt (Impact Communication Partners, Inc., New York City, NY) for editorial support

542 related to preparation of the reference list, development of tables and figures,

543 preparation of the manuscript for submission, and assisting with submission.

References

1. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults. *Journal of the American College of Cardiology*. 2017:24430-24430.
2. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J*. 2018;39(33):3021-3104.
3. Noubiap JJ, Nansseu JR, Nyaga UF, Sime PS, Francis I, Bigna JJ. Global prevalence of resistant hypertension: a meta-analysis of data from 3.2 million patients. *Heart*. 2019;105(2):98-105.
4. Williams B, MacDonald TM, Morant SV, et al. Endocrine and haemodynamic changes in resistant hypertension, and blood pressure responses to spironolactone or amiloride: the PATHWAY-2 mechanisms substudies. *Lancet Diabetes Endocrinol*. 2018;6(6):464-475.
5. De Nicola L, Gabbai FB, Agarwal R, et al. Prevalence and prognostic role of resistant hypertension in chronic kidney disease patients. *J Am Coll Cardiol*. 2013;61(24):2461-2467.
6. Jha V, Garcia-Garcia G, Iseki K, et al. Chronic kidney disease: global dimension and perspectives. *Lancet*. 2013;382(9888):260-272.
7. Rossignol P, Massy ZA, Azizi M, et al. The double challenge of resistant hypertension and chronic kidney disease. *Lancet*. 2015;386(10003):1588-1598.
8. Williams B, MacDonald TM, Morant S, et al. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. *Lancet*. 2015;386(10008):2059-2068.
9. Dahal K, Kunwar S, Rijal J, et al. The Effects of Aldosterone Antagonists in Patients With Resistant Hypertension: A Meta-Analysis of Randomized and Nonrandomized Studies. *American journal of hypertension*. 2015;28(11):1376-1385.
10. Bolignano D, Palmer SC, Navaneethan SD, Strippoli GF. Aldosterone antagonists for preventing the progression of chronic kidney disease. *Cochrane Database Syst Rev*. 2014(4):CD007004.
11. Veltassa ® (patiromer): SmPC. European Medicines Agency. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/004180/human_med_002141.jsp&mid=WC0b0. Last accessed: May 2018.
12. Veltassa® (patiromer): Prescribing information. Redwood City, CA: Relypsa, Inc; 2018. Available at: https://www.accessdata.fda.gov/scripts/cder/daf/. Last accessed: May 2018.
13. Pitt B, Anker SD, Bushinsky DA, Kitzman DW, Zannad F, Huang IZ. ; PEARL-HF Investigators. Evaluation of the efficacy and safety of RLY5016, a polymeric potassium binder, in a double-blind, placebo-controlled study in patients with chronic heart failure (the PEARL-HF) trial. *European heart journal*. 2011;32(7):820-828.
14. Agarwal R, Rossignol P, Garza D, et al. Patiromer to Enable Spironolactone Use in the Treatment of Patients with Resistant Hypertension and Chronic Kidney Disease: Rationale and Design of the AMBER Study. *Am J Nephrol*. 2018;48(3):172-180.

15. Weir MR, Bakris GL, Bushinsky DA, et al. Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. *The New England journal of medicine*. 2015;372(3):211-221.
16. Bakris GL, Pitt B, Weir MR, et al. Effect of Patiromer on Serum Potassium Level in Patients With Hyperkalemia and Diabetic Kidney Disease: The AMETHYST-DN Randomized Clinical Trial. *JAMA*. 2015;314(2):151-161.
17. Pergola PE, Spiegel DM, Warren S, Yuan J, Weir MR. Patiromer Lowers Serum Potassium When Taken without Food: Comparison to Dosing with Food from an Open-Label, Randomized, Parallel Group Hyperkalemia Study. *American journal of nephrology*. 2017;46(4):323-332.
18. Muntner P, Shimbo D, Carey RM, et al. Measurement of Blood Pressure in Humans: A Scientific Statement From the American Heart Association. *Hypertension*. 2019:HYP0000000000000087.
19. Agarwal R, Pappas MK, Sinha AD. Masked Uncontrolled Hypertension in CKD. *J Am Soc Nephrol*. 2016;27(3):924-932.
20. Agarwal R. Implications of Blood Pressure Measurement Technique for Implementation of Systolic Blood Pressure Intervention Trial (SPRINT). *J Am Heart Assoc*. 2017;6(2).

Figure Legends

Figure 1. Study Profile

Figure 2. Time to Spironolactone Discontinuation (Panel A) and Time to Serum Potassium ≥5.5 mmol/L (Panel B). Censored observations/circles: patients who did not have any event are censored on the last date with a serum potassium assessment.

Figure 3. Systolic AOBP Over Time (Panel A) and Change from Baseline to Week 12 (Panel B)

Table 1. Baseline Characteristics of Randomised Patients*

Characteristic	Spironolactone + Placebo (n=148)	Spironolactone + Patiromer (n=147)
Age*, mean (SD) years ≥65, n (%)	68.5 (11.1) 104 (70.3)	67.8 (12.2) 98 (66.7)
Male, n (%)	77 (52.0)	76 (51.7)
White race, n (%)	145 (98.0)	145 (98.6)
Weight, mean (SD) kg	83.5 (14.4)	82.6 (15.5)
Diabetes mellitus, n (%)	72 (48.6)	73 (49.7)
History of stroke or cerebrovascular accident, n (%)	15 (10.1)	14 (9.5)
History of myocardial infarction, n (%)	26 (17.6)	31 (21.1)
History of heart failure, n (%)	69 (46.6)	63 (42.9)
History of atrial fibrillation, n (%)	17 (11.5)	11 (7.5)
Number of antihypertensive medications, mean (SD) Median (Q1, Q3)	3.6 (0.7) 3 (3,4)	3.7 (0.9) 4 (3,4)
Antihypertensive medications, n (%) Beta blockers Calcium channel blockers Diuretics RAASi Other	 86 (58.1) 106 (71.6) 145 (98.0) 147 (99.3) 31 (20.9)	 87 (59.2) 107 (72.8) 146 (99.3) 147 (100) 40 (27.2)
Medications used for diabetes, n (%)	68 (45.9)	69 (46.9)
Systolic AOBP, mean (SD) mmHg	144.9 (7.0)	143.3 (6.5)
Serum potassium, mean (SD) mmol/L <4.3 mmol/L, n (%) 4.3 to >4.7 mmol/L, n (%) 4.7 to 5.1 mmol/L, n (%) >5.1 mmol/L, n (%)	4.69 (0.37) 17 (11.5) 52 (35.1) 65 (43.9) 14 (9.5)	4.74 (0.36) 7 (4.8) 55 (37.4) 65 (44.2) 20 (13.6)
eGFR, mean (SD) mL/min/1.73m^2	36.1 (7.6)	35.4 (7.3)
Serum creatinine, median (Q1, Q3), µmol/L	151.6 (129.1, 173.3)	150.3 (129.1, 176.8)
24-hour urine albumin-creatinine ratio, median (Q1, Q3), mg/g	73.0 (18.8, 400.0)	87.4 (18.4, 466.7)
24-hour urine Na, median (Q1, Q3), mmol/24-hr	189.3 (142.0, 234.9)	175.0 (119.9, 258.0)

*At informed consent. ACEi, angiotensin-converting enzyme inhibitor; ACR, urine albumin-to-creatinine ratio; AOBP, automated office blood pressure; ARB, angiotensin receptor blocker; Cr: creatinine; eGFR, estimated glomerular filtration rate; MRA, mineralocorticoid receptor antagonist; Na, sodium; NYHA, New York Heart Association; RAASi, renin angiotensin aldosterone system inhibitor; SD, standard deviation.

Table 2. Primary Endpoint, Key Secondary Endpoint and Spironolactone Dose

	Spironolactone + Placebo (n=148)	Spironolactone + Patiromer (n=147)
Primary Endpoint		
Patients who remained on spironolactone at week 12, n (%)	98 (66.2)	126 (85.7)
Difference between groups, % (95% CI)	19.5 (10.0, 29.0)	
P value for between-group difference	<0.0001	
Secondary Endpoint		
Systolic AOBP, mean (SE), mmHg		
Baseline	144.9 (0.6)	143.3 (0.5)
Week 12	133.9 (1.4)	131.9 (1.2)
Change from baseline in systolic AOBP, LS mean (95% CI), mmHg	-10.8 (-13.2, -8.3) *(n=141)*	-11.7 (-14.1, -9.3) *(n=144)*
P value for change from baseline	<0.0001	<0.0001
Difference between groups, LS mean (95% CI), mmHg	-1.0 (-4.4, 2.4)	
P value for between-group difference	0.58	
Spironolactone Dose		
Cumulative dose of spironolactone, mean (SE), mg	2580.7 (95.8)	2942.3 (80.1)
Difference between groups, LS mean (95% CI), mg	384.7 (140.4, 629.0)	
P value for between-group difference	0.0021	

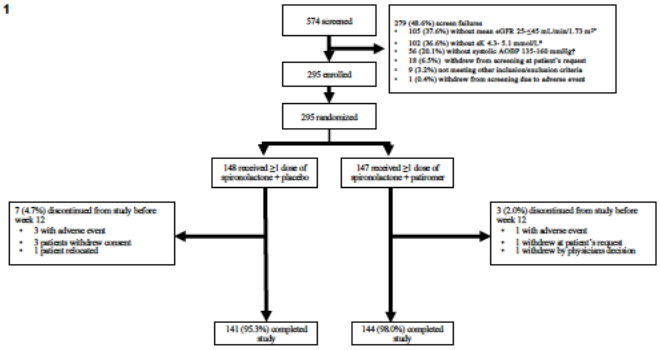
*For difference between groups (spironolactone + patiromer minus spironolactone + placebo). AOBP, automated office blood pressure; CI, confidence interval; LS, least squares; SE, standard error.

Table 3. Adverse Event Summary and Most Common Adverse Events

	Spironolactone + Placebo (n=148)	Spironolacto (n=
Adverse Event Summary		
Adverse events Severe adverse events	79 (53.4) 3 (2.0)	82 2
Serious adverse events*	4 (2.7)	1
Adverse event leading to study treatment discontinuation Hyperkalaemia	21 (14.2) 11 (7.4)	10 2
Adverse event leading to death	1 (0.7)	
Most Common Adverse Events†		
Hyperkalaemia or blood potassium increased	14 (9.4)	9
Renal impairment	10 (6.8)	13
Headache	11 (7.4)	9
Diarrhoea	8 (5.4)	9
Hypotension‡	6 (4.1)	9

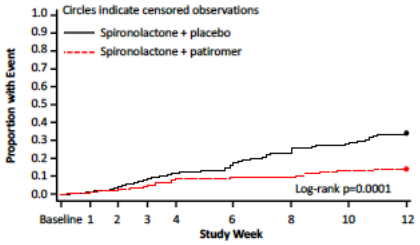
Data are n (%) of patients with at least one event; each patient is counted only once for each AE. *In the spironolactone + placebo group, one serious adverse event occurred in each of 4 patients (renal colic, renal failure, hypersensitivity, and aortic rupture [the adverse event leading to death]); in the spironolactone + patiromer group, one serious adverse event occurred in one patient (humerus fracture). † In at least 5% of patients in either treatment group; results are presented in descending order in either treatment group and then in alphabetical order. ‡ See supplemental appendix for details.

FIGURE 1



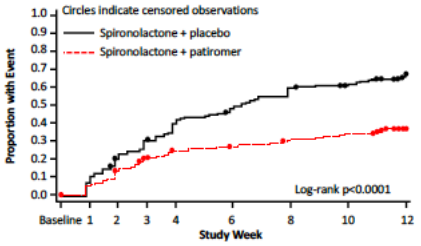
* Patients who met all study entry criteria except for eGFR and/or serum K+ were considered screen failures, but could be rescreened (once) at least 2 weeks after initial screen failure
† Systolic ADBP can be <135 mmHg at screening visit 2 or 3 (but not both).

FIGURE 2A. Time to Spironolactone Discontinuation



Discontinued due to HK									
Spironolactone + placebo	0	1	4	8	12	14	24	29	34
Spironolactone + patiromer	0	0	2	3	4	5	5	9	10
Discontinued due to other reasons									
Spironolactone + placebo	0	1	1	3	5	8	11	13	16
Spironolactone + patiromer	0	1	2	6	8	9	9	10	11
No. at risk									
Spironolactone + placebo	148	146	142	136	130	124	113	106	98
Spironolactone + patiromer	147	146	143	140	135	133	133	127	126

FIGURE 2B. Time to Serum Potassium ≥5.5 mmol/L



No. at risk									
Spironolactone + placebo	148	136	115	100	86	73	57	51	18
Spironolactone + patiromer	147	138	124	112	104	100	94	89	31

FIGURE 3A. Systolic AOBP over time

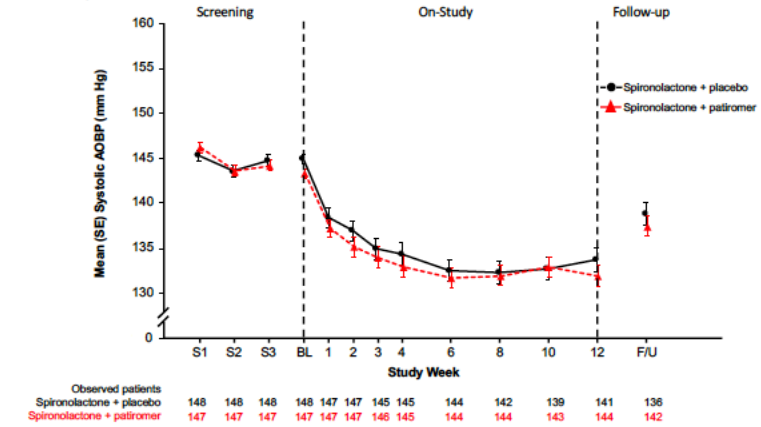
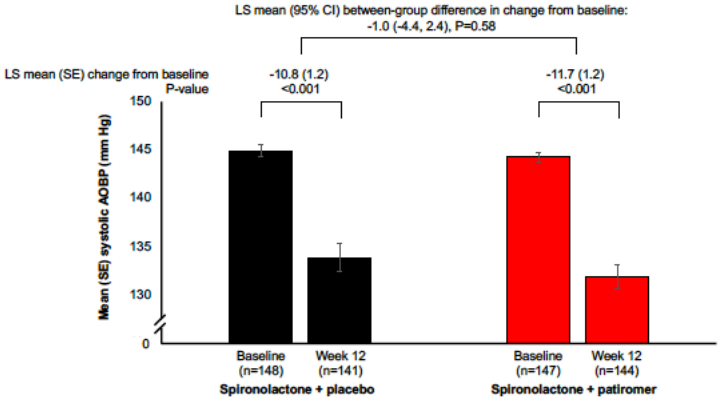


FIGURE 3B. Systolic AOBP change from baseline to week 12



Supplemental Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Agarwal R, Rossignol P, Romero A, et al. Patiromer versus placebo to enable spironolactone use in the treatment of patients with resistant hypertension and chronic kidney disease (AMBER): a randomised, double-blind, placebo-controlled trial

Table of Contents

Study Sites

***Bulgaria*:** Diyan Genov, MC (Comac Medical), Sofia; ***Croatia*:** Marinko Bilusic, Polyclinic Bonifarm, Zagreb; Mario Laganovic, University Hospital Centre Zagreb, Zagreb; Đivo Ljubičić , University Hospital Dubrava, Zagreb; Kresimir Galesic, University Hospital Dubrava, Zagreb; ***Georgia*:** Vakhtang Chumburidze, Acad. G. Chapidze Emergency Cardiology Center, LTD, Tbilisi; Gulnara Chapidze, Acad. G. Chapidze Emergency Cardiology Center, LTD, Tbilisi; Merab Mamatsashvili, ADAPTI, LTD, Tbilisi; Irakli Megreladze, Al. Tsulukidze National Center of Urology, LTD, Tbilisi; Irakli Khintibidze, Aleksandre Aladashvili Clinic, LLC, Tbilisi; Arsen Kvitsiani, Archangel St. Michael Multiprofile Clinical Hospital, LTD, Tbilisi; Rusudan Agladze, Bokhua Memorial Cardiovascular Center, LTD, Tbilisi; Ivlita Verulava, Cardioclinic - Digomi Medical Center, LTD, Tbilisi; George Khabeishvili, Diagnostic Service, LTD, Tbilisi; Bondo Kobulia, Institute of Clinical Cardiology, Tbilisi; Nodar Emukhvari, Israel-Georgia Research Clinic, Helsicore, Tbilisi; Elene Giorgadze, National Institute of Endocrinology, LTD, Tbilisi; Tamaz Shaburishvili, Tbilisi Heart and Vascular Clinic, LTD, Tbilisi; ***Hungary*:** Csaba Hajdú, BKS Research Ltd., Hatvan, Hungary; András Vértes, Central Hospital of Southern Pest National Institute of Hematology and infectious Diseases, Budapest; Botond Csiky, Coromed SMO Kft, Pecs; Andrea Hornyik, CRU Hungary Ltd., Miskolc; Denes Pall, Debreceni Egyetem Klinikai Kozpont Belgyogyaszati Klinika, Debrecen; Éva Péterfai, DRC Kft, Balatonfured; Róbert Kirschner, Flór Ferenc Pest County Hospital, Kistarcsa; Judit Hegedűs, IPR Hungary Ltd., Miskolc; Zoltán Czégány, Petz Aladár County Teaching Hospital, Gyor; János Takács, TaNa Med Kft., Mosonmagyarovar; ***Ukraine*:** Olga Godlevska, Municipal Noncommercial Enterprise City Clinical Emergency Hospital n.a. prof. O.I. Meshchaninov of Kharkiv City Council, Kharkiv; Oleksii Korzh, Medical-Sanitary Base of JSC Kharkiv Tractor Plant named after S.Ordzhonikidze, Khar'kov; Vadym Vizir, Municipal Institution City Hospital #7, Zaporizhzhia; Ivan Fushtey, Municipal Institution Zaporizhzhia City Clinical Hospital №10, Zaporizhzhia; Viktoriia Zharinova, State Institution Institute of Gerontology named after D.F. Chebotaryov NAMS Ukraine, Kiev; Yevgenia Svyshchenko, State Institution National Scientific Center M.D. Strazhesko Institute of Cardiology NAMS of Ukraine, Kiev; Anna Isayeva, The Government Institution National Institute of Therapy named by

L.T. Malaya of National Ukrainian Academy of Medical Science, Kharkiv; ***France*:*** Jean-Michel Halimi, Hôpital Bretonneau – Service de Néphrologie-Immunologie Clinique, Tours; Patrick Rossignol, CHRU Nancy – Hôpitaux de Brabois Centre Investigations Cliniques Plurithématique, Vandoeuvre les Nancy; Atul Pathak, Clinique Pasteur / GCVI, Toulouse; Alexandre Karras, Hôpital APHP Européen Georges Pompidou, Paris; ***Germany*:** Amaar Ujeyl, ASKLEPIOS , Hamburg; Michael Böhm, Universitaetsklinikum des Saarlandes, Homburg; Stephan von Haehling, University Medical Center Goettingen, Gottingen, ***South Africa*:** Tom Mabin, Helderberg Research Institute; Clive Corbett, Corbod Clinical Research; Essack Mitha, Newtown Clinical Research Centre, Johannesburg; ***United Kingdom*:** Madhu Menon, Royal Stoke University Hospital, Stoke-on-Trent; Andrew Moriarty, Cardiovascular Research Unit Craigavon Area Hospital, Portadown; Iain Macdougall, Kings College Hospital NHS foundation Trust, London; Matthew Hall, Nottingham University Hospitals NHS Trust, Nottingham; Jonathan Barratt, University Hospitals of Leicester NHS Trust, Leicester; ***United States*:** Aamir Jamal, North America Research Institute, San Dimas, California; Niloofar Nobakht-Haghighi, UCLA, Los Angeles, California; Kianoosh Kaveh, Coastal Nephrology Associates, Port Charlotte, Florida; James Reich, Research Physicians Alliance Network, Hollywood, Florida; Belkis Delgado, San Marcus Research Clinic, Miami Lakes, Florida; Alan Miller, Alta Pharmaceutical Research Center, Dunwoody, Georgia; Jennifer Tuazon, Northwestern University, Chicago, Illinois; Susan Steigerwalt, University of Michigan, Ann Arbor, Michigan; Nelson Kopyt, Northeast Clinical Research Center, Bethlehem, Pennsylvania; German Hernandez, MedResearch, El Paso, Texas.

* Patients were screened but no patients were enrolled at sites in France.

Data Safety and Monitoring Committee (DSMC)

The study was overseen by an independent Data Safety and Monitoring Committee (DSMC), which was responsible for reviewing and evaluating all relevant information that may have had an impact on the safety of the study participants, assessing risks and benefits to study participants, providing recommendations to the study sponsor concerning continuation, termination or amendments to the study and reviewing safety, dosing and pharmacodynamic data of both spironolactone and patiromer throughout the study.

Adverse Event Details

Hypotension (all mild-to-moderate in severity and none serious) as an adverse event occurred in 6 (4.1%) patients in the placebo group and in 9 (6.1%) patients in the patiromer group; symptomatic hypotension led to discontinuation of study drugs in 2 (1.4%) and 4 (2.7%) patients, respectively. Other vascular events within the vascular disorders class were hypertension (5 [3.4%] patients in the placebo group and 3 [2.0%] patients in the patiromer group; all were mild to moderate in intensity and none were serious) and hypertensive crisis (0 and 2 [1.4%] patients, respectively). The 2 reported events of accelerated hypertension were not associated with other adverse events, did not require hospitalization or emergency department visits, and led to only transient (<2 days) increases in antihypertensive medications.

Serious Renal Adverse Events

Serious renal adverse events occurred in 2 (1.4%) placebo-treated patients (renal colic and renal failure) and in none of the patiromer-treated patients. The patient with a serious adverse event of renal colic was a 55-year-old male with a history of renal coral calculus and chronic obstructive pyelonephritis. He presented with nephrocolic and was hospitalised. The patient underwent lithotripsy and an unknown surgical procedure. The serious adverse event of renal colic was not attributed by the investigator to study drugs.

The patient with the serious adverse event of renal failure was admitted to the hospital for subacute renal insufficiency. There was a decline in eGFR of >30 mL/min/1.73m^2 by central lab. The patient was treated with IV normal saline and recovered. The serious adverse event led to withdrawal of both study drugs and was not attributed by the investigator to study drugs.

Death Due to Serious Adverse Event

One patient (placebo group) died due to a serious adverse event of aortic rupture. This was an 84-year-old male with history of a CKD, diabetes mellitus, resistant hypertension, and heart failure on the concomitant medications lercanidipine, nebivolol, perindopril, indapamide, and glimepiride. The patient presented with a brief episode of anamnesis and abdominal and lumbar pain and shock. Abdominal aortic aneurysm with rupture was diagnosed by ultrasound. Surgery was attempted but the patient sustained ventricular flutter during the procedure and could not be resuscitated. The event was not attributed by the investigator to study drugs.

Mean Serum Magnesium and Calcium Levels During the Study

Mean levels of serum magnesium and calcium remained within the normal range in both treatment groups during the study (**Supplemental Table 2**). In the patiromer group, mean (SE) serum magnesium was 0.9 (0.0) mmol/L at baseline, with a change from baseline to week 12 of 0.0 (0.0) mmol/L, and a change from baseline to follow-up of 0.0 (0.0) mmol/L. Hypomagnesaemia as an adverse event was reported in 2 (1.4%) patiromer patients. In one of these patients, serum magnesium was 0.8 mmol/L at baseline, 0.6 mmol/L when the adverse event was reported and 0.7 and 0.8 mmol/L at week 12 and at follow-up, respectively. In the other patient, baseline serum magnesium was 0.9 mmol/L, and the lowest serum magnesium level in this patient during the study was 0.8 mmol/L; at an unscheduled visit at day 126, serum magnesium was 0.8 mmol/L. There was no change in mean serum magnesium in the placebo group through week 12. For serum calcium, the change from baseline at week 12 was 0.0 (0.0) mmol/L with placebo and 0.0 (0.0) mmol/L with patiromer, from a mean (SE) baseline value of 2.3 (0.0) mmol/L in both groups. Hypercalcaemia as an adverse event was reported in 1 (0.7%) patient on patiromer. Serum calcium levels at screening visit 1 and at baseline were 2.6 mmol/L and 2.9 mmol/L, respectively. The adverse event was noted on days 50-77, with the serum calcium level of 2.9 mmol/L on day 50; the adverse event was mild and was not considered related to patiromer. At week 12, the patient's serum calcium level was 2.2 mmol/L.

Supplemental Table 1. Reasons for Early Discontinuation of Study Treatment

	Spironolactone + Placebo (n=148)	Spironolactone + Patiromer (n=147)
Discontinued early from study treatment	50 (33.8)	21 (14.2)
Met 1 of 3 protocol-specified withdrawal criteria* for high serum potassium 1) Patiromer/placebo dose = max, confirmed* potassium ≥ 5.5 and < 6.0 2) Patiromer/placebo dose increased by 2 packets/day, confirmed† potassium ≥5.5 and <6.0 3) Confirmed* potassium ≥ 6.0	34 (23.0) 21 (42.0) 7 (14.0) 6 12.0)	10 (6.8) 3 (14.3) 6 (28.6) 1 (4.8)
Had protocol-defined symptomatic hypotension‡	2 (1.4)	4 (2.7)
Had protocol-defined decline in eGFR§	4 (2.7)	3 (2.0)
Other Adverse event Patient withdrawal Low serum potassium Investigator decision	11 (7.4) 5 (3.4) 5 (3.4) 1 (1.0) 0	6 (4.1) 3 (2.0) 1 (1.0) 1 (1.0) 1 (1.0)

Data are n (%). Note: patients could have more than one reason for discontinuing early from study treatment.
* Repeat potassium measurement (taken within 1 day) that confirms the initial measurement
† Repeat potassium measurement (taken within 3 days after the 2-packet dose increase) that confirms the initial measurement
‡ Systolic AOBP < 100 mmHg, or symptoms of hypotension and systolic AOBP < 120 mmHg.
§ eGFR decrease of 30–50% from baseline that did not return to ≤ 30% of baseline within 4 weeks.

Supplemental Table 2. Usage of ACEI and ARB at Baseline and During the Study

Preferred drug name	Spironolactone + placebo n=148		Spironolactone + patiromer n=147	
	Baseline	During Study	Baseline	During Study
Perindopril	51 (34.5)	51 (34.5)	54 (36.7)	54 (36.7)
Valsartan	27 (18.2)	27 (18.2)	38 (25.9)	38 (25.9)
Losartan	26 (17.6)	26 (17.6)	20 (13.6)	20 (13.6)
Enalapril	14 (9.5)	14 (9.5)	11 (7.5)	11 (7.5)
Ramipril	12 (8.1)	12 (8.1)	8 (5.4)	8 (5.4)
Lisinopril	7 (4.7)	7 (4.7)	5 (3.4)	5 (3.4)
Irbesartan	4 (2.7)	4 (2.7)	5 (3.4)	5 (3.4)
Candesartan	3 (2.0)	3 (2.0)	1 (0.7)	1 (0.7)
Fosinopril	1 (0.7)	1 (0.7)	2 (1.4)	2 (1.4)
Telmisartan	2 (1.4)	2 (1.4)	1 (0.7)	1 (0.7)
Zofenopril	1 (0.7)	1 (0.7)	2 (1.4)	2 (1.4)
Captopril	0	0	1 (0.7)	1 (0.7)
Trandolapril	1 (0.7)	1 (0.7)	0	0

Data are n (%).

Supplemental Table 3. Spot Urine Albumin-to-Creatinine Ratio Over Time and Change from Baseline

	Spironolactone + placebo	N	Spironolactone + patiromer	N
Urine ACR, mean (SE) mg/g				
Baseline	393.7 (59.7)	148	432.2 (68.0)	147
Week 4	336.1 (60.8)	143	432.8 (64.7)	144
Week 8	338.9 (52.5)	141	405.3 (78.0)	142
Week 12	336.6 (60.0)	139	399.1 (73.5)	143
Change from baseline to week 12	-48.8 (36.3)	139	-27.7 (28.5)	143
Difference between groups, mg/g (95% CI)*	20.0 (-70.6, 110,6)			
P value for between-group difference	0.6644			

*For difference between groups (spironolactone + patiromer minus spironolactone + placebo).
ACR, albumin-to-creatinine ratio

Supplemental Table 4. EQ-5D-5L Visual Analog Scale Questionnaire Results

	Spironolactone + placebo	N	Spironolactone + patiromer	N
EQ-VAS, mean (SE) score Baseline Week 12	 66.3 (1.3) 69.1 (1.3)	 148 144	66.9 (1.3) 71.7 (1.3)	147 145
Change from baseline to week 12	2.8 (1.0)	144	4.8 (0.8)	145

EQ-5D-5L = EuroQol Group 5-domain 5-level (EQ-5D-5L) questionnaire[1]; EQ-VAS = EuroQol visual analog scale; SE = standard error.

The EQ VAS records the patient's self-rated health status on a graduated scale that ranges from 0-100, with higher scores indicating higher health-related quality of life.

EQ-5D-5L data were analysed descriptively.

1. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, Bonsel G, Badia X: Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res 2011; 20: 1727–1736.

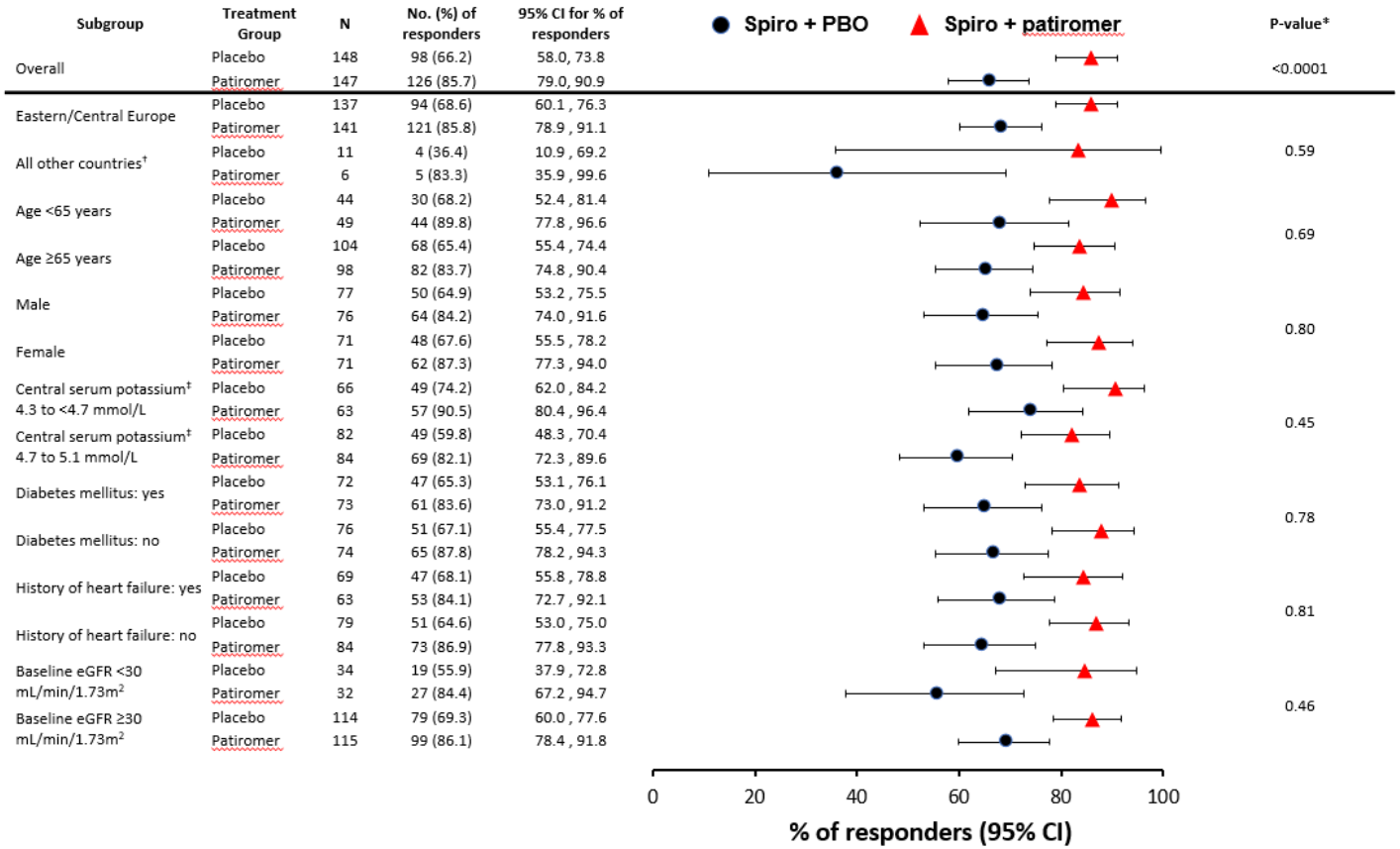
Supplemental Table 5. Serum Chemistry Results Over Time and Change from Baseline

Serum Parameter	Spironolactone + placebo	N	Spironolactone + patiromer	N
Magnesium, mean (SE) mmol/L				
Baseline	0.9 (0.009)	148	0.9 (0.009)	147
Week 1	0.9 (0.009)	147	0.9 (0.009)	147
Week 2	0.9 (0.009)	147	0.8 (0.009)	147
Week 3	0.9 (0.009)	145	0.9 (0.011)	146
Week 4	0.9 (0.008)	145	0.8 (0.009)	145
Week 6	0.9 (0.008)	144	0.8 (0.010)	144
Week 8	0.9 (0.009)	142	0.9 (0.009)	144
Week 10	0.9 (0.009)	137	0.9 (0.010)	142
Week 12	0.9 (0.008)	141	0.8 (0.009)	144
Change from baseline to week 12	0.0 (0.007)		0.0 (0.007)	
Follow-up	0.9 (0.009)	135	0.9 (0.010)	141
Change from baseline to follow-up	0.0 (0.007)		0.0 (0.007)	
Calcium, mean (SE) mmol/L				
Baseline	2.3 (0.01)	148	2.3 (0.01)	147
Week 1	2.3 (0.01)	147	2.3 (0.01)	147
Week 2	2.3 (0.01)	146	2.3 (0.01)	147
Week 3	2.3 (0.01)	145	2.3 (0.01)	146
Week 4	2.3 (0.01)	145	2.3 (0.01)	145
Week 6	2.3 (0.01)	143	2.3 (0.01)	144
Week 8	2.3 (0.01)	142	2.3 (0.01)	144
Week 10	2.3 (0.01)	137	2.3 (0.01)	141
Week 12	2.3 (0.01)	141	2.3 (0.01)	144
Change from baseline to week 12	0.0 (0.01)		0.0 (0.01)	
Follow-up	2.3 (0.01)	135	2.3 (0.01)	141
Change from baseline to follow-up	0.0 (0.01)		0.0 (0.01)	

Creatinine, median (Q1, Q3) µmol/L				
Baseline	151.6 (129.1, 173.3)	148	150.3 (129.1, 176.8)	147
Week 1	150.3 (129.1, 176.8)	147	152.9 (135.3, 184.8)	147
Week 2	155.6 (130.8, 182.1)	147	154.7 (130.8, 174.1)	147
Week 3	152.9 (129.1, 175.9)	145	151.2 (135.3, 181.2)	146
Week 4	158.2 (137.0, 186.5)	145	156.5 (134.4, 187.4)	145
Week 6	160.9 (135.3, 186.1)	144	160.9 (133.9, 190.5)	144
Week 8	158.2 (132.6, 188.3)	142	159.6 (133.0, 187.0)	144
Week 10	160.0 (135.3, 184.8)	138	154.3 (129.1 188.3)	142
Week 12	155.6 (130.8, 190.1)	141	155.1 (130.8, 190.1)	144
Change from baseline to week 12	8.8 (-7.1, 23.0)		5.3 (-8.0, 19.9)	
Follow-up	154.7 (129.1 179.5)	136	156.5 (128.2, 188.3)	141
Change from baseline to follow-up	5.3 (-11.5, 16.4)		2.7 (-10.6, 20.3)	
eGFR, mean (SE) mL/min/1.73m^2				
Baseline	36.1 (0.6)	148	35.4 (0.6)	147
Week 1	35.6 (0.7)	147	34.1 (0.6)	147
Week 2	34.6 (0.7)	147	34.9 (0.7)	147
Week 3	35.4 (0.8)	145	34.6 (0.7)	146
Week 4	34.0 (0.7)	145	33.2 (0.6)	145
Week 6	33.8 (0.7)	144	33.7 (0.7)	144
Week 8	34.1 (0.7)	142	33.8 (0.7)	144
Week 10	34.1 (0.7)	138	34.6 (0.7)	142
Week 12	34.1 (0.7)	141	33.9 (0.7)	144
Change from baseline to week 12	-2.1 (0.6)		-1.4 (0.6)	
Follow-up	35.1 (0.7)	136	35.2 (0.8)	141
Change from baseline to follow-up	-1.3 (0.6)		-0.3 (0.8)	

Supplemental Figure 1. Forest Plot of Percentage of Patients Remaining on Spironolactone at Week 12 by Subgroups.

Prespecified subgroup analysis of the primary end-point.



Subgroup	Treatment Group	N	No. (%) of responders	95% CI for % of responders	P-value*
Overall	Placebo	148	98 (66.2)	58.0, 73.8	<0.0001
	Patiromer	147	126 (85.7)	79.0, 90.9	
Eastern/Central Europe	Placebo	137	94 (68.6)	60.1 , 76.3	
	Patiromer	141	121 (85.8)	78.9 , 91.1	
All other countries†	Placebo	11	4 (36.4)	10.9 , 69.2	0.59
	Patiromer	6	5 (83.3)	35.9 , 99.6	
Age <65 years	Placebo	44	30 (68.2)	52.4 , 81.4	
	Patiromer	49	44 (89.8)	77.8 , 96.6	0.69
Age ≥65 years	Placebo	104	68 (65.4)	55.4 , 74.4	
	Patiromer	98	82 (83.7)	74.8 , 90.4	
Male	Placebo	77	50 (64.9)	53.2 , 75.5	
	Patiromer	76	64 (84.2)	74.0 , 91.6	0.80
Female	Placebo	71	48 (67.6)	55.5 , 78.2	
	Patiromer	71	62 (87.3)	77.3 , 94.0	
Central serum potassium‡ 4.3 to <4.7 mmol/L	Placebo	66	49 (74.2)	62.0 , 84.2	
	Patiromer	63	57 (90.5)	80.4 , 96.4	0.45
Central serum potassium‡ 4.7 to 5.1 mmol/L	Placebo	82	49 (59.8)	48.3 , 70.4	
	Patiromer	84	69 (82.1)	72.3 , 89.6	
Diabetes mellitus: yes	Placebo	72	47 (65.3)	53.1 , 76.1	
	Patiromer	73	61 (83.6)	73.0 , 91.2	0.78
Diabetes mellitus: no	Placebo	76	51 (67.1)	55.4 , 77.5	
	Patiromer	74	65 (87.8)	78.2 , 94.3	
History of heart failure: yes	Placebo	69	47 (68.1)	55.8 , 78.8	
	Patiromer	63	53 (84.1)	72.7 , 92.1	0.81
History of heart failure: no	Placebo	79	51 (64.6)	53.0 , 75.0	
	Patiromer	84	73 (86.9)	77.8 , 93.3	
Baseline eGFR <30 mL/min/1.73m^2	Placebo	34	19 (55.9)	37.9 , 72.8	
	Patiromer	32	27 (84.4)	67.2 , 94.7	0.46
Baseline eGFR ≥30 mL/min/1.73m^2	Placebo	114	79 (69.3)	60.0 , 77.6	
	Patiromer	115	99 (86.1)	78.4 , 91.8	

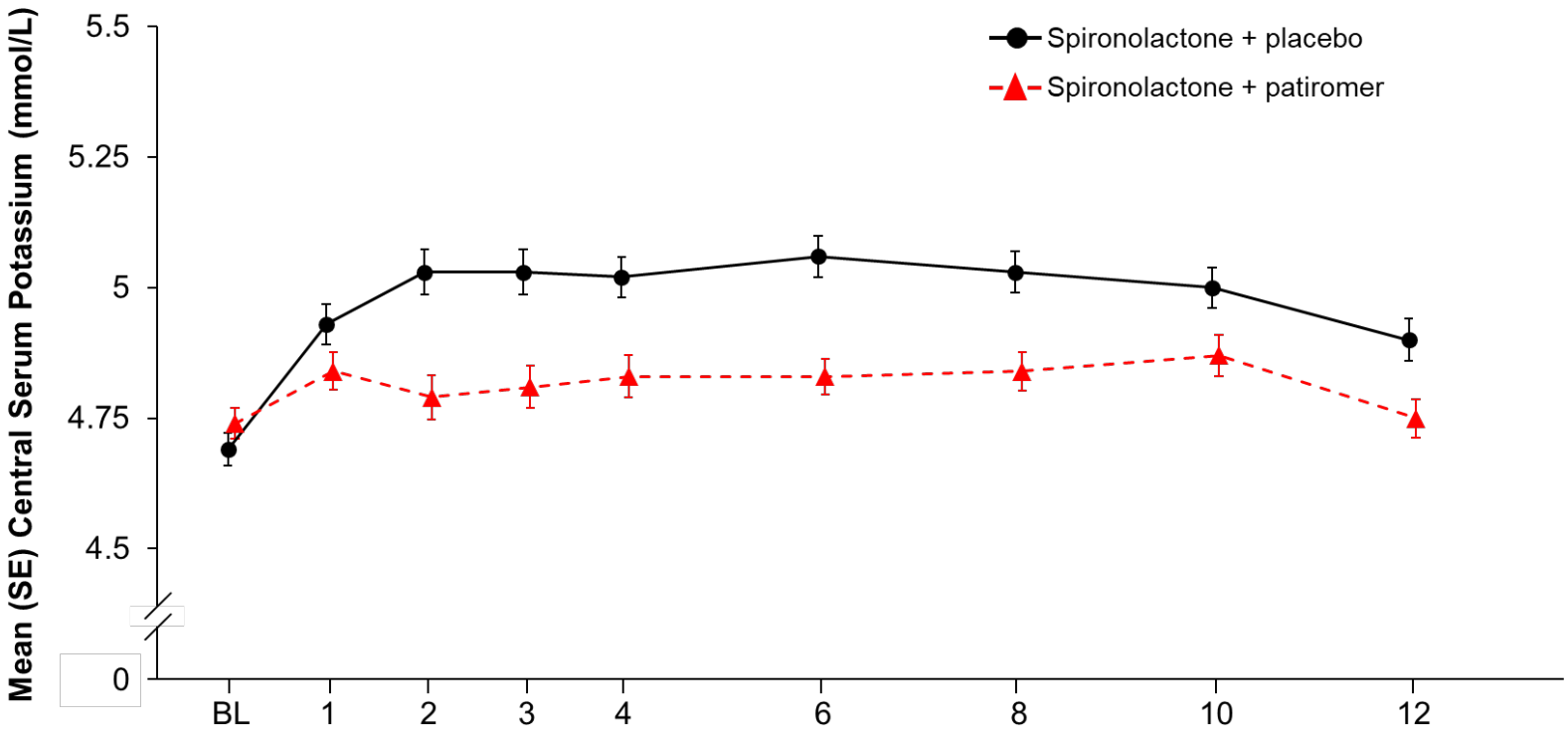
*For the overall population, the P-value corresponds to the between-group difference for the overall ITT population; for the subgroups, the p-values correspond to the Breslow-Day Test interaction between subgroups.
†Germany, South Africa, United Kingdom, and United States. Note: 5 patients were screened at sites in France, but no patients were enrolled.
‡The two baseline potassium subgroups, 4.3 to < 4.7 mmol/L versus 4.7 to 5.1 mmol/L, are based on central laboratory data. If a patient's serum potassium result was not in one of these two subgroups, the patient's potassium stratum at randomisation was used.

*For the overall population, the P-value corresponds to the between-treatment group difference; for the subgroups, the P-values correspond to the Breslow-Day Test interaction.

†Germany, South Africa, United Kingdom, and United States. Note: 5 patients were screened at sites in France, but no patients were enrolled.

‡The two baseline potassium subgroups, 4.3 to <4.7 mmol/L versus 4.7 to 5.1 mmol/L, are based on central laboratory data. If a patient's serum potassium result was not in one of these two subgroups, the patient's potassium stratum at randomisation was used.

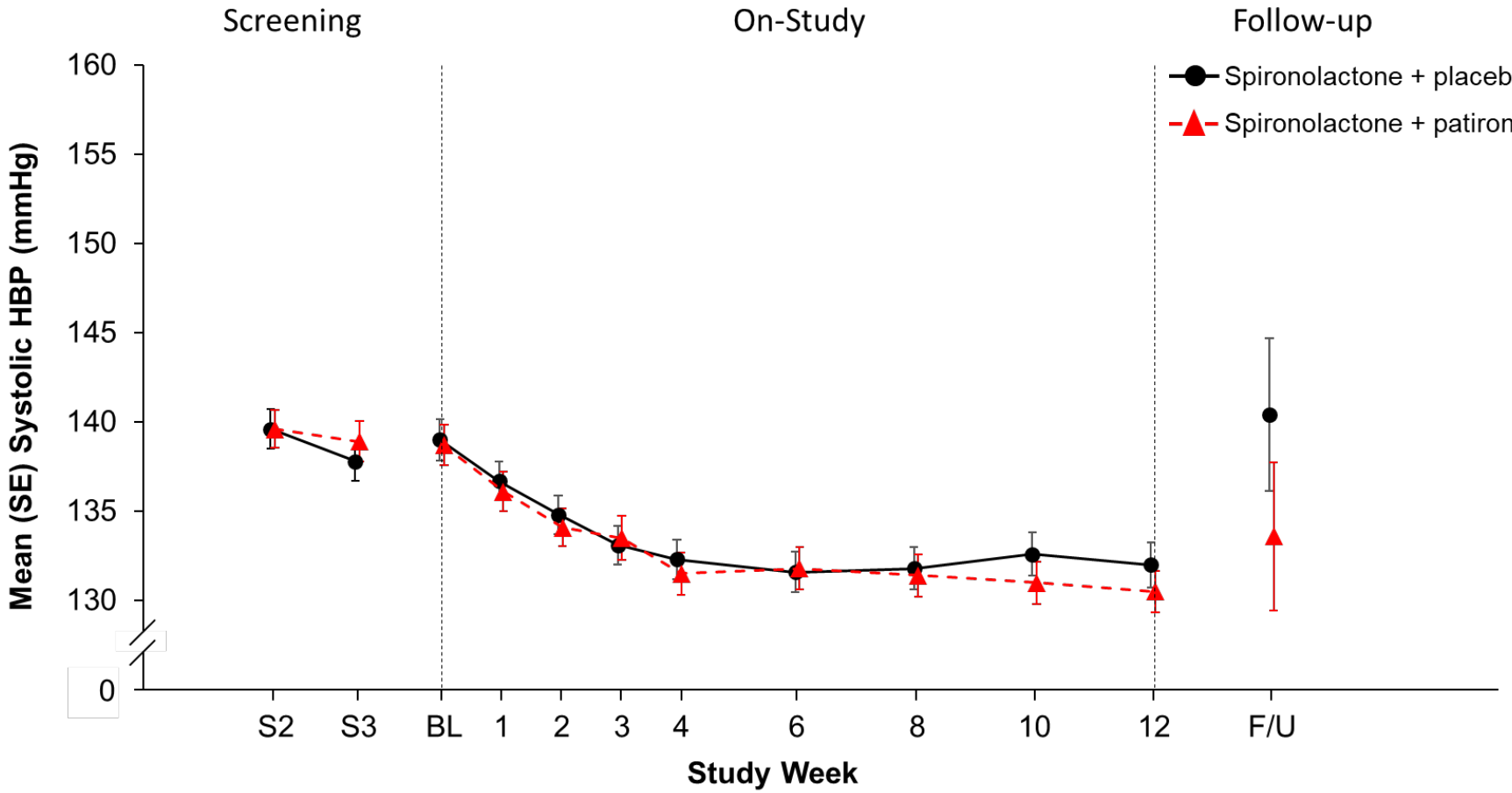
Supplemental Figure 2. Serum Potassium During Active Treatment



	BL	1	2	3	4	6	8	10	12
Discontinued due to HK									
Spironolactone + placebo	0	1	4	8	12	14	24	29	34
Spironolactone + patiromer	0	0	2	3	4	5	5	9	10
Observed patients									
Spironolactone + placebo	148	146	147	145	145	144	142	137	140
Spironolactone + patiromer	147	146	147	146	145	144	144	142	144

HK, hyperkalaemia.
Observed patients = Number of patients who have non-missing values at a study visit.
Discontinued patients = Number of patients who discontinued study treatment early for hyperkalaemia prior to or at a study visit.

Supplemental Figure 3. Systolic Home Blood Pressure Over Time, ITT Population*



Observed patients												
Spironolactone + placebo	131	134	140	138	139	135	132	128	129	122	125	10
Spironolactone + patiromer	124	126	128	135	133	131	128	126	123	125	123	6

* Regardless of increase in antihypertensive medications.