CLINICAL STUDY PROTOCOL

Title:	A Randomized, Double-Blind, Placebo-controlled, Parallel Group Study of Patiromer for the Enablement of Spironolactone Use for Blood Pressure Control in Patients with Resistant Hypertension and Chronic Kidney Disease: Evaluation of Safety and Efficacy (AMBER)
Investigation Drug:	Patiromer for Oral Suspension
US IND #:	75,615
Protocol Number:	RLY5016-207
EudraCT:	2016-002657-38
Sponsor:	Relypsa, Inc. 100 Cardinal Way Redwood City, CA 94063 USA +1.650.421.9500 Phone +1.650.421.9700 Fax
Relypsa Medical Monitor:	[redacted] +1.650.421.9700 Fax
Original Protocol Date:	14 July, 2016
Amendment 1 Date:	18 October, 2016
Amendment 2 (Administrative) Date:	4 November, 2016

CONFIDENTIAL INFORMATION

PROTOCOL SIGNATURE FORM

Protocol Title:	A Randomized, Double-Blind, Placebo-controlled, Parallel Group Study of Patiromer for the Enablement of Spironolactone Use for Blood Pressure Control in Patients with Resistant Hypertension and Chronic Kidney Disease: Evaluation of Safety and Efficacy (AMBER)
Protocol Number:	RLY5016-207
Original Protocol Date:	14 July, 2016
Amendment 1 Date:	18 October, 2016
Amendment 2 (Administrative) Date:	4 November, 2016

I agree to conduct the study as detailed herein and in compliance with the protocol, ICH Guidelines for Good Clinical Practice (GCP) and other applicable regulatory requirements.

Principal Investigator Signature **Date**

Principal Investigator Name (print)

SPONSOR SIGNATURE PAGE

Declaration of Sponsor or Responsible Medical Expert

Protocol Title:	A Randomized, Double-Blind, Placebo-controlled, Parallel Group Study of Patiromer for the Enablement of Spironolactone Use for Blood Pressure Control in Patients with Resistant Hypertension and Chronic Kidney Disease: Evaluation of Safety and Efficacy (AMBER)
Protocol Number:	RLY5016-207
Original Protocol Date:	14 July, 2016
Amendment 1 Date:	18 October, 2016
Amendment 2 (Administrative) Date:	4 November, 2016

This clinical study protocol was subjected to critical review. The information provided is consistent with current knowledge of the risks and benefits of the investigational medicinal product (IMP), as well as with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki (Version 2008), and the guidelines on Good Clinical Practices (GCP) applicable to this clinical study.

Sponsor Signatory/Responsible Medical Expert

[redacted]

[redacted]

Date

RLY5016-207
PROTOCOL AMENDMENT 2
SUMMARY AND RATIONALE FOR CHANGES

The following is a summary of the changes made in this protocol amendment, the sections affected, and the rationale for each change.

No.	Section(s)	Description of Changes	Rationale
1	All	***Global Change:*** • Updated title page, Protocol and Review Signature Form, footers and text to reflect amended protocol version and date • Updated the Table of Contents • Punctuation changes	Typographical /Administrative
2	Synopsis, Section 4.2	The term 'untreated' is added to the exclusion that subjects with secondary causes of hypertension should be excluded.	Clarifies that it is subjects with untreated secondary causes of hypertension that should be excluded
3	Synopsis, Sections 3.1.2, 5.5, 6.1	Instructions to the subject to delay taking their BP medications on the morning of the study visits until after office BP measurements have been completed	Clarifies that blood pressure measurements should be done before BP medications are administered on the morning of the visit
4	Sections 6.1.2, 6.1.3, 6.1.4, 6.2.2, 6.2.3, 7.3.2.2,	The order of the visit activities specifies that BP measurements should be conducted before other scheduled activities (except for S4 and Week 12 Visits where EQ-5D-5L will be the first assessment)	Clarifies the order of visit activities

STUDY SYNOPSIS

Title:	A Randomized, Double-Blind, Placebo-controlled, Parallel Group Study of Patiromer for the Enablement of Spironolactone Use for Blood Pressure Control in Patients with Resistant Hypertension and Chronic Kidney Disease: Evaluation of Safety and Efficacy (AMBER)
Protocol Number:	RLY5016-207
Phase:	2
Description of Agent or Intervention:	Patiromer for Oral Suspension (patiromer) is a polymeric drug designed to bind and remove potassium from the gastrointestinal tract leading to removal of potassium from the body and lowering of serum potassium levels. Patiromer (Veltassa®) is approved by the Food and Drug Administration (FDA) for the treatment of hyperkalemia in adult patients.
Study Objective:	To determine if patiromer treatment in chronic kidney disease (CKD) subjects receiving spironolactone for the treatment of resistant hypertension will result in more persistent use of spironolactone through prevention of hyperkalemia and lead to improved blood pressure control compared with treatment with spironolactone alone (placebo)
Study Outcomes	
Primary Endpoint:	Treatment group difference (spironolactone plus patiromer vs. spironolactone plus placebo) in proportion of subjects remaining on spironolactone at Week 12.
Secondary Endpoint:	Treatment group difference in change in systolic blood pressure (SBP) by automated office blood pressure (AOBP) measurements from baseline to Week 12 or last available AOBP measurement prior to addition of any new blood pressure (BP) medications or changes to any baseline BP medications.
Other Endpoints:	Other endpoints include: • Change in AOBP SBP from baseline to Week 12 • Potassium levels over time (measured both centrally and locally) • Proportion of subjects with serum $K^+ \geq 5.5$ mEq/L • Average daily dose and cumulative dose of spironolactone • Time to discontinuation of spironolactone • Change in albuminuria (urine albumin to creatinine ratio [ACR]) from baseline to Week 12 • EQ-5D-5L questionnaire results at Baseline and Week 12/Early Termination (ET)
Safety:	Safety endpoints will consist of adverse events ([AEs]) including newly observed clinically significant physical examination abnormalities), clinical laboratory tests, vital signs, clinically significant electrocardiogram (ECG) findings and reasons for discontinuing study drugs.
Study Design	
Description:	This is a randomized, double-blind, placebo-controlled, parallel group study of patiromer or placebo treatment (patiromer/placebo) in conjunction with spironolactone in subjects with resistant hypertension and CKD. The study will consist of a Screening/Run-in Period (up to 4 weeks), a 12-week Double-Blind Treatment Phase and a Follow-up Visit 2 weeks after Week 12 or ET Visit. **Screening/Run-in Period (up to 4 weeks):** The purpose of the Screening/Run-in Period is to ensure that all enrolled subjects are on stable doses of baseline medications, do not have "white coat" hypertension, can demonstrate proper and reliable use of the home BP (HBP) monitoring device prior to study drug treatment, and meet all study inclusion/exclusion criteria.

	The Screening/Run-in Period will consist of 4 Screening Visits (S1, S2, S3, and S4) that are approximately 7 days (at least 4 days but no more than 10 days) after the prior Screening Visit (Appendix A). Subjects will be instructed to delay taking their blood pressure medications on the morning of their subsequent study visits until after office blood pressure measurements have been completed. Visit S1: Each subject will be issued a HBP monitor and provided with training on device use. Subjects will be instructed to measure HBP in triplicate twice daily after Visit S1 (Section 7.3.2.1). Visits S2, S3 and S4: Two types of office BP measurements will be performed before other scheduled activities (except for S4 where the EQ-5D-5L will be the first assessment). Both measurements will be performed with the subject alone after 5 minutes of seated rest (Section 7.3.2.2): 1. Performed by an automatic oscillometric BP monitoring device that can measure BP in triplicate (automated office BP, AOBP) 2. Performed by the subject using their issued HBP monitoring device in triplicate (subject-measured BP, SMBP) Note: Study staff should <u>not</u> be present while both office BP measurements are being performed. Subjects will be instructed to bring their issued HBP device to every visit. To be eligible for this study, subjects will be required to meet all of the following criteria: 1. AOBP SBP 135 to 160 mmHg at each Screening Visit; however, AOBP SBP may be < 135 mmHg at either S2 or S3 Visits 2. Estimated glomerular filtration rate (eGFR) of 25 – ≤ 45 mL/min/1.73 m^2 (mean [calculated by the Interactive Web Response System – IWRS] of two values measured at S1 and S3 (or 7 to 28 days apart) during the Screening/Run-in Period) 3. Local laboratory measurements of K^+ level of 4.3 – 5.1 mEq/L obtained at Visits S1, S3 and S4 (all measurements must be within range) 4. Does not meet any exclusion criteria If hemolysis of the local sample is detected or suspected (see Section 7.1.1) at Screening Visits (S1 and S3), a repeat of the potassium measurement from a separate blood draw will be performed within 1 day. If the repeated potassium level does not meet entry criteria, then the subject is considered a Screen Failure. For Visit S4, if hemolysis of the local sample is detected or suspected, the subject is not randomized and a repeat of the potassium measurement from a separate blood draw will be performed within 1 day. If the subject qualifies, the subject will be randomized on the same day. All assessments performed at Visit S4, aside from the hemolyzed potassium level, will be considered baseline assessments, and the day the repeat potassium measurement was obtained will be designated the Randomization/Baseline (Day 0) Visit. If the repeated potassium level does not meet entry criteria, then the subject is considered a Screen Failure. If a subject fails any qualifying criteria at any of the Screening Visits, the subject will be considered a Screen Failure at that Visit. Subjects who meet all study entry criteria except for eGFR and/or serum potassium will be screen failures but may be rescreened once at least 2 weeks after initial screen failure (Section 6.1.5). **Double-Blind Treatment Period (12 weeks):** <u>Randomization Visit (Baseline/Day 0):</u> Subjects who meet all eligibility criteria at Visit S4 will be randomized on the same day to either patiromer or placebo treatment (1:1) with stratification based on the local potassium level at Visit S4 (4.3 – < 4.7 or 4.7 – 5.1 mEq/L) and history of Type 1 or 2

	diabetes mellitus (Yes or No). The S4 assessments will become the baseline assessments. A combined visit (S4/Randomization [Baseline/Day 0]) will be recorded for all randomized subjects. All randomized subjects will be provided with detailed instructions regarding when to take spironolactone, patiromer/placebo, and other baseline medications after considering the subject's current medication regimen, patiromer/placebo instructions regarding administration, and subject preference (see Section 5.5.1). The subject will be instructed to begin taking study drugs (spironolactone and patiromer/placebo) on the day following randomization (Day 1) and on the morning of their subsequent study visits to delay taking their blood pressure medications until office blood pressure measurements have been completed. Treatment Period Visits (refer to Appendix A): During the Double-Blind Treatment Period, study visits will occur at Week 1 (Day 8 ± 3 days), Week 2 (Day 15 ± 3 days), Week 3 (Day 22 ± 3 days), Week 4 (Day 29 ± 3 days), Week 6 (Day 43 ± 7 days), Week 8 (Day 57 ± 7 days), Week 10 (Day 71 ± 7 days), and Week 12 (Day 85 ± 7 days). *Patiromer/placebo treatment:* Patiromer/placebo will be taken at a starting dose of two packets once daily (QD). Based upon the treatment algorithm, patiromer/placebo will be increased in two-packet per day increments for local $K^+ > 5.1$ mEq/L in intervals of at least 1 week up to a maximum dose of six packets QD. For subjects with $K^+ < 4.0$ mEq/L, patiromer/placebo dose will be decreased by at least two packets per day. The minimum dose of patiromer/placebo is 0 packets. Patiromer/placebo should be taken with food, at least 3 hours before or 3 hours after administration of other oral concomitant medications including spironolactone. Refer to Appendix B (Patiromer/Placebo Titration) for complete dosing and monitoring instructions. Throughout the Double-Blind Treatment Period, subjects who develop $K^+ \geq 5.5$ mEq/L that cannot be managed with blinded patiromer/placebo escalation according to the treatment algorithm (refer to Appendix B) will discontinue spironolactone and patiromer/placebo, but will remain in the study (refer to Appendix C, Spironolactone Dosing) and complete all remaining scheduled visits. After discontinuation of spironolactone and patiromer/placebo, hyperkalemia may be treated using the standard of care per the Investigator's judgment. *Spironolactone treatment*: Spironolactone will be initiated for all randomized subjects on Day 1, at a dose of 25 mg taken orally QD. At Week 3, for subjects with AOBP SBP ≥ 120 mmHg and $K^+ \leq 5.1$ mEq/L, spironolactone will be increased to 50 mg QD. For subjects with AOBP SBP ≥ 120 mmHg and $K^+ > 5.1$ mEq/L at Week 3, the 25 mg daily dose of spironolactone will be continued until the first subsequent visit when K^+ is ≤ 5.1 mEq/L (and AOBP SBP is ≥ 120 mmHg) at which time spironolactone will be increased to 50 mg QD. Subjects with AOBP SBP < 120 mmHg at the Week 3 Visit will continue spironolactone at 25 mg per day. If a subject has an AOBP SBP < 100 mmHg or experiences symptoms of hypotension with AOBP SBP < 120 mmHg, the spironolactone dose may be reduced (e.g., 25 mg every other day) or discontinued at the discretion of the Investigator (Appendix C, Spironolactone Dosing). If spironolactone is discontinued, patiromer/placebo must be discontinued at the same time. These subjects will remain in the study and be followed per protocol. *Blood pressure management*: When spironolactone has been discontinued and AOBP SBP is ≥ 165 to < 200 mmHg, alternative antihypertensive medication may be added to the blood pressure regimen (Appendix D, Blood Pressure Management and Alternative BP Medication

	Suggestions). Baseline antihypertensive medication doses should not be changed except for AE-related reasons where changes to baseline medications can be justified by the Investigator (e.g., increases in loop diuretics for new edematous states or discontinuation of baseline medication for drug-related AEs). For subjects on spironolactone 25 mg QD (before Week 3), spironolactone may be increased to 50 mg QD before the Week 3 Visit for persistent SBP ≥ 180 mmHg (AOBP), at the investigator's discretion. For subjects on spironolactone 50 mg QD, an additional BP medication may be added to control persistent SBP ≥ 165 mmHg AOBP) at the discretion of the Investigator. This decision may reflect the degree of blood pressure elevation, the time since last spironolactone dose adjustment, and the level of urgency to lower blood pressure, in the Investigator's judgment. Baseline medication doses should not be changed except for AE-related reasons where changes to baseline medications can be justified by the Investigator (e.g., increases in loop diuretics for new edematous states or discontinuation of baseline medication for drug-related AEs). For all subjects (on or off spironolactone) with AOBP SBP ≥ 200 mmHg, subjects should be treated in accordance with the standard of care for BP management per the Investigator's judgment (i.e., additional medications or change in baseline medication dose are permitted, Appendix D). Note: <u>All subjects will remain in the study</u> and complete all study assessments in accordance with the protocol. <u>Unscheduled Visits:</u> For subjects with study drug (spironolactone or patiromer/placebo) modifications based on BP assessments or potassium levels, an Unscheduled Visit should be conducted within 1 week after this modification unless the next scheduled visit is within 1 week of the study drug modification, in which case the subject will return at the next scheduled visit. Upon completion of all Double-Blind Treatment Period assessments at the Week 12 Visit (or ET Visit), subjects will discontinue all study drugs that they are receiving (patiromer/placebo/spironolactone). After study drug discontinuation, the treatment of hypertension should proceed in accordance with the standard of care for BP management per the Investigator's judgment. **Follow-up Visit (2 Weeks after Week 12 or ET Visit + up to 7 Days Window):** All subjects will be instructed to return for a Follow-up Visit 2 weeks after the Week 12 Visit or after ET Visit (+ up to 7 days). The Investigator may request the subject to return to the study site prior to the Follow-up Visit to evaluate potassium levels, BP, or AEs, at his/her discretion. If a subject arrives at the Follow-up Visit prior to 2 Weeks, subjects will receive a Follow-up Phone Call at 2 weeks (+ up to 7 days) after Week 12 or ET Visit.
Data Safety Monitoring Committee:	A Data and Safety Monitoring Committee (DSMC) will review laboratory and blood pressure data, all reports of AEs (including deaths from any cause), discontinuations from spironolactone and patiromer/placebo, withdrawals from the study, and other data as described in the DSMC Charter. The DSMC Charter will include a description of the scope of planned reviews. When reviewing data, including individual data, the DSMC may be unblinded to treatment assignment (patiromer or placebo).
Study Duration:	Up to 18 weeks: Screening/Run-in Period (up to 4 weeks), Double-Blind Treatment Period (12 weeks), and a Follow-up Visit 2 weeks after the Week 12 Visit.
Study Sites:	Approximately 60 sites.
Study Population:	Approximately 290 subjects will be randomized.
Study Treatments	
Dose and Route of Administration:	**Investigational Products:** <u>Patiromer for Oral Suspension:</u> Patiromer will be provided blinded as a powder for oral suspension in packets of 4.2 g each. In the Double-Blind Treatment Period, the starting dose of patiromer will be 8.4 g (two packets, 4.2 g each) QD, taken orally with food.

	Patiromer QD doses for the study will be adjusted as needed (Appendix B) and will be 0 packets (minimum dose), two packets, four packets, or six packets (maximum dose). Placebo: Placebo (microcrystalline cellulose) will be provided blinded as a powder for oral suspension in packets identical in appearance to patiromer packets. In the Double Blind Treatment Period, the starting dose will be two packets QD, taken orally with food. The number of packets for titration and instructions for use will be the same as for patiromer (Appendix B). Spironolactone: Spironolactone will be administered orally to all subjects at a starting dose of 25 mg QD (at least 3 hours before or after patiromer/placebo) and increased to 50 mg QD at Week 3 (or after) for all subjects with AOBP SBP $\geq$ 120 mmHg and $K^+ \leq 5.1$ mEq/L (Appendix C).
Eligibility Criteria	
Inclusion Criteria:	Eligible subjects must meet all the following criteria: 1. Provide written informed consent prior to participation in the study 2. Age $\geq$ 18 years 3. Taking at least three antihypertensive medications, one of which is a diuretic, for at least 28 days at a stable dose. Angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) should be included among these three antihypertensive medications, unless previously not tolerated or contraindicated. 4. Uncontrolled hypertension as documented by AOBP SBP 135 to 160 mmHg at each Screening Visit; however, AOBP SBP may be < 135 mmHg at either S2 or S3 Visits (see Section 7.3.2.2) 5. eGFR of 25 – $\leq$ 45 mL/min/1.73 m^2 (mean [calculated by the IWRS] of two values measured at Visits S1 and S3 (or 7 to 28 days apart) during the Screening/Run-in Period and calculated using CKD Epidemiology Collaboration [CKD-EPI] formula) 6. Qualifying local laboratory K^+ measurements of 4.3 – 5.1 mEq/L obtained at Visits S1, S3 and S4 (all measurements must be within range) 7. Females of child-bearing potential must be non-lactating, must have a negative serum pregnancy test at screening, must use a medically acceptable form of birth control from 28 days prior to screening through the study and for 28 days after completion of the study
Exclusion Criteria:	Subjects must not meet any of the following: 1. History of untreated secondary causes of hypertension (other than CKD) including but not limited to Cushing's syndrome, primary hyperaldosteronism, renal vascular stenosis, or coarctation of the aorta 2. Inability to measure BP (e.g., the largest sized arm BP cuff is inadequate given the circumference of the subject's arm) 3. Noncompliance with antihypertensive medications, in the investigator's judgment 4. Change in renal function requiring hospitalization or dialysis within 3 months prior to screening 5. Renal transplant or anticipated need for renal transplantation during planned study participation 6. History of malignancy within the previous 12 months except for cured non-melanocytic skin cancer 7. Recent cardiovascular event (within the last 3 months): myocardial infarction, unstable angina, hospitalization for heart failure, revascularization, or stroke (or transient ischemic attack)

	8. Clinically significant ventricular arrhythmia 9. Atrial fibrillation with HR > 100 beats per minute (bpm) 10. Previous use of patiromer in a clinical study 11. Any current use of spironolactone or other mineralocorticoid antagonists (e.g., eplerenone) 12. Hypersensitivity to patiromer, spironolactone, or any of their components 13. Use of any of the following permitted potassium-altering chronic medications if doses have not been stable for at least 28 days prior to screening or if doses are anticipated to change during study participation: bronchodilators, theophylline, heparin, and canagiflozin 14. Use of the following prohibited medications within 7 days prior to Screening: calcium acetate or calcium carbonate supplements (unless for occasional antacid use, at the discretion of the Investigator), digoxin, direct renin inhibitors (e.g., aliskiren), lanthanum carbonate, lithium, sevelamer, quinidine, sodium polystyrene sulfonate or calcium polystyrene sulfonate, colesevelam, colestipol, cholestyramine, drospirenone, potassium supplements, bicarbonate or baking soda (unless for occasional antacid use, at the discretion of the Investigator), triamterene, amiloride, trimethoprim, tacrolimus, cyclosporine, systemic glucocorticoids, nonsteroidal anti-inflammatory drugs (NSAIDs) or COX-2 inhibitors (with the exception of low dose aspirin), sympathomimetics 15. Use of any investigational product within 30 days or 5 half-lives, whichever is longer, prior to screening 16. History of bowel obstruction, swallowing disorders, clinically significant gastroparesis, severe gastrointestinal disorders or major gastrointestinal surgery (e.g., large bowel resection) 17. Inability to take the study medications or comply with the protocol, in the opinion of the Investigator 18. History of alcohol or drug abuse within 1 year of screening 19. Any medical condition, uncontrolled systemic disease, or serious intercurrent illness that would significantly decrease study compliance or jeopardize the safety of the subject or affect the validity of the trial results, in the opinion of the Investigator
Statistical Methods	
Determination of Sample Size:	This study will randomize approximately 290 subjects, to ensure that at least 280 subjects will be available for the primary analysis. This allows for the possibility that up to 10 subjects are randomized but never take study medication. A sample size of 280 subjects has 90% power to detect a difference between treatment groups of 20% or more in the proportion of subjects remaining on spironolactone at Week 12, at $\alpha = 0.05$.
Randomization:	Eligible subjects will be randomized 1:1 to either spironolactone + patiromer or spironolactone + placebo. The randomization will be stratified using the locally measured potassium at Visit S4 (4.3 to < 4.7 mEq/L or 4.7 to 5.1 mEq/L) and history of Type 1 or 2 diabetes mellitus (Yes or No).
Efficacy Analysis:	
Primary Efficacy Endpoint:	The proportion of subjects remaining on spironolactone at Week 12 will be compared between treatment groups (spironolactone/patiromer vs. spironolactone/placebo) using the Cochran-Mantel-Haenszel test, stratified by baseline serum potassium category (K^+ 4.3 – < 4.7 mEq/L or 4.7 – 5.1 mEq/L).
Secondary Endpoint:	AOBP SBP change from baseline to Week 12 or last available assessment prior to addition of any new BP medications or changes to any baseline BP medications will be analyzed using analysis of covariance (ANCOVA) methods.

Other Endpoints:	Change in AOBP SBP at Week 12 will be analyzed using repeated measures as well as ANCOVA methods. Average daily dose and cumulative dose of spironolactone, and change in albuminuria (ACR) from baseline to Week 12, will be compared between treatment groups using ANCOVA methods. Kaplan-Meier methods will be used to analyze the time to discontinuation of spironolactone. Potassium levels will be summarized for local and central values at each time point. Counts (%) of subjects who have experienced no potassium measurement ≥ 5.5 mEq/L will be presented at each time point. The EQ-5D-5L questionnaire results will be summarized at Baseline and Week 12/ET.
Safety Analysis	Safety variables will consist of all AEs (including newly observed clinically significant physical examination abnormalities and events of interest, such as allergic reactions and gastrointestinal events), renal events (e.g., worsening renal failure, acute kidney injury, changes in eGFR), clinical laboratory test results (including serum potassium < 3.0 mEq/L, < 3.5 mEq/L, > 5.0 mEq/L, and clinically significant changes in serum calcium, magnesium, phosphorus), vital signs (including blood pressure), clinically significant ECG findings, potassium-related ECG changes and reasons for discontinuing patiromer/placebo/spironolactone.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF APPENDICES

GLOSSARY OF ABBREVIATIONS

ABPM	ambulatory blood pressure monitoring
ACE	angiotensin-converting enzyme
ACR	albumin to creatinine ratio
AE	adverse event
ANCOVA	analysis of covariance
AOBP	automated office blood pressure
ARBs	angiotensin receptor blockers
ASCOT-BPLA	Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm
BID	twice daily
BP	blood pressure
BPM	beats per minute
CI	confidence interval
CKD	chronic kidney disease
CKD-EPI	CKD Epidemiology Collaboration
D	day
DBP	diastolic blood pressure
DDI	drug-drug interaction
DSMC	data safety monitoring committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
ET	Early Termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFR	glomerular filtration rate
HBP	home blood pressure
HIPAA	Health Insurance Portability and Accountability Act
HR	heart rate

ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	intent-to-treat
IWRS	Interactive Web Response System
K^+	potassium
MedDRA	Medical Dictionary for Regulatory Activities
MRA	mineralocorticoid receptor antagonists
NSAID	nonsteroidal anti-inflammatory drugs
QD	once daily
R	randomization
RALES	Randomized Aldactone Evaluation Study
S1	Screening 1
S2	Screening 2
S3	Screening 3
S4	Screening 4
SAE	serious adverse event
SBP	systolic blood pressure
SD	standard deviation
SE	standard error
SMBP	subject-measured blood pressure
TEAE	treatment-emergent adverse event
TID	three times daily
W	week
WBC	white blood cell count
US	United States

1 INTRODUCTION

Treatment resistant hypertension (defined as blood pressure above goal despite treatment with optimally tolerated doses of three antihypertensive agents of different classes, including a diuretic) (Calhoun, 2008) remains a significant problem, affecting up to 8% of hypertensive patients identified from registry data using 24-hour ambulatory blood pressure monitoring (ABPM) (de la Sierra, 2011). Other sources estimate the prevalence as significantly greater in specific cohorts, for example, CKD with albuminuria, in which rates reach nearly 50% (Tanner, 2013, Wolley, 2016). The true prevalence of this condition is unknown, however, since most studies have not included information regarding key diagnostic criteria for determining true resistant hypertension rather than apparent resistant hypertension. Key diagnostic criteria include antihypertensive medication doses (often suboptimal), treatment adherence (a frequent cause of apparent resistant hypertension), systematic exclusion of measurement artifacts including poor measurement technique and exclusion of "white-coat hypertension", adherence to dietary sodium restriction, and exclusion of secondary causes of hypertension (Rossignol, 2015).

Observational studies have shown a significant positive association between greater plasma aldosterone levels and blood pressure in both nonhypertensive and hypertensive populations (Vasan, 2004, Rossi, 2006), as well as a greater prevalence of primary hyperaldosteronism in those with treatment resistant hypertension (Calhoun 2002). Although there are likely multiple causes for resistant hypertension, one potential mechanism among patients treated with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) is abnormal sodium retention mediated by aldosterone breakthrough despite blockade of the renin-angiotensin-aldosterone system with ACE inhibitors or ARBs. This occurs in 10% of patients treated with ACE inhibitors/ARBs over 6 months, and > 50% over 1 year, leading to excess sodium retention, hypertension and other adverse cardiovascular effects (Bomback, 2007). Accordingly, there has been much interest in the use of mineralocorticoid receptor antagonists (MRAs) to treat resistant hypertension (Narayan, 2016).

A recently published review (Narayan, 2016) evaluated new evidence of MRA use in the treatment of resistant hypertension, and included results from the PATHWAY 2 study (Williams, 2015). In PATHWAY 2, the average reduction in home systolic blood pressure (SBP) by spironolactone was superior to placebo (-8.7 mmHg, 95% CI: 9.72 to -7.69; $p < 0.0001$), superior to the mean of the other two active treatments (doxazosin and bisoprolol, -4.2, 95% CI: -5.13 to -3.38; $p < 0.0001$), and superior when compared with the individual treatments. Spironolactone was the most effective blood pressure-lowering treatment, irrespective of baseline plasma renin levels. Lower renin levels, however, were most predictive of the greatest BP response. Narayan, et al. concluded that there is sufficient evidence to recommend MRAs, in particular spironolactone, as the first choice medication to treat resistant hypertension in large part because of the PATHWAY 2 findings (Narayan, 2016).

Most studies in resistant hypertension to date (including PATHWAY 2) have largely been limited to patients with either normal or only mildly impaired renal function, although resistant hypertension is common in patients with chronic kidney disease (CKD) (Horowitz, 2015). The prevalence of resistant hypertension is twice as high in patients with CKD compared to patients without CKD, and the prevalence increases with both decreased estimated glomerular filtration

rate (eGFR) and raised albuminuria. In the CRIC study, 42% of 3612 patients with established CKD had apparent treatment-resistant hypertension (Rossignol, 2015, Muntner 2010).

Due to the risks of hyperkalemia and acute kidney injury, MRA use has been limited in advanced CKD. In patients with resistant hypertension and CKD Stage 3, MRAs raised serum potassium levels by an average of 0.4 mEq/L and serum creatinine concentrations increased from a mean of 1.5 to 1.8 mg/dL. In a Cochrane review (Bolignano, 2014), MRAs added to ACE or ARB therapy increased the risk of hyperkalemia twofold (95% CI: 1.25 – 3.0) in patients with mild to moderate CKD, dependent on baseline GFR, potassium, the dose of the drug, and concomitant medications. In CKD with proteinuria and hypertension, spironolactone effectively reduced both BP and urine protein levels. However, caution has been advised when starting spironolactone in patients who have a baseline serum potassium greater than 4.6 mEq/L (Judd, 2015). In the Kholsa, et al. observational study, where patients had aldosterone antagonists added to a diuretic and renin-angiotensin system drug regimen, similar findings were reported. Kholsa et al. defined the patient cohort in their study at the greatest risk for developing hyperkalemia as those with a serum potassium level of > 4.5 mEq/L and eGFR of ≤ 45 mL/min/1.73m2, and whose kidney function was further decreased by approaching goal BP (Khosla, 2009). Therefore, despite the potential benefit of MRA treatment for resistant hypertension in patients with CKD, the risk of hyperkalemia has often limited their use. More recently, though, the development of potassium binders with the potential for chronic use may now provide new options for the treatment of this patient population.

Veltassa® (patiromer) for Oral Suspension (also known as RLY5016 for Oral Suspension) is approved by the Food and Drug Administration (FDA) for the treatment of hyperkalemia (Veltassa PI, 2016). Patiromer contains a new chemical entity (the drug substance, RLY5016S) belonging to the pharmacologic class of Potassium Binders. The drug substance consists of the polymer anion (the active moiety, patiromer) and a calcium-sorbitol counterion complex. Patiromer is a nonabsorbed, cation-exchange polymer that binds potassium predominantly in the lumen of the colon where potassium is the most abundant cation. This increases fecal potassium excretion, leading to removal of potassium from the body and lowering of serum potassium levels in the hyperkalemic patient.

The hypothesis of this study is that the concomitant use of spironolactone and patiromer in patients with resistant hypertension and CKD will prevent or manage hyperkalemia and allow the use of spironolactone for the management of blood pressure.

1.1 Effects of Study Drugs in Humans

1.1.1 Patiromer

The clinical development program for patiromer included 20 completed clinical studies: three Phase 1 studies, four Phase 2 studies, one two-part Phase 3 study (RLY5016-301), and 12 drug-drug interaction (DDI) clinical studies. Subjects who participated in these clinical studies included patients with hyperkalemia, CKD, HF, diabetes mellitus, hypertension and/or patients on hemodialysis, and healthy volunteer subjects. A total of 1099 subjects received at least one dose of patiromer and the duration of dosing ranged from a single dose to up to 1 year.

The pivotal Phase 3 study (RLY5016-301) evaluated the treatment of hyperkalemia in subjects with CKD at two starting doses, 4.2 g patiromer BID or 8.4 g patiromer BID (subjects with screening serum potassium [K^+] of > 5.0 to < 5.5 mEq/L were assigned the lower starting dose and subjects with screening serum K^+ of 5.5 to < 6.5 mEq/L were assigned the higher starting dose) (Weir, 2015). The study consisted of two parts (Part A, a 4-week treatment phase, and Part B, an 8-week, placebo-controlled, randomized withdrawal phase). In Part A, the mean (SE) change in serum potassium from baseline (mean [SD] 5.58 [0.51] mEq/L) to Week 4 was -1.01 (0.031) mEq/L (95% CI: [-1.07, -0.95]); this mean reduction in serum potassium was statistically and clinically significant. The proportion of subjects with a serum potassium level in the Part A target range of target range of 3.8 to < 5.1 mEq/L at Week 4 was 76% overall. The proportion of subjects in the target range was similar in both starting dose groups, which had been assigned according to severity of starting serum potassium level. Randomized withdrawal of the drug in the second part (Part B) confirmed the efficacy observed in Part A and provided evidence of the benefit of continued treatment with patiromer once serum potassium is controlled.

A comprehensive assessment of safety of patiromer for the treatment of hyperkalemia was conducted. A total number of 1099 subjects were exposed to at least one dose of patiromer and a pooled safety analysis was conducted in 666 subjects receiving patiromer and 49 subjects receiving placebo. Data from the overall safety population demonstrated that patiromer was well-tolerated. Adverse events (AEs) and serious adverse events (SAEs) were reported in 60.8% and 8.3% of subjects, respectively, of the overall safety population receiving patiromer for up to 52 weeks. Approximately 20% of subjects receiving patiromer experienced AEs considered related to study drug but no SAEs were considered drug related. The proportion of subjects discontinuing study drug due to an AE was relatively low at 9%, indicating the therapy was generally well tolerated in subjects, including those who were treated for up to 1 year in the long-term efficacy and safety Phase 2 Study RLY5016-205. Overall, the most common reported AEs were gastrointestinal in nature and predominantly were events of constipation and diarrhea. These events tended to occur early after treatment initiation, were mild to moderate in nature, occurred in less than 10% of subjects, were self-limited and typically did not require dose reductions or discontinuations. Hypokalemia AEs and measured potassium levels < 3.5 mEq/L did occur but were infrequent and none of these events were serious or associated with electrocardiogram (ECG) changes. AEs of chronic renal failure, acute renal failure and cardiac disorders events were also observed, however these events generally were not assessed as being attributable to patiromer but consistent with AEs expected in study population with a high burden of CKD, diabetes mellitus, HF, and coronary artery disease.

Refer to the current version of the Investigator's Brochure for a more detailed summary of these clinical studies (Investigator's Brochure, 2016).

1.1.2 Spironolactone

Spironolactone is a potent, nonselective, steroidal MRA that competitively inhibits aldosterone binding to the mineralocorticoid receptor (MR) and renders it transcriptionally inactive, thus antagonizing the genomic effects of aldosterone. It does not antagonize aldosterone-induced nongenomic renal and extrarenal effects (Tamargo, 2014).

Activation of MRs by aldosterone promotes multiple renal, cardiac, and vascular deleterious effects, including endothelial dysfunction, hypertension, neurohumoral activation, cardiovascular (CV) and renal remodeling (hypertrophy, fibrosis, and apoptosis), decreases arterial compliance, increases expression of cell adhesion molecules, platelet activation, plasminogen activator inhibitortype1 (PAI-1) activity, and oxidative stress, and exerts proarrhythmic and proinflammatory effects (Tamargo, 2014). In addition, activation of central MRs increases central sympathetic tone to the kidneys, heart, and vascular smooth muscles, increases vasopressin release, and decreases baroreceptor sensitivity. These effects are reported to be genomic (i.e., dependent on transcription and translation). Additionally, aldosterone produces rapid, translation- and transcription-independent effects (nongenomic effects). Nongenomic effects also occur independently of hemodynamic factors and play an important role in the mechanisms by which aldosterone contributes to endothelial dysfunction, vasoconstriction, resistant arterial hypertension, CV and renal remodeling, inflammation, heart failure, insulin resistance, and chronic renal disease (CKD) (Tamargo, 2014). Endothelial MR activation has been linked to enhanced vasoconstrictor and/or impaired vasodilator responses, as well.

Spironolactone was introduced into clinical use in the early 1960's as a potassium-sparing diuretic for the treatment of hypertension, primary hyperaldosteronism, volume-overload states, and hypokalemia. Its mode of action was thought to be complementary to that of the diuretics used for the treatment of these conditions at the time, mediated at the aldosterone-dependent sodium-potassium exchange site in the distal convoluted renal tubule where it caused increased amounts of sodium and water to be excreted, while potassium was retained. It was thought to act both as a diuretic and as an antihypertensive by this mechanism. Early studies demonstrated efficacy for blood pressure reduction. Spironolactone has also been indicated as a diuretic in patients with cirrhosis and ascites, in whom secondary hyperaldosteronism is present, and hypokalemia is a hazard (Aldactone®, 2014).

Since that time, the extrarenal effects of aldosterone have become more widely appreciated and the potential benefits of MRAs more extensively studied. More recently, MRAs as antihypertensive drugs have been preferentially indicated in the treatment of primary and secondary hyperaldosteronism. They have been increasingly recommended in hypertensive patients with metabolic syndrome or target organ damage represented by left ventricular (LV) hypertrophy or albuminuria (Tarmargo, 2014) and spironolactone has most recently been recommended as add-on therapy in patients with resistant hypertension in whom MRAs have shown positive results.(Tamargo, 2014, Williams, 2015) Spironolactone is indicated in patients with chronic congestive HF (NYHA Class II-IV) with reduced ejection fraction to improve survival and reduce hospitalization for heart failure when added to standard therapy (Tamargo, 2014).

Until recently, MRAs had received little attention in patients with CKD because of the risk of hyperkalemia. However, low doses of MRAs may offer additional antihypertensive and anti-inflammatory benefits in selected CKD populations. Spironolactone (and eplerenone) reduce aldosterone induced renal damage and decrease proteinuria in hypertensive patients. In patients with CKD, the addition of MRAs to ACE inhibitors or ARBs significantly reduced BP and glomerular filtration rate (GFR) and decreased proteinuria. However, a meta-analysis of 11 RCTs using MRAs, alone or in combination with ACE inhibitors/ARBs for preventing the progression of CKD in patients with albuminuria and diabetic or nondiabetic nephropathy, found

that MRAs reduce 24-hour proteinuria and BP, but this did not translate into an improvement in end-of-treatment GFR. Therefore, long-term effects of MRAs on renal outcomes, mortality, and safety remains uncertain (Tamargo, 2014).

Due to the lack of receptor selectivity, spironolactone also blocks androgen receptors and activates progesterone receptors, causing progestogenic and antiandrogenic adverse effects. Long-term use has been associated with gynecomastia and other endocrine-adverse effects, such as breast tenderness, impotence, loss of libido and menstrual irregularities which has limited its use. Gynecomastia is a dose-dependent reversible AE reported in 13% of men prescribed spironolactone, alone or in combination with other antihypertensives; at doses of 50mg/d or less the incidence was 6.9% in a hypertension study. In large clinical outcome studies, (the Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm [ASCOT–BPLA] and RALES trials), gynecomastia was reported in 6 to 10% of men and was the reason for spironolactone discontinuation in 3% of patients in the ASCOT–BPLA (Tamargo, 2014).

Oral spironolactone is absorbed rapidly but has a short half-life (1.4 h) because it is metabolized rapidly and extensively into active metabolites including canrenone, which is marketed as a MRA in some countries and has a half-life of 16 – 35 h in healthy volunteers). These active metabolites explain a peak response which occurs after 48 or more hours. The steady-state effect of spironolactone is consequently not reached until after 6 weeks of treatment. This pharmacokinetic profile allows for once-daily or alternate-day administration of spironolactone. Also, the slow clearance of the active metabolites may explain why the duration of the natriuretic and antikaliuretic effects of spironolactone differ, the latter often persisting for several days after drug discontinuation. The persistence of hyperkalemia is important in patients treated with ACE inhibitors or ARBs, especially in patients with CKD. The half-life of spironolactone is prolonged significantly (24 – 58h) in patients with cirrhotic ascites or heart failure. Spironolactone and its metabolites are highly bound (> 90%) to plasma proteins, mainly to albumin. Because spironolactone does not rely on GFR or tubular secretion to reach its site of action it remains effective even in patients with advanced CKD (Tamargo, 2014).

1.2 Rationale for the Clinical Study RLY5016-207

The use of patiromer to prevent hyperkalemia associated with the treatment of resistant hypertension with spironolactone has not been evaluated. The hypothesis of this study is that the concomitant use of spironolactone and patiromer in patients with resistant hypertension and CKD will prevent or manage hyperkalemia and allow the use of spironolactone for the management of blood pressure.

In the PEARL-HF study (Pitt, 2011), heart failure patients on at least one ACE inhibitor, ARB, or β blocker, and eligible for spironolactone treatment, received placebo or patiromer in addition to spironolactone. Among subjects with eGFR ≤ 45 mL/min/1.73m^2 and baseline serum potassium 4.3 to ≤ 5.1 mEq/L, 56% of subjects receiving placebo compared with 0% of subjects receiving patiromer developed a serum potassium > 5.5 mEq/L. These data suggest that patiromer may prevent hyperkalemia in other cohorts treated with spironolactone with risk factors for hyperkalemia.

The aim of this study is to evaluate whether the use of patiromer to prevent and manage hyperkalemia in subjects with CKD and resistant hypertension treated with spironolactone will result in more persistent use of spironolactone compared to subjects treated with spironolactone without patiromer. We anticipate that this will lead to greater reduction of blood pressure in the group treated with patiromer compared with the group treated with spironolactone alone, in whom discontinuation of spironolactone may occur due to hyperkalemia.

Since there are substantial differences in international guideline recommendations for target BP in CKD, Rossignol, et al. (Rossignol, 2015) recommend BP levels for defining resistant hypertension that are consistent with those of the general population (ie, office SBP $\geq$ 140 mmHg or diastolic blood pressure [DBP] $\geq$ 90 mmHg). Out of office blood pressure measurements have been shown to be more accurate compared with office BP measurements and can exclude white coat hypertension and masked hypertension, both common in patients with CKD. However, more recently, data suggest that automated office BP (AOBP) using an automatic oscillometric monitoring device without study staff present may have less variability; therefore, AOBP measurements will be used in this study for subject selection, treatment decisions, and the primary evaluation of BP effects, and target blood pressure for these patients will be 135/85 mmHg. Home blood pressure (HBP) measurements and subject-measured blood pressure (SMBP) performed at the study site by the patient using the HBP monitor will also be performed. Home blood pressure measurements may also improve adherence to medications by increasing patient involvement (Wolley, 2016).

In this study, the BP comparison of greatest interest will be the between group difference in change from baseline blood pressure which theoretically should reflect the difference in proportion of subjects remaining on spironolactone at Week 12. It is anticipated that a larger proportion of subjects in the placebo plus spironolactone group will meet spironolactone discontinuation thresholds for potassium during the treatment period. To insure the safety of these subjects without confounding the between group comparisons unduly, subjects randomized to the study will be limited to those with systolic AOBP from 135 to < 160 mmHg, who are less likely to require urgent treatment of hypertension should spironolactone be discontinued. All subjects who experience persistent systolic BP of 165 mmHg or greater may be treated with additional antihypertensive therapy chosen by the investigator.

2 TRIAL OBJECTIVES

To determine if patiromer treatment of CKD subjects receiving spironolactone for the treatment of resistant hypertension will result in:

- More persistent use of spironolactone through prevention of hyperkalemia
- Improved blood pressure control through more persistent use of spironolactone

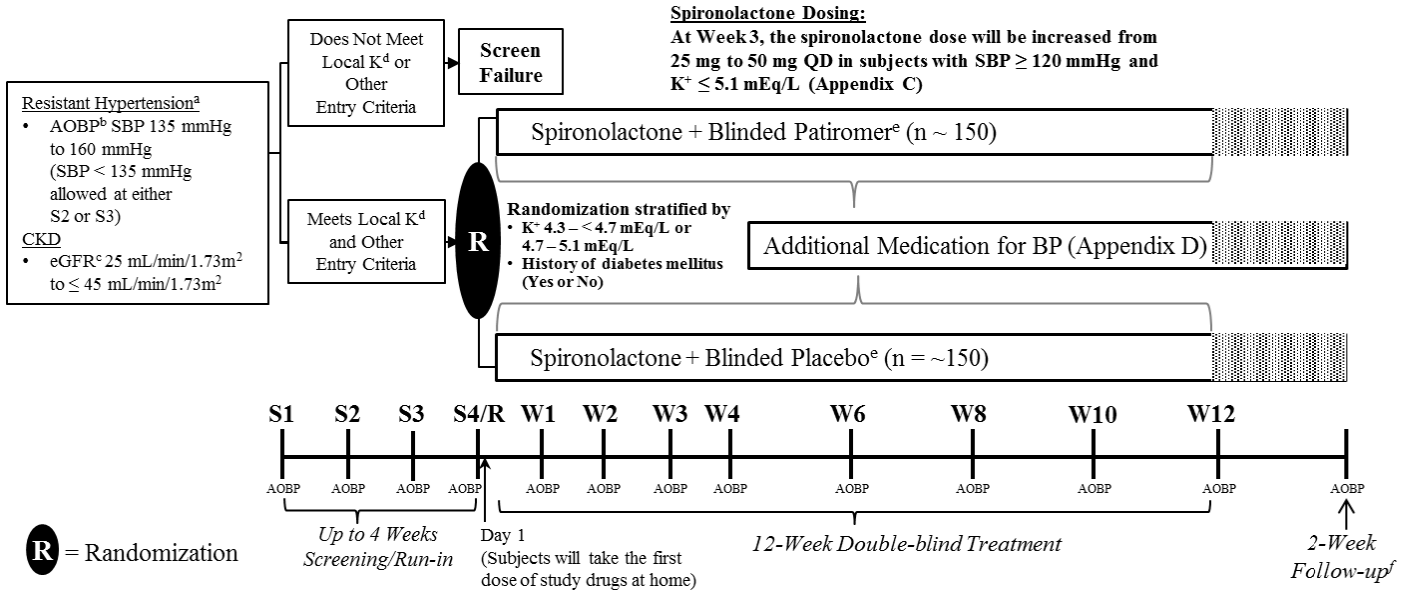
3 TRIAL DESIGN

3.1 Description

This study is a randomized, double-blind, placebo-controlled, parallel group study of patiromer or placebo treatment (patiromer/placebo) in conjunction with spironolactone in subjects with resistant hypertension and CKD. Approximately 290 subjects will be randomized.

The study will consist of (Figure 1): Screening/Run-in Period (up to 4 weeks); Double-Blind Treatment Period (12 weeks); Follow-up Visit 2 weeks after Week-12 Visit or Early Termination (ET) Visit.

Figure 1: Study Schema



AOBP = automated office blood pressure; BP = blood pressure; eGFR = estimated glomerular filtration rate; K^+ = potassium measurement; R = Randomization/Baseline (Day 0) Visit; S = Screening Visit; SBP = systolic blood pressure; SMBP = subject-measured blood pressure; W = week

[a] Receiving at least three antihypertension drugs including diuretic. ACE inhibitors or ARBs should be included among these three antihypertensive medications, unless previously not tolerated or contraindicated (see Inclusion Criteria, Section 4.1).

[b] Performed by an oscillometric BP monitoring device that will automatically measure subject's BP in triplicate after 5 minutes of sitting quietly without the aid of study staff, AOBP (Section 7.3.2.2).

[c] Mean (calculated by the IWRS) of two values measured at Visits S1 and S3 (or 7 to 28 days apart) during the Screening/Run-in Period.

[d] Qualifying local laboratory K^+ measurements of 4.3 – 5.1 mEq/L obtained at Visits S1, S3 and S4 (all measurements must be within range)

[e] Subjects who develop hyperkalemia ($K^+ \geq 5.5$ mEq/L) that cannot be managed with blinded patiromer/placebo escalation according to the treatment algorithm (Appendix B) will discontinue spironolactone and patiromer/placebo, but still remain in the study (Appendix C). Thereafter, hyperkalemia may be treated using standard of care.

[f] Two (2) weeks after the Week 12 (+ 7 days) or ET Visit. Subjects who complete the Follow-up Visit prior to 2 Weeks will receive a Follow-up Phone Call at 2 weeks (+ up to 7 days) after Week 12 or ET Visit.

Note: For subjects with study drug (spironolactone or patiromer/placebo) modifications based on BP assessments or potassium levels, an Unscheduled Visit will be conducted within 1 week after this modification unless the next scheduled visit is within 1 week of the study drug modification, in which case, the subject will return at the next scheduled visit. For all study visit windows, refer to the Schedule of Events (Appendix A). For all visits except for S1 and the Follow-up Visit, SMBP measurements will be performed (see Section 7.3.2.1).

3.1.1 Screening/Run-in Period (Up to 4 weeks)

The purpose of the Screening/Run-in Period is to ensure that all enrolled subjects are on stable doses of baseline medications, do not have "white coat" hypertension, can demonstrate proper and reliable use of the BP monitoring device prior to study drug treatment, and meet all study inclusion/exclusion criteria.

The Screening/Run-in Period will consist of four Screening Visits (S1, S2, S3, and S4) that are approximately 7 days (at least 4 days but no more than 10 days) after the prior screening Visit (Appendix A).

Visit S1: Each subject will be issued a HBP monitor and provided with training on device use. Subjects will be instructed to measure HBP in triplicate twice daily after Visit S1 (Section 7.3.2.1).

Visits S2, S3 and S4: Two types of office BP measurements will be performed before other scheduled activities (except for S4 where the EQ-5D-5L will be the first assessment). Both measurements will be performed with the subject alone after 5 minutes of seated rest (Section 7.3.2.2):

1. Performed by an automatic oscillometric BP monitoring device that can measure BP in triplicate (automated Office BP, AOBP)
2. Performed by the subject using their issued HBP monitoring device in triplicate (subject-measured BP, SMBP)

Note: Study staff should <u>not</u> be present while both office BP measurements are being performed. Subjects will be instructed to bring their issued HBP device to every visit.

To be eligible for this study, subjects will be required to meet all of the following criteria (see Section 4 for complete criteria):

1. AOBP SBP 135 to 160 mmHg at each Screening Visit; however, AOBP SBP may be < 135 mmHg at either S2 or S3 Visits
2. eGFR of 25 – ≤ 45 mL/min/1.73 m^2 (mean [calculated by the Interactive Web Response System – IWRS] of two values measured at S1 and S3 (or 7 to 28 days apart) during the Screening/Run-in Period)
3. Local laboratory measurements of K^+ level of 4.3 – 5.1 mEq/L obtained at Visits S1, S3 and S4 (all measurements must be within range)
4. Does not meet any exclusion criteria

If hemolysis of the local sample is detected or suspected (see Section 7.1.1) at Screening Visits (S1 and S3), a repeat of the potassium measurement from a separate blood draw will be performed within 1 day. If the repeated potassium level does not meet entry criteria, then the subject is considered a Screen Failure.

For Visit S4, if hemolysis of the local sample is detected or suspected, the subject is not randomized and a repeat of the potassium measurement from a separate blood draw will be

performed within 1 day. If the subject qualifies, the subject will be randomized on the same day. All assessments performed at Visit S4, aside from the hemolyzed potassium level, will be considered baseline assessments, and the day the repeat potassium measurement was obtained will be designated the Randomization/Baseline (Day 0) Visit. If the repeated potassium level does not meet entry criteria, then the subject is considered a Screen Failure.

If a subject fails any qualifying criteria, at any of the Screening Visits, the subject will be considered a Screen Failure at that Visit. Subjects who meet all study entry criteria except for eGFR and/or serum potassium will be screen failures but may be rescreened once at least 2 weeks after initial screen failure (Section 6.1.5).

3.1.2 Double-Blind Treatment Period (12 weeks)

Randomization (Baseline – Day 0) Visit:

Subjects who meet all eligibility criteria at Visit S4 will be randomized on the same day to either patiromer or placebo treatment (1:1) with stratification based on the local potassium level at Visit S4 (4.3 – < 4.7 or 4.7 – 5.1 mEq/L) and history of Type 1or 2 diabetes mellitus (Yes or No). The S4 assessments will become the baseline assessments. A combined visit (S4/Randomization [Baseline/Day 0]) will be recorded for all randomized subjects.

All randomized subjects will be provided with detailed instructions for when to take spironolactone, patiromer/placebo, and other baseline medications after considering the subject's current medication regimen, patiromer/placebo instructions regarding administration, and subject preference (see Section 5.5.1). The subject will be instructed to begin taking study drugs (spironolactone and patiromer/placebo) on the following day (Day 1) and on the morning of their subsequent study visits to delay taking their blood pressure medications until office blood pressure measurements have been completed.

Treatment Period Visits (refer to Appendix A):

During the Double-Blind Treatment Period, study visits will occur at Week 1 (Day 8 ± 3 days), Week 2 (Day 15 ± 3 days), Week 3 (Day 22 ± 3 days), Week 4 (Day 29 ± 3 days), Week 6 (Day 43 ± 7 days), Week 8 (Day 57 ± 7 days), Week 10 (Day 71 ± 7 days), and Week 12 (Day 85 ± 7 days).

Patiromer/placebo treatment:

Patiromer/placebo will be taken at a starting dose of two packets once daily (QD). Based upon the treatment algorithm, patiromer/placebo will be increased in two-packet per day increments for local $K^+ > 5.1$ mEq/L in intervals of at least 1 week up to a maximum dose of six packets QD. For subjects with $K^+ < 4.0$ mEq/L, patiromer/placebo dose will be decreased by at least two packets per day. The minimum dose of patiromer/placebo is 0 packets. Patiromer/placebo should be taken with food, at least 3 hours before or 3 hours after administration of other concomitant medications including spironolactone. Refer to Appendix B for complete dosing and monitoring instructions.

Throughout the Double-Blind Treatment Period, subjects who develop $K^+ \geq 5.5$ mEq/L that cannot be managed with blinded patiromer/placebo escalation according to the treatment algorithm (refer to Appendix B) will discontinue spironolactone and patiromer/placebo, but will remain in the study (refer to Appendix C) and complete all remaining scheduled visits. After discontinuation of spironolactone and patiromer/placebo, hyperkalemia may be treated using the standard of care per the Investigator's judgment.

Spironolactone treatment:

Spironolactone will be initiated for all randomized subjects on Day 1, at a dose of 25 mg taken orally QD. At Week 3, for subjects with AOBP SBP $\geq$ 120 mmHg and $K^+ \leq 5.1$ mEq/L, spironolactone will be increased to 50 mg QD. For subjects with $K^+ > 5.1$ mEq/L, 25 mg daily dose of spironolactone will be continued until the first subsequent visit when K^+ is ≤ 5.1 mEq/L (and AOBP SBP $\geq$ 120 mmHg), at which time spironolactone will be increased to 50 mg QD.

Subjects with AOBP SBP < 120 mmHg at the Week 3 Visit will continue their 25 mg daily dose, unless symptoms of hypotension are present with SBP < 120 mmHg, or if SBP is < 100 mmHg (Appendix C), in which case the spironolactone dose may be reduced to 25 mg every other day or discontinued altogether, at the discretion of the Investigator. Spironolactone may be reduced or discontinued for SBP < 100 mmHg. If spironolactone is discontinued, patiromer/placebo must be discontinued at the same time. These subjects will remain in the study and be followed per protocol.

Note: During all study visits, if a subject experiences symptoms of hypotension with AOBP SBP < 120 mmHg, or if SBP < 100 mmHg, spironolactone dose may be reduced (e.g., 25 mg every other day) or discontinued at the discretion of the Investigator.

Throughout the treatment period, creatinine will be measured at each study visit (and may be measured at Unscheduled Visits). Subjects should be monitored for changes in renal function, especially during periods of medication changes or adjustments. Acute reductions in GFR have been seen with the initiation of spironolactone, similar to those seen with initiation of ACE inhibitors and ARBs that have been attributed to transient changes in glomerular hemodynamics (Bianchi, 2015, KDIGO, 2012). These changes typically do not impact long-term renal function. In this study, use of the KDOQI recommendations for the detection and management of early decrease in GFR (when initiating ACE inhibitors/ARBs) for monitoring the initiation of spironolactone (NKF, 2004) should be considered.

Based on KDOQI guidelines:

- An early decline in eGFR is defined as > 15% reduction from baseline within 4 weeks of initiation of spironolactone
- For decreases in eGFR up to 30%, no changes to spironolactone dosing need to be made, and eGFR may be followed routinely
- Decreases in eGFR > 30%, however, should prompt a search for other etiologies of abrupt renal function decline, including prerenal and postrenal causes, toxic reactions, and renal artery disease

- For a decline in eGFR from 30 to 50%, the spironolactone dose should be decreased and the eGFR followed weekly. If the eGFR does not return to within 30% of baseline within 4 weeks, spironolactone should be discontinued
- Spironolactone should be discontinued for a decline in eGFR > 50% and eGFR should be followed at least weekly until eGFR has returned to within 15% of the baseline value, and biweekly thereafter through the end of the study

Blood pressure management should proceed as outlined below.

Blood pressure management:

When spironolactone has been discontinued and AOBP SBP is ≥ 165 to < 200 mmHg, alternative antihypertensive medication may be added to the blood pressure regimen (Appendix D). Baseline medication doses should not be changed except for AE-related reasons where changes to baseline medications can be justified by the Investigator (e.g., increases in loop diuretics for new edematous states or discontinuation of baseline medication for drug-related AEs).

For subjects on spironolactone 25 mg QD (before Week 3), spironolactone may be increased to 50 mg QD before the Week 3 Visit for persistent SBP ≥ 180 mmHg (assessed by AOBP), at the investigator's discretion. For subjects on spironolactone 50 mg QD, additional BP medication may be added to control persistent SBP ≥ 165 mmHg (assessed by AOBP) at the discretion of the investigator. This decision may reflect the degree of blood pressure elevation, the time since last spironolactone dose adjustment, and the level of urgency to lower blood pressure, in the investigator's judgment. Baseline medication doses should not be changed except for AE-related reasons where changes to baseline medications can be justified by the Investigator (e.g., increases in loop diuretics for new edematous states or discontinuation of baseline medication for drug-related AEs).

For all subjects (on or off spironolactone) with AOBP ≥ 200 mmHg, subjects should be treated in accordance with the standard of care for BP management and the Investigator's judgment (i.e., additional medications or change in baseline medication dose are permitted, Appendix D). Note: All subjects will remain in the study and complete all study assessments in accordance with the protocol.

Unscheduled Visits:

For subjects with study drug (spironolactone or patiromer/placebo) modifications based on BP assessments or potassium levels, an Unscheduled Visit should be conducted within 1 week after this modification unless the next scheduled visit is within 1 week of the study drug modification, in which case the subject will return at the next scheduled visit.

Upon completion of all Double-Blind Treatment Period assessments at the Week 12 Visit (or ET Visit), subjects will discontinue all study drugs that they are receiving (patiromer/placebo/spironolactone). After study drug discontinuation, the treatment of hypertension should proceed in accordance with the standard of care for BP management and the Investigator's judgment.

3.1.3 Follow-up Visit (2 Weeks after Week 12 or ET Visit + up to 7 day window)

All subjects will return for a Follow-up Visit, 2 weeks after the Week 12 Visit (+ up to 7 days, if necessary). The Investigator may request the subject to return to the study site prior to the 2-week Follow-up Visit to evaluate potassium levels, AOBP, or AEs, at his/her discretion. In the case where a subject completes the Follow-up Visit prior to 2 Weeks, the subject will receive a Follow-up Phone Call at 2 weeks (+ up to 7 days) after Week 12 or ET Visit.

Subjects who terminate early from the study will complete the ET Visit assessments and return for a Follow-up Visit 2 weeks (+ up to 7 days) after the ET Visit.

4 SUBJECT SELECTION AND WITHDRAWAL

All potential study subjects will be evaluated using the inclusion and exclusion criteria, described below.

4.1 Inclusion Criteria

Eligible subjects must meet all the following criteria:

1. Provide written informed consent prior to participation in the study
2. Age ≥ 18 years
3. Taking at least three antihypertensive medications, one of which is a diuretic, for at least 28 days at a stable dose. ACE inhibitors or ARBs should be included among these three antihypertensive medications, unless previously not tolerated or contraindicated.
4. Uncontrolled hypertension as documented by AOBP SBP 135 to 160 mmHg at each Screening Visit; however, AOBP SBP may be < 135 mmHg at either S2 or S3 Visits (see Section 7.3.2.2)
5. eGFR of 25 – ≤ 45 mL/min/1.73 m^2 (mean [calculated by the IWRS] of two values measured at S1 and S3 or 7 to 28 days apart during the Screening/Run-in and calculated using CKD Epidemiology Collaboration [CKD-EPI] formula)
6. Qualifying local laboratory K^+ measurements of 4.3 – 5.1 mEq/L obtained at Visits S1, S3 and S4 (all measurements must be within range)
7. Females of child-bearing potential must be non-lactating, must have a negative serum pregnancy test at screening, must use a medically acceptable form of birth control from 28 days prior to screening through the study and for 28 days after completion of the study

4.2 Exclusion Criteria

Subjects must <u>not</u> meet any of the following criteria:

1. History of untreated secondary causes of hypertension (other than CKD) including but not limited to Cushing's syndrome, primary hyperaldosteronism, renal vascular stenosis, or coarctation of the aorta

2. Inability to measure BP (e.g., the largest sized arm BP cuff is inadequate given the circumference of the subject's arm)
3. Noncompliance with antihypertensive medications, in the investigator's judgment
4. Change in renal function requiring hospitalization or dialysis within 3 months prior to screening
5. Renal transplant or anticipated need for renal transplantation during planned study participation
6. History of malignancy within the previous 12 months except for cured non-melanocytic skin cancer
7. Recent cardiovascular event (within the last 3 months): myocardial infarction, unstable angina, hospitalization for heart failure, revascularization, or stroke (or transient ischemic attack)
8. Clinically significant ventricular arrhythmia
9. Atrial fibrillation with HR > 100 bpm
10. Previous use of patiromer in a clinical study
11. Any current use of spironolactone or other mineralocorticoid antagonists (e.g., eplerenone)
12. Hypersensitivity to patiromer, spironolactone, or any of their components
13. Use of any of the following permitted potassium-altering chronic medications if doses have not been stable for at least 28 days prior to screening or if doses are anticipated to change during study participation: bronchodilators, theophylline, heparin, and canagiflozin
14. Use of the following prohibited medications within 7 days prior to Screening: calcium acetate or calcium carbonate supplements (unless for occasional antacid use, at the discretion of the Investigator), digoxin, direct renin inhibitors (e.g., aliskiren), lanthanum carbonate, lithium, sevelamer, quinidine, sodium polystyrene sulfonate or calcium polystyrene sulfonate, colesevelam, colestipol, cholestyramine, drospirenone, potassium supplements, bicarbonate or baking soda (unless for occasional antacid use, at the discretion of the Investigator), triamterene, amiloride, trimethoprim, tacrolimus, cyclosporine, systemic glucocorticoids, nonsteroidal anti-inflammatory drugs (NSAIDs) or COX-2 inhibitors (with the exception of low dose aspirin), sympathomimetics
15. Use of any investigational product within 30 days or 5 half-lives, whichever is longer, prior to screening
16. History of bowel obstruction, swallowing disorders, clinically significant gastroparesis, severe gastrointestinal disorders or major gastrointestinal surgery (e.g., large bowel resection)
17. Inability to take the study medications or comply with the protocol, in the opinion of the Investigator
18. History of alcohol or drug abuse within 1 year of screening

19. Any medical condition, uncontrolled systemic disease, or serious intercurrent illness that would significantly decrease study compliance or jeopardize the safety of the subject or affect the validity of the trial results, in the opinion of the Investigator

4.3 Subject Withdrawal from Study

Within the provisions of informed consent and good clinical judgment with respect to the subject's safety, every attempt should be made to have subjects complete both the Double-Blind Treatment Period and the Follow-up Visit. Subjects will be informed that they will be free to withdraw from the study at any time. However, should a subject withdraw, every effort will be made to determine the reason why the subject has withdrawn his/her consent. Although subjects will not be obliged to give a reason for withdrawing consent, the Investigator will make an effort to obtain the reason, while fully respecting the subject's rights. Reasons for withdrawal of consent, when provided by the subject, will be recorded in the electronic case report form (eCRF), and the procedures described for ET (Sections 6.4 and 6.2.3) will be performed, if possible. Every effort will be made to contact a subject who fails to attend a study visit, or does not respond by telephone, in order to ensure that the subject is in satisfactory health.

The Investigator and/or the Medical Monitor may exercise his or her medical judgment to terminate a subject's participation in the study if they determine that the subject's continued participation in the study is a potential safety concern. The Investigator will immediately inform the Medical Monitor of removal or early withdrawal of a subject from the study. All subjects withdrawn early from the study for any reason will complete the procedures described for ET and be followed for safety for at least 2 weeks after receiving the last dose of study medications. Subjects withdrawn from the study for any reason will not be replaced.

In addition to other protocol specified discontinuations of study drugs for hyperkalemia and hypotension (Appendix B and Appendix C), spironolactone and patiromer/placebo treatment will be discontinued for subjects who require maintenance dialysis, become pregnant, or who experience a treatment-related SAE during the study. These subjects will remain in the study until study completion and will be treated with in accordance with the standard of care per the Investigator's judgment.

5 STUDY TREATMENTS

5.1 Treatment Blinding

To minimize the potential for bias, treatment randomization information will be kept confidential by the unblinded biostatistician and will not be released to the investigator or investigator site personnel until the study database has been locked. The blind will be maintained for subjects, site personnel, and all Relypsa and vendor staff, with the exception of unblinded staff required for the development of the final randomization schedule and for production of unblinded materials for the Data Safety Monitoring Committee (DSMC) in addition to Relypsa Drug Safety staff in situations where unblinding is necessary to comply with Regulatory requirements.

The Relypsa staff who may be unblinded will be identified prior to the start of study enrollment. If the Investigator, site study staff, or site Investigational Pharmacist becomes aware of a subject's study treatment assignment, efforts should be made to not disclose treatment

assignments to other study staff, subjects, or their care-givers. Blinded Relypsa staff will also remain blinded to treatment assignment.

Subjects should refrain from discussion of their study drugs with the site staff or other subjects, and any questions regarding the physical properties or appearance of the study drugs should be directed to the dispensing Investigational Pharmacist only.

5.1.1 Breaking the Blind

In the case of a medical emergency, the Investigator may request that the blind be broken if it is considered important to the management of the medical emergency. In such cases, the Investigator will be unblinded via the IWRS. The Investigator should make every reasonable attempt to notify the study Medical Monitor before breaking the blind. The investigator may inform the subject and/or his/her treating physician of the treatment assignment.

5.2 Allocation to Treatments

All subjects will begin treatment with spironolactone 25 mg QD on the day after randomization to patiromer/placebo (Day 1). Subsequent dosing decisions will be made in accordance with Appendix C.

Randomization to patiromer or placebo (Day 0) will be 1:1, stratified by baseline potassium level (4.3 – < 4.7 and 4.7 – 5.1 mEq/L) based on the potassium value measured by the local laboratory at Visit S4 and history of Type 1 or 2 diabetes mellitus (Yes or No), will be performed at the Randomization Visit using the IWRS.

5.3 Investigational Product Supplies

5.3.1 Formulation and Packaging

Patiromer or placebo will be provided to the subject blinded, as a powder for oral suspension in packets. The individual packets will be assembled as a kit for dispensing containing 20 packets each. Each packet will contain patiromer (4.2g) or placebo (microcrystalline cellulose). Patiromer or placebo will be shipped to and stored at the study site refrigerated (2 – 8°C). Study subjects will be instructed to store patiromer or placebo refrigerated (2 – 8°C) for the duration of the study.

Spironolactone 25 mg tablets will be provided to all subjects for oral administration and should be stored below 77 degrees Fahrenheit (25 degrees Celsius) (Aldactone PI, 2014).

5.3.2 Preparation and Dispensing of Patiromer/Placebo

Patiromer/placebo are for oral administration only. Each dose should be prepared immediately prior to administration.

Patiromer/placebo suspension should not be heated (e.g., microwaved) or added to heated foods or liquids. Patiromer or placebo should not be taken in its dry form but mixed with water only. Patiromer or placebo doses should be prepared following the steps below:

- Measure 1/3 cup (approximately 80 mL) of water. Pour half of the water into a glass, then add patiromer and stir. Add the remaining half of the water and stir thoroughly. The powder will not dissolve and the mixture will look cloudy. Add more water to the mixture as needed for desired consistency.
- Drink the mixture immediately. If powder remains in the glass after drinking, add more water, stir and drink immediately. Repeat as needed to ensure the entire dose is administered.

The Investigational Pharmacist(s) or qualified designee will be responsible for dispensing the investigational product and documenting the dispensation. The Investigational Pharmacist(s) or qualified designee will be someone who does not perform any other study assessments.

At each Double-Blind Treatment Period Visit, subjects should return all empty packets and unopened packets in their closed, original box. Drug accountability will be performed by the drug dispensing Investigational Pharmacist or qualified designee.

5.3.3 Dosing and Administration of Patiromer/Placebo and Spironolactone

The starting dose of patiromer/placebo will be two packets QD taken with food for randomized subjects. Patiromer/placebo should be taken at least 3 hours before or 3 hours after administration of other orally administered medications, including spironolactone (see Section 5.5.1 and Investigator's Brochure for additional information).

Based upon the patiromer/placebo treatment algorithm (Section 3.1.2 and Appendix B), patiromer/placebo will be increased in two-packet per day increments for serum $K^+ > 5.1$ mEq/L in intervals of at least 1 week. Doses of patiromer/placebo will be two packets, four packets, and six packets (maximum dose). Patiromer/placebo will be decreased by at least two packets per day for serum $K^+ < 4.0$ mEq/L. The minimum daily dose of patiromer/placebo will be 0 packets.

All subjects will initiate spironolactone 25 mg QD on Day 1. At the Week 3 visit (or after), the spironolactone dose will be increased to 50 mg QD for subjects with AOBP SBP $\geq$ 120 mmHg and $K^+ \leq 5.1$ mEq/L. For subjects with $K^+ > 5.1$ mEq/L, 25 mg daily dose of spironolactone will be continued until the first subsequent visit when K^+ is ≤ 5.1 mEq/L (and AOBP SBP $\geq$ 120 mmHg), at which time spironolactone will be increased to 50 mg QD (see Appendix C).

Note: During all study visits, if a subject experiences symptoms of hypotension with SBP < 120 mmHg, or if SBP < 100 mmHg, spironolactone dose may be reduced to 25 mg every other day or discontinued at the discretion of the Investigator.

5.3.4 Study Drug Adherence

At Randomization on Day 0, subjects will be instructed on proper dosing of study drugs with detailed instructions on when to take study drugs and all concomitant medications after considering the subject's current medication regimen, patiromer/placebo instructions regarding administration, and subject preference. The subject will be instructed to follow the agreed dosing instructions for the remainder of the study to encourage compliance. The Investigator

will determine if the dosing instruction requires changes at each visit and any changes will be communicated to the subject.

Subjects will also be instructed to return any unused spironolactone tablets and to save their empty/used patiromer or placebo packets and bring them together with any unopened packets to the next visit for compliance assessment. Subjects will be instructed to return empty/used patiromer or placebo packets in the box or containers in which originally provided. In order to minimize the potential of study staff unblinding, the Investigational Pharmacist or the qualified designee who is not involved in subject study procedures will assess compliance based on returned empty and unopened packets and returned spironolactone tablets during the 12-week Double-Blind Treatment Period to confirm that the subject is taking patiromer or placebo and spironolactone according to the protocol instructions.

Compliance will be documented in the eCRF as detailed in the electronic data capture (EDC) completion guidelines. Compliance will be assessed on the basis of the prescribed patiromer/placebo and spironolactone doses, the duration of treatment, and the quantity of dispensed and returned kits/packets (used and unused) and returned tablets. The Investigational Pharmacist will inform the study personnel if any compliance issues are identified so that the subject can be retrained on proper dosing and administration.

5.4 Investigational Product Storage and Accountability

The Investigational Pharmacist or designee will verify and acknowledge receipt of each shipment of patiromer/placebo and spironolactone. Patiromer/placebo will be shipped and stored under refrigeration (2 – 8 degrees Celsius). Spironolactone should be shipped and stored at temperatures less than 77 degrees Fahrenheit (25 degrees Celsius) (Aldactone PI, 2014). All study drugs will be stored in a secure location. No subject other than those enrolled in this specific clinical study shall take patiromer/placebo or spironolactone provided for this study. Patiromer/placebo or spironolactone provided for this study may not be utilized for any laboratory or animal research. All investigational product dispensed to subjects must be accurately recorded on the Investigational Product Accountability Record maintained at the Study Site by the Investigational Pharmacist or the qualified designee. Subjects should be instructed to return all investigational product dispensed to them (including empty containers) at each study visit. All investigational product and empty containers will be retained at the site by the Investigational Pharmacist/qualified designee for the Study Monitor's verification. Investigational Product accountability and compliance for all investigational products will be performed by the site Investigational Pharmacist or the qualified designee at each scheduled study visit starting at the Baseline Visit and ending on the Week 12 or ET Visit.

5.5 Concomitant Medications

Information on concomitant medication (prescription, over-the-counter, herbal and naturopathic remedies, etc.) will be collected beginning at the Screening Visit and continuing for the duration of the study (including ET Visit) until the Follow-up visit or Follow-up Phone Call.

In general, subjects should continue on the same medications and regimens that were ongoing at the study entry. Subjects should be instructed to delay taking their blood pressure medications on

the morning of study visits until after office blood pressure measurements have been completed. Doses of these medications should be kept as stable as possible during the study. Medications that the Investigator deems indicated for treatment of any intercurrent illness or a pre-existing condition that are not on the prohibited medication list or do not form an exclusion criterion for participation in this study will generally be allowed. If new medications for mild to moderate pain relief are required, NSAIDs and COX-2 inhibitors should be avoided, as they are prohibited medications due to their effects on BP and serum potassium, and alternatives such as acetaminophen should be used.

5.5.1 Timing of Oral Drug Administration

Based on data from human in vivo DDI studies, patiromer/placebo should be taken at least 3 hours before or 3 hours after administration of other orally administered medications (see Investigator's Brochure and Section 5.3.3 for further details). Each subject will be provided with individualized instructions for when to take spironolactone, patiromer/placebo, and other medications after consideration of the subject's current medication regimen and subject's preference. The instructions will be updated during the study if any changes to the subject's medication regimen occurs during the study.

For subjects taking medications with a narrow therapeutic index, careful monitoring is advised.

5.5.2 Permitted Medications

The following potassium-altering chronic medications will be permitted provided that the treatment doses are stable for at least 28 days prior to screening and no changes are anticipated during the study:

- bronchodilators
- theophylline
- heparin
- canagliflozin

5.5.2.1 Permitted Antihypertensive Medications

All antihypertensive drugs (except spironolactone, eplerenone, or other MRAs, and aliskiren or other direct renin inhibitors) will be permitted at screening and baseline if the subject has been on a stable dose for at least 28 days prior to screening. During subject's participation in the study, no new antihypertensive medications will be initiated, except as outlined in the protocol (Section 3.1.2 and Appendix D). Baseline antihypertensive medication doses will not be changed and new ACE inhibitors or ARBs will not be initiated during the study except in the management of AOBP > 200 mmHg (see Appendix D). Spironolactone may not be reinitiated if it has been discontinued during the study. Treatment of hypertension in these subjects should be standard of care, in accordance with the clinical judgment of the Investigator.

5.5.3 Permitted Medications for Heart Failure

The following medications will be permitted at screening and baseline for the management of heart failure as long as doses have remained stable for 28 days prior to screening: thiazide and loop diuretics, ACE inhibitors, ARBs, beta-adrenergic blockers, hydralazine and long-acting nitrates.

During the study, no new ACE inhibitors or ARBs will be initiated except as described in the protocol (see Appendix D) and every effort will be made to keep the doses of all these medications stable.

5.5.4 Prohibited Medications

During the entire study, the following medications will be prohibited while being treated with patiromer/placebo:

- calcium acetate or calcium carbonate supplements (unless for occasional antacid use, at the discretion of the Investigator)
- digoxin
- eplerenone or other MRAs
- lanthanum carbonate
- sevelamer
- quinidine
- sodium polystyrene sulfonate or calcium polystyrene sulfonate
- colesevelam
- colestipol
- cholestyramine
- drospirenone
- therapeutic potassium supplements
- bicarbonate or baking soda (unless for occasional antacid use, at the discretion of the Investigator)
- trimethoprim
- tacrolimus
- cyclosporine
- systemic glucocorticoids

- NSAIDs or COX-2 inhibitors, except low dose aspirin
- sympathomimetics
- lithium
- aliskiren or any direct renin inhibitor
- potassium sparing diuretics such as triamterene and amiloride

6 TRIAL PROCEDURES

Refer to the Schedule of Events (Appendix A) for the frequency and timing of the required study assessments and activities. For dietary counseling refer to Section 7.5. The following chronology of events should be adhered to at each visit:

1. EQ-5D-5L Questionnaire (S4 and Week 12 Visits only)
2. AOBP
3. SMBP
4. Other procedures

6.1 Screening/Run-in Period (up to 4 Weeks):

Before any study-specific procedures are performed, the subject will receive an explanation of all study procedures and must sign and date a written informed consent form (ICF) approved by an institutional review board (IRB) (see Section 12.2 for additional requirements). The timing of the Screening Visit (and all subsequent visits) must take into account planned absences at the research facility and the need for study visits according to the Schedule of Events (Appendix A).

The subjects will be instructed to arrive at the scheduled time for each Screening Visit to allow for completion of all assessments including measurement of the potassium level by the local laboratory. At the first Screening Visit, subjects will be assigned a unique subject identification number, which will be generated during Screening Visit registration in IWRS. On the morning of all study visits after S1, the subjects will be instructed to delay taking their BP medications until office BP measurements have been completed.

The Screening/Run-in Period will consist of 4 Screening Visits (S1, S2, S3, and S4) that will occur approximately 7 days (at least 4 days but no more than 10 days) after the prior Screening Visit (Appendix A).

6.1.1 S1

The following activities will be performed (Appendix A):

- Subject signs informed consent

- IWRS registration
- Review inclusion and exclusion criteria
- Collect demographic information
- Review medical history
- Measure height and weight
- Measure resting heart rate (pulse) after the subject has been sitting quietly for 5 minutes
- Perform physical examination
- Perform 12-lead ECG
- Record AOBP (Section 7.3.2.2) performed using automatic oscillometric office device with the capability of performing automatic multiple measurements after the study staff has left the room (unwitnessed measurement after the subject has been sitting quietly for 5 minutes)
- Issue HBP monitor and appropriate size blood pressure cuff
- Train subject on use of HBP monitor and collection of twice daily measurements (see Section 7.3.2.1)
- Collect blood samples for evaluation of (see Appendix E):
  - Potassium level (measured locally and by central laboratory)
  - Serum chemistry including creatinine, eGFR (central laboratory)
  - Hematology (central laboratory)
  - Pregnancy (central laboratory)
- Collect urine sample for urinalysis (central laboratory)
- Dietary counselling
- AE assessment
- Record concomitant medications

6.1.2 S2 (1 week [a least 4 days but no more than 10 days] after S1)

At each study visit beginning with S2, the office blood pressure (AOBP and SMBP) should be performed before other scheduled activities. The following activities will be performed (Appendix A):

- IWRS registration
- Measure resting heart rate (pulse) after the subject has been sitting quietly for 5 minutes

- Record AOBP (Section 7.3.2.2) performed using automatic oscillometric office device with the capability of performing automatic multiple measurements after the study staff has left the room (unwitnessed measurement after the subject has been sitting quietly for 5 minutes)
- Record SMBP (Section 7.3.2.2) performed onsite using the subject's HPB monitor. If a subject does not bring their issued HBP monitor to the visit, the SMBP will be missing for that Visit
- Train subject on use of HBP monitor and collection of twice daily measurements as necessary (see Section 7.3.2.1)
- Dietary counselling
- AE assessment
- Record concomitant medications

6.1.3 S3 (1 week [at least 4 days but no more than 10 days] after S2)

The office blood pressure (AOBP and SMBP) should be performed before other scheduled activities. The following activities will be performed (Appendix A):

- IWRS registration
- Measure resting heart rate (pulse) after the subject has been sitting quietly for 5 minutes
- Record AOBP (Section 7.3.2.2) performed using automatic oscillometric office device with the capability of performing automatic multiple measurements after the study staff has left the room (unwitnessed measurement after the subject has been sitting quietly for 5 minutes)
- Record SMBP (Section 7.3.2.2) performed onsite using the subject's HPB monitor. If a subject does not bring their issued HBP monitor to the visit, the SMBP will be missing for that Visit
- Train subject on use of HBP monitor and collection of twice daily measurements as necessary (see Section 7.3.2.1)
- Collect blood samples for evaluation of:
  - Potassium level (measured locally and by central laboratory)
  - Serum chemistry including creatinine, eGFR (central laboratory; see Appendix E)
- Dispense 24-hour urine collection container for urine sodium, potassium, creatinine, and albumin (for ACR) (to be collected for 24 hours beginning at least 24 hours before the S4 Visit)
- Train subject on 24-hour urine collection. The 24-hour urine collection should begin immediately after the first morning void at least 24 hours before the S4 visit.

- Dispense urine collection cups for S4 urine ACR determination (total of 2 urine specimens to be collected on the morning of the second and third days before the S4 visit). These samples will be sent to the central laboratory on day of S4.
- Train subject for ACR collection
- Dietary counselling
- AE assessment
- Record concomitant medications

6.1.4 S4 (1 week [a least 4 days but no more than 10 days] after S3)

The EQ-5D-5L assessment should be performed first, then the office blood pressure (AOBP and SMBP) second, and all other scheduled activities should be performed after. The following activities will be performed (Appendix A):

- IWRS registration
- Review inclusion and exclusion criteria
- Measure resting heart rate (pulse) after the subject has been sitting quietly for 5 minutes
- Record AOBP (Section 7.3.2.2) performed using automatic oscillometric office device with the capability of performing automatic multiple measurements after the study staff has left the room (unwitnessed measurement after the subject has been sitting quietly for 5 minutes)
- Record SMBP (Section 7.3.2.2) performed onsite using the subject's HPB monitor. If a subject does not bring their issued HBP monitor to the visit, the SMBP will be missing for that Visit
- Train subject on use of HBP monitor and collection of twice daily measurements as necessary (see Section 7.3.2.1)
- Collect blood samples for evaluation of (see Appendix E):
  - Potassium level (measured locally, and central laboratory if subject meets all eligibility criteria)
  - Serum chemistry including creatinine, eGFR (send to central laboratory only if subject meets all eligibility criteria)
  - Hematology (send to central laboratory only if subject meets all eligibility criteria)
  - NT-proBNP (see Section 7.2.1, send to central laboratory only if subject meets all eligibility criteria)
  - Aldosterone and plasma renin activity (send to central laboratory only if subject meets all eligibility criteria)
- Collect 24-hour urine specimen for sodium, potassium, creatinine and albumin (for ACR) (collected for 24 hours prior to Visit S4)

- Collect ACR urine specimens (samples from first morning voids on the second and third day before S4, see Appendix A).
- Perform urine pregnancy test for women of child bearing potential
- AE assessment
- Record concomitant medications

Discard all central laboratory samples for subjects who do not meet study entry criteria.

6.1.5 Rescreening of Subjects

Subjects who meet all study entry criteria except for eGFR and/or serum potassium will be screen failures but may be rescreened once at least 2 weeks after initial screen failure.

To rescreen a subject:

- The Medical Monitor must be contacted for rescreening approval
- The subject must be re-consented
- The subject must receive a new subject identification number assigned by IWRS
- ***All Screening Visits (S1-S4)*** and assessments must be repeated (see Section 6.1)

6.2 Double-Blind Treatment Period (12 Weeks)

Subjects who meet all eligibility criteria at ***Visit S4*** will be randomized on the same day, and S4 assessments will be considered the baseline assessments and will not be repeated. For these subjects, ***Visit S4*** will be designated as the S4/Randomization (Baseline, Day 0) Visit.

6.2.1 Randomization (Baseline, Day 0) Visit

The following activities will be performed at Randomization (Baseline, Day 0) Visit in addition to those performed for the S4 Visit (Section 6.1.4 and Appendix A):

- Confirm subject meets all entry criteria
- IWRS randomization to patiromer or placebo (assignment blinded)
- Measure weight
- Send urine samples for baseline urinalysis (central laboratory)
- Establish dosing schedule for study drugs and all concomitant medications in collaboration with the subject; instruct the subject to begin study medications on the following day (Day 1)

- Investigational Pharmacist or qualified designee dispenses spironolactone and blinded patiromer/placebo based on kit number assigned by IWRS and instructs subject to begin taking medications on Day 1 (see Section 3.1.2)
- Subject completes EQ-5D-5L Questionnaire
- Dietary counselling

6.2.2 Week 1 – Week 4 (± 3 days); Week 6, Week 8, and Week 10 (± 7 days)

At all scheduled or unscheduled study visits during the Double-Blind Treatment Period after Day 1, the local potassium level will be used for adjustments to patiromer/placebo dose and spironolactone administration in accordance with the study patiromer/placebo and spironolactone dosing algorithms (see Appendix B and Appendix C). AOBP will also be assessed and adjustments to spironolactone administration or BP management will be made in accordance with Section 3.1.2, Appendix C and Appendix D. Modification of baseline antihypertensive medications will not be allowed, except in subjects with SBP ≥ 200 mmHg or for AE-related reasons where changes to baseline medications can be justified by the Investigator (e.g., increases in loop diuretics for new edematous states or discontinuation of baseline medication for drug-related AEs), as described in Section 3.1.2 and Appendix D.

The office blood pressure measurements (AOBP and SMBP) should be performed before other scheduled activities. The following activities will be performed (Appendix A):

- IWRS registration
- Measure resting heart rate after the subject has been sitting quietly for 5 minutes
- Record AOBP (Section 7.3.2.2) performed using automatic oscillometric office device with the capability of performing automatic multiple measurements after the study staff has left the room (unwitnessed measurement after the subject has been sitting quietly for 5 minutes)
- Record SMBP (Section 7.3.2.2) performed onsite using the subject's HPB monitor. If a subject does not bring their issued HBP monitor to the visit, the SMBP will be missing for that Visit
- Review HBP measurement procedure with subject, as necessary
- Collect blood samples for evaluation of:
  - Potassium level (measured locally and by central laboratory)
  - Serum chemistry including creatinine, eGFR (central laboratory; see Appendix E)
  - Hematology, (central laboratory; ***Week 4 only***; see Appendix E)
  - Spironolactone level (at ***Week1, Week 4 and Week 8 only***, see Section 7.2.2)
- Dispense urine ACR collection cups and train subject regarding ACR collection at Week 3, Week 6 and Week 10 ***(for Week 12 Visit)*** visits. Instruct the subject to collect three first morning void urine samples for evaluation of urine ACR (central laboratory; ***Week 4 and***

Week 8 only; see Appendix A). Urine specimens will be collected at home from first morning void for the days specified below, and sent to the central laboratory with the visit samples; see Section 7.7)

- Week 4 samples (3 separate samples)
  - 2 days before the visit
  - 1 day before the visit
  - Day of the visit
- Week 8 samples (3 separate samples)
  - 2 days before the visit
  - 1 day before the visit
  - Day of the visit

- Investigational Pharmacist or qualified designee dispenses blinded patiromer/placebo based on kit number assigned by IWRS in accordance with Section 3.1.2 (see Appendix B)
- Investigational Pharmacist or qualified designee dispenses spironolactone in accordance with instructions in Section 3.1.2 (Appendix C)
- Investigational Pharmacist or qualified designee performs drug accountability
- Review potassium measured locally and AOBP results and adjust study medications according to Section 3.1.2 and Appendix B, Appendix C, and Appendix D.
- Dietary counselling
- AE assessment
- Record concomitant medications

6.2.3 Week 12 Visit (± 7 days)

The Week 12 Visit is the last visit for the Double-Blind Treatment Period of the study. At the Week 12 Visit, all study drug treatments will be discontinued. Investigators may prescribe out of study (i.e., standard of care) antihypertensive medication if needed.

The EQ-5D-5L assessment should be performed first, then the office blood pressure (AOBP and SMBP) second, and all other scheduled activities should be performed after. The following activities will be performed (Appendix A):

- IWRS registration
- Record AOBP (Section 7.3.2.2) performed using automatic oscillometric office device with the capability of performing automatic multiple measurements after the study staff has left the room (unwitnessed measurement after the subject has been sitting quietly for 5 minutes)

- Record SMBP (Section 7.3.2.2) performed onsite using HPB monitor. If a subject does not bring their issued HBP monitor to the visit, the Subject-measured Office BP will be missing for that Visit
- Measure resting heart rate after the subject has been sitting quietly for 5 minutes
- Measure weight
- Perform physical examination
- Perform 12-Lead ECG
- Collect HBP monitors
- Collect blood samples for evaluation of:
  - Potassium level (measured locally and by central laboratory)
  - Serum chemistry including creatinine, eGFR (central laboratory; (see Appendix E)
  - Hematology, (central laboratory; see Appendix E)
  - Pregnancy (central laboratory; see Appendix E)
  - NT-proBNP (see Section 7.2.1)
  - Spironolactone level (see Section 7.2.2)
- Collect urine sample for evaluation of urinalysis (central laboratory; see Appendix E)
- Collect subject's three first morning void urine samples for evaluation of urine ACR (central laboratory) Week 12 (see Section 7.7)
  - Week 12 samples (3 separate samples)
    - 2 days before the visit
    - 1 day before the visit
    - Day of the visit
- Subject completes EQ-5D-5L Questionnaire
- Investigational Pharmacist or qualified designee performs drug accountability
- AE assessment
- Dietary counselling
- Record concomitant medications

6.3 Follow-up Visit (2 weeks after Week-12 or ET Visit, + up to 7 day window)

The office blood pressure (AOBP) should be performed before other schedule activities. The following activities will be performed (Appendix A):

- IWRS registration
- Measure resting heart rate after the subject has been sitting quietly for 5 minutes
- Record AOBP (Section 7.3.2.2) performed using automatic oscillometric office device with the capability of performing automatic multiple measurements after the study staff has left the room (unwitnessed measurement after the subject has been sitting quietly for 5 minutes)
- Collect blood samples for evaluation of:
  - Potassium level (measured locally and by central laboratory)
  - Serum chemistry including creatinine, eGFR (central laboratory; see Appendix E)
- AE assessment
- Record concomitant medications

The Investigator may request the subject to return to the study site for unscheduled visits prior to the Follow-up Visit to evaluate potassium levels, blood pressure, or AEs (see Section 6.5).

6.3.1 Follow-up Phone Call

Only for subjects with a Follow-up Visit < 2 weeks after Week-12 or ET Visit or those who did not attend the Follow-up Visit will receive a Follow-up Phone call 2 weeks after Week-12 or ET Visit (+ up to 7 days window).

Assessments performed over the phone call:

- AE assessment
- Concomitant medication assessment for any drugs used to treat an AE

6.4 Early Termination Visit

Subjects who withdraw prematurely from the study before the Week 12 Visit will complete the ET Visit, which will be performed on the day of the withdrawal or as soon as possible. All assessments (aside from those that require activities prior to the ET Visit; i.e., urine collections for ACR) applicable to the Week 12 Visit (Section 6.2.3) will be performed at the ET Visit.

6.5 Unscheduled Visits

At any study visit, if a hyperkalemia event ($K^+ \geq 5.5$ mEq/L) and/or modification of study drug(s) occurs, an Unscheduled visit will be conducted within 1 week after modification of study drugs (Appendix B and Appendix C) unless the next scheduled visit is within 1 week of the study drug modification, in which case, the subject will return at the next scheduled visit.

Additional Unscheduled Visits may be conducted during the study as needed, at the discretion of the Investigator.

The following activities will occur any time an Unscheduled Visit is performed during the study:

The office blood pressure (AOBP and SMBP) should be performed before other scheduled activities.

- IWRS registration
- Measure resting heart rate
- Measure AOBP using automatic oscillometric office device with the capability of performing automatic multiple measurements after the study staff has left the room (unwitnessed measurement after the subject has been sitting quietly for 5 minutes; Section 7.3.2.2)
- Potassium level (measured locally and by central laboratory)
- Dietary counselling
- AE assessment
- Record concomitant medications

The following activities are optional during an Unscheduled Visit:

- Measure weight
- Perform physical exam and/or ECG as indicated

- Dispense blinded patiromer or placebo according to the kit number assigned by IWRS (except for Unscheduled Visits after Week 12 or ET Visit)
- Collect blood samples for evaluation of the following (central laboratory; see Appendix E):
  - Serum chemistry including creatinine, eGFR
  - Hematology
- Dispense spironolactone, as necessary (see Appendix B and Appendix C) (except for Unscheduled Visits after Week 12 or ET Visit)
- Investigational Pharmacist or qualified designee performs drug accountability

7 ASSESSMENTS

7.1 Potassium

Serum potassium levels will be assessed locally and by central laboratory at all study visits including unscheduled visits (Appendix A). Screen Failure subjects who meet all other study entry criteria except for potassium level and/or eGFR may be rescreened once (see Section 6.1.5). Detailed instructions on how to draw blood and prepare specimens for analysis are provided in the Laboratory Manual.

7.1.1 Preventing, Identifying and Handling Hemolyzed Samples

Hemolysis of blood specimens may result in spuriously high potassium levels, potentially leading to inappropriate up-titrating of patiromer/placebo or inappropriate discontinuations of spironolactone in this study

The Laboratory Manual provides detailed descriptions of the recommended phlebotomy, sample preparation and transportation procedures to minimize hemolysis. Upon receipt of each blood sample for potassium analysis, the central laboratory will perform a semiquantitative test to assess for evidence of hemolysis. Predefined criteria will be established for determining whether the test result is indicative of potential hemolysis. These criteria and the criteria for removing serum potassium value from the efficacy analyses on the basis of hemolysis are described in the Laboratory Manual. When a central laboratory sample has been identified as hemolyzed after it has been received and processed by the central laboratory, the blood draw will not be repeated by the site personnel. The statistical analysis plan (SAP) summarizes how the data analyses will account for the missing central laboratory potassium value. If the central laboratory blood sample has been identified as hemolyzed by the site personnel (i.e., visual inspection) before it has been sent to the central laboratory, a repeat blood draw can be performed if the subject is still at the site.

When a blood sample, which will be used by the site for study drug titration and subject management, has hemolyzed (e.g., by visual inspection of the local laboratory serum sample), the site will repeat the potassium measurement from a separate blood draw within 1 day in order to ensure accurate decision-making regarding patiromer/placebo titration.

7.2 Laboratory Tests

All laboratory assessments will be performed by central laboratory unless specified in the Schedule of Events (Appendix A). All central laboratory assessments are detailed in Appendix E.

7.2.1 NT-proBNP

Blood samples collected at the S4/Baseline (Day 0) Visit and Week-12 visit or ET Visit will be analyzed for NT-proBNP levels. Please refer to the Laboratory Manual for additional information.

7.2.2 Spironolactone Level (Mass Spectrometry Analysis)

Blood samples collected at Week 1, Week 4, Week 8, and Week 12 or ET Visit from subjects who are still receiving spironolactone at the indicated visit will be analyzed for spironolactone levels using mass spectrometry. Please refer to the Laboratory Manual for additional information.

7.3 Vital Signs

The subject should avoid eating, smoking, or exercising for 30 minutes before vital sign measurements are taken. The subject should rest, sitting quietly, for approximately 5 minutes prior to the measurements.

7.3.1 Heart Rate

Heart rate should be measured after the subject has been sitting quietly for 5 minutes prior to BP measurement, and should be measured for a full 60 seconds.

7.3.2 Blood Pressure

7.3.2.1 Home Blood Pressure

At the first Screening Visit (S1), subjects will be issued a HBP monitor and an appropriate size BP cuff by the study site personnel and will be trained on use of the device. Subjects will be asked to measure their BP at home twice daily during the Screening/Run-in Period and during the 12-Week Double-Blind Treatment Period.

Subjects will be instructed to perform HBP measurements twice daily (morning and evening) at approximately the same times each day (e.g., at 8:00 [morning] and 20:00 in the [evening]) in triplicate (see HBP Training Materials and Manual of Operations; Mancia, 2013).

Note: Subjects will be instructed to bring their issued monitors to each scheduled visit. If a subject does not bring their issued monitor, only an automatic oscillometric Office BP will be measured (Section 7.3.2.2). The site will be notified regarding out-of-range HBP and subject noncompliance.

7.3.2.2 Office Blood Pressure

AOBP measurements will be performed by an automatic oscillometric BP measurement device that can measure BP in triplicate and with no study staff present. See Manual of Operations for complete instructions. At all scheduled visits except for Visit S1, two types of BP measurements will be performed onsite. Both measurements will be performed before other scheduled activities (except for S4 and Week 12 Visits where EQ-5D-5L will be the first assessment) with the subject alone with no study staff present after the subject has been seated quietly for 5 minutes:

1. Performed by an automatic oscillometric BP measurement device that can measure BP in triplicate (automated office BP, AOBP)
2. Performed by the subject using their issued HBP monitoring device in triplicate (subject-measured BP, SMBP)

For subjects who do not bring their issued HBP monitor to the study visit, the onsite SMBP data will be missing for that Visit.

7.4 Physical Examination

Physical examination will be performed as indicated in the Schedule of Events (see Appendix A). The following body systems are to be examined:

- Cardiovascular
- Lungs and chest, including respirations
- Head and neck
- Abdomen
- Musculoskeletal
- Skin
- Neurological

Any new clinically significant physical examination abnormality identified during the study will be reported as an AE.

7.5 Diet

Hypertension in subjects with CKD is often accompanied by a decrease in the kidney's ability to excrete salt. Addressing this salt sensitivity is critical for the management of hypertension in CKD. Dietary counseling will be conducted at each visit in accordance with the standard practices of the Investigator and should address all the dietary requirements of the subject (e.g., diabetes mellitus), as appropriate. The dietary intake of potassium containing foods should not be changed during the study.

7.6 ECG Assessment

If the Investigator is concerned regarding any potassium value, a retest of potassium level and/or ECG evaluation for electrophysiological manifestations can be initiated by the Investigator at their discretion.

The subject should be resting quietly for a minimum of 5 minutes prior to obtaining the ECG. If a new potassium-related ECG change is observed, the Investigator should apply the appropriate standard of care to evaluate and treat hyperkalemia. Any subject with new potassium-related ECG changes and local $K^+ \geq 5.5$ mEq/L will discontinue spironolactone and patiromer/placebo immediately but will remain in the study and complete all remaining study visits while receiving appropriate therapy as indicated. BP management will proceed in accordance with Section 3.1.2 and Appendix D.

7.7 Urine Collection for ACR

Urine samples will be collected at the S4/Baseline, Week 4, Week 8, Week 12 (or ET Visit), in order to calculate the ACR. Section 6 and Appendix A describe the visits at which urine sample containers will be dispensed. Urine collection for this purpose will be collected by the subject at

home. Urine specimens will be collected from the first morning void for the 2 days prior to and the morning of the Visit (see Section 6 and Appendix A) for the Week 4, Week 8, and Week 12 collections. For the S4/Baseline (Day 0) Visit, urine from the first morning void will be collected on the second and third days before the Visit. After the first morning void sample is collected on the second day before the Visit, the 24-hour urine sample collection will begin and should be completed on the morning of the S4/Baseline Visit (see Section 7.8). At an ET Visit, a single spot urine specimen may be collected at the clinic if time permits. Detailed description of the urine collection process for ACR measurements is provided in the Laboratory Manual.

7.8 24-Hour Urine Collection for Sodium, Potassium, Creatinine, Albumin (for ACR)

A single 24-hour urine collection will be performed beginning at least 24 hours prior to the S4/Baseline (Day 0) Visit to assess the baseline urine sodium, potassium, albumin, and creatinine levels (for baseline ACR). These urine albumin and creatinine measurements will be used in addition to those from first morning void samples for assessment of baseline ACR (section 7.7). Detailed description of the urine collection process for 24-hour urine sodium, potassium, albumin, creatinine measurements (for ACR) is provided in the Laboratory Manual.

7.9 EQ-5D-5L Questionnaire

Subject reported outcome will be assessed using the EQ-5D-5L questionnaire, comprised of five questions each with five levels (e.g., no problems, slight problems, moderate problems, severe problems and extreme problems) representing five health domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-5D-5L also includes a visual analog scale (VAS) that records the subject's self-rated health status on a graduated scale that ranges from 0–100, with higher scores indicating higher health-related quality of life.

Subjects will complete the EQ-5D-5L questionnaire at the Baseline (Day 0) and Week-12 or ET Visits. Subjects will complete the EQ-5D-5L questionnaire before study staff performs any clinic or study assessments to avoid biasing the subjects' responses. The study coordinators will review the subject's responses to the EQ-5D-5L questionnaire immediately after completion by subject to ensure that all questions are answered with a single response.

8 ADVERSE EVENT REPORTING

8.1 Definition of an Adverse Event

An AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment (Clinical Safety Data Management, 1995). An AE can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. This includes: 1) any new medical condition, sign or symptom, clinically significant physical examination abnormality or newly diagnosed event that occurs during the AE reporting period (see Section 8.2.1), including signs or symptoms associated with an underlying condition that were not present prior to the AE reporting period; 2) a preexisting condition that has worsened in severity or frequency or changed in character after the subject signs the informed consent during the AE reporting period; and 3) complications

that occur as a result of protocol-mandated interventions. An AE can arise from any use of the investigational drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose. It also includes any side effects, injury, toxicity or sensitivity reactions that may be experienced by a subject in this clinical trial.

Out of range laboratory results, ECGs, vital signs and other safety assessments will be considered AEs if they meet at least one of the following criteria:

- Associated with symptoms or lead to a diagnosis (in such case the symptom or diagnosis will be recorded as an AE)
- Lead to discontinuation of patiromer
- Required treatment or subject referral for further testing outside the protocol (repeat testing or titration are within protocol procedures)
- The Investigator or Relypsa considered the abnormality as clinically significant in its own right (e.g., asymptomatic creatinine kinase > 5000 IU/L)

For the purposes of this protocol, events that will not be considered AEs include:

- Anticipated fluctuating signs or symptoms of a pre-existing medical condition (e.g., tremor in a subject with Parkinson's disease; migraine episodes) that have not worsened in severity or frequency or changed in character during the AE reporting period
- Surgeries or medical procedures are not AEs, however, the medical condition (new or worsened) that led to the surgery or medical procedure is the reported AE (e.g., for appendicitis resulting in appendectomy, appendicitis would be reported as the AE).
- Overdose without clinical signs or symptoms
- Pregnancy (see Section 8.4 for reporting obligations)

8.1.1 Definition of Serious Adverse Event

An SAE is an AE that meets one or more of the following criteria:

- **Death**
- **Life threatening experience** defined as any AE that in the view of the Investigator or Relypsa, places the subject at immediate risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it had been more severe
- **Requires inpatient hospitalization or prolongation of existing hospitalization,** with the exception of:
  - Visits to the emergency room or hospital department that do not result in an overnight hospital admission
  - Elective surgery for a pre-existing condition that has not worsened

- Routine health assessments requiring admission
- Social admission (lack of housing, family circumstances, etc.)

- **Results in persistent or significant disability/incapacity** (i.e.: a substantial disruption of the ability to conduct normal life functions/ normal activities of daily living)
- Is a **congenital anomaly or birth defect** in an offspring of a female subject taking patiromer or a congenital anomaly or birth defect in the female partner of a male subject taking patiromer during the conduct of the clinical study
- Is an **important medical event** that may not be immediately life-threatening or result in death or hospitalization but based upon medical judgment, jeopardizes the subject and may require medical or surgical intervention to prevent one of the outcomes above (e.g., blood dyscrasias; convulsions)

Either the Investigator or Relypsa can determine that an AE meets the definition of serious. If either believes that the event is serious, the event must be considered serious and evaluated by Relypsa for expedited reporting

8.2 Procedures for Eliciting, Recording and Reporting Adverse Events

8.2.1 Adverse Event Reporting Period

AEs, including SAEs, will be collected throughout the study period, beginning from the time the subject signs the ICF until the subject's last study visit (normally Follow-up Visit). Any AE or SAE will be followed until the event or its sequelae resolves or becomes stable or otherwise justified by the Investigator in agreement with Relypsa. The Investigator must report any AEs that occur after the protocol specified reporting period if according to the Investigator's assessment there was a reasonable possibility that the AE was related to patiromer or any study procedures.

8.2.2 Eliciting Adverse Events

Information on AEs and SAEs will be elicited at each AE assessment time point specified in the Schedule of Events by asking the subject an open-ended question such as: "Since you were last asked, have you felt unwell or different from usual in any way?" The subject may report AEs spontaneously at any time.

8.2.3 Assessing Adverse Events

The Investigator will follow the guidelines for rating severity of AEs:

Mild: No disruption to normal activities. Awareness of signs or symptoms, but easily tolerated; symptoms are transient and would not require medication or medical evaluation.

Moderate: Some disruption to normal activities. May lead to discomfort, treatment may be required.

Severe: Significant disruption to normal activities. May be incapacitating; may require medical evaluation and/or treatment.

The term "severe" is often used to describe the intensity of a specific event; the event itself, however, may be of relatively minor medical significance, such as severe headache. Severity of the event is not the same as seriousness, which is a regulatory definition. Regardless of the severity, an AE is serious if it meets seriousness criteria (see Section 8.1.1).

8.2.4 Causality Assessments

The Investigator will provide a causality assessment for all AEs using his/her best clinical judgment based upon the available medical information of the event that is being reported. The causality assessment will be re-assessed as new medical information becomes available. If the Investigator's causality assessment is not reported it will be considered as "related" until it is received. The Investigator and Relypsa will each assess relatedness of the AE to the investigational drugs, patiromer/placebo and spironolactone, using the following definitions:

Not Related: There is no reasonable possibility that patiromer caused or contributed to the AE.

- The event is related to an etiology other than the investigational such as underlying disease, study or non-study procedures, concomitant medications, or the subject's clinical state
- The time of the occurrence of the AE is not reasonably related to the administration of the study drug

Related: There is a reasonable possibility that patiromer caused or contributed to the AE.

- There is a compatible temporal association between the event and the administration of investigational drug
- There is a biologically plausible mechanism for the study treatment to cause or contribute to the AE
- The event improves or diminishes upon withdrawal of the study drug without the initiation of any specific treatments for the event (dechallenge), and/or the event recurs or worsens with the rechallenge of the study therapy
- The event cannot be reasonably attributed to concurrent or underlying illness, other drugs or procedures

For causality assessment purposes "reasonable possibility" is meant to convey that, based on the Investigator's medical judgment of the available information, there are facts or arguments to suggest a positive causal relationship.

8.2.5 Recording Adverse Events

All AEs and SAEs, whether spontaneously reported by the subject or elicited or noted by study staff, will be recorded in the subject's medical record and on the appropriate AE case report form (CRF) or eCRF page. In addition, the SAE Report Form must be completed for each SAE.

For AEs related to an etiology other than the investigational drug, the alternative etiology, such as underlying disease, study or non-study procedures, concomitant medications, or the subject's clinical state, must be documented in the study subject's medical record and provided in the AE eCRF and, if applicable, the SAE report.

All AEs will be recorded using the words of the subject (verbatim term) to describe the AE whenever possible. However, if the verbatim term is vague or ambiguous (e.g., cramps), the study staff will try to obtain clarification by asking a follow-up question (e.g., what kind of cramps?) and record the words the subject used to clarify the event (e.g., menstrual cramps, calf muscle cramps). Additionally, if the subject reports a group of symptoms that the Investigator uses to make a unifying diagnosis, the diagnosis will be recorded instead of the symptoms (e.g., rhinopharyngitis instead of runny nose, cough, sore throat and sneezing). If a diagnosis is unknown, signs and symptoms need to be recorded separately until a diagnosis is determined, at which time the diagnosis will be reported in lieu of the symptoms.

The following information will be captured for each AE: date of onset and resolution, outcome, severity (as defined in Section 8.2.3), seriousness criteria, Investigator's causality assessment for the relatedness of the AE to the investigational drug, action taken with the investigational drug and treatments administered. Any treatment administered as a result of an AE will be recorded on the Concomitant Medication CRF and/or Surgical and Medical Procedure CRF as applicable.

8.2.6 Data and Safety Monitoring Committee

A Data and Safety Monitoring Committee (DSMC) will review laboratory and blood pressure data, all reports of AEs (including deaths from any cause), discontinuations from spironolactone and patiromer/placebo, withdrawals from the study, and other data as described in the DSMC Charter. The DSMC Charter will include a description of the scope of planned reviews. When reviewing data, including individual data, the DSMC may be unblinded to treatment assignment (patiromer or placebo). The DSMC will advise the Steering Committee regarding the need for changes in the conduct of the study as outlined in the DSMC Charter.

8.3 Serious Adverse Events Reporting

8.3.1 SAE Notification

The Investigator has the obligation to report each SAE to Relypsa or designee within **24 hours** of knowledge of the occurrence. Follow-up reports must be submitted in a timely fashion as additional information becomes available. If the Investigator learns of any SAE that occurred

after the Follow-up Period for which there is a reasonable possibility of relatedness to the investigational drugs, that event and subsequent follow-up information must be reported within 24 hours.

Cause of death is required whenever known. If an autopsy was performed, an autopsy report will be provided. If an autopsy was not conducted, a Death Certificate will be provided if obtainable. Death will be reported as an outcome and not as an event.

SAEs must be reported by entering the SAE information into the AE CRF in the EDC system. If the event meets seriousness criteria, SAE reporting via the paper SAE Report Form will also be required. The Investigator must complete a paper copy of SAE report form, scan and e-mail or fax it to the contact provided in the SAE or Pregnancy and Lactation Reporting Form Completion Guidelines. All SAEs should be followed until they are resolved, stabilized or otherwise justified by the Investigator in agreement with Relypsa and all relevant information is compiled.

The SAE Form will be completed with the following information at a minimum:

- Trial number/ trial site
- Name of reporter/Investigator
- Subject identification number
- SAE term
- Date of onset
- Date of outcome or resolution (when medically applicable)
- Outcome
- Criteria of seriousness
- Severity of the event
- Relatedness to patiromer/placebo and spironolactone

Additional information that is medically pertinent to the SAE must be provided when available, or as requested by the Sponsor (hospital Discharge Summary, Autopsy Report/Death Certificate, diagnostic study reports, etc.).

8.3.2 SAE Expedited Reporting

Relypsa will notify all Investigators of all SAEs requiring expedited reporting to Regulatory Authorities.

The Investigator is responsible for notifying the IRB in accordance with local regulations of all SAEs that occur. The Investigator must review and file the safety report with the Investigator's Brochure.

Relypsa is responsible for notifying the applicable Health Authorities of SAEs in accordance with applicable laws and regulations.

8.4 Procedures for Reporting Pregnancy Exposure and Birth Events

Should a female subject become pregnant or be suspected of being pregnant while participating in this study, the investigational product will be permanently discontinued, and the event must be reported to Relypsa upon receipt of information by the study staff. Pregnancies must be reported throughout the conduct of the study including two weeks following the last dose of study drug received. Pregnancy reporting includes exposure of the female partner of a male subject. While pregnancy is not considered an SAE, it must be reported to Relypsa within 24 hours of becoming aware on the Pregnancy Monitoring Form. Pregnancy complications are reported as AEs or SAEs (if applicable). Any pregnancy will be followed through delivery for the observation of any SAEs. Fatalities, elective or spontaneous abortions, congenital abnormalities/birth defects and AEs/SAEs occurring in the newborn must be reported as SAEs. Newborns potentially exposed to study drug via maternal or paternal sources who experience a SAE before, during, or after delivery (including lactation by the maternal subject) will be followed until resolution of the event or for a minimum of 1 year).

9 DATA ANALYSIS / STATISTICAL METHODS

This section briefly describes the planned statistical methods for this study. A Statistical Analysis Plan (SAP) will describe the methods in detail. If there is a difference between the language of this protocol and the language of the SAP, the SAP will take precedence over the protocol.

9.1 Sample Size Determination

This study will randomize approximately 290 subjects, to ensure that at least 280 subjects will be available for the primary analysis. This allows for the possibility that up to 10 subjects are randomized but never take study medication. A sample size of 280 subjects has 90% power to detect a difference between treatment groups of 20% or more in the proportion of subjects remaining on spironolactone at Week 12, at $\alpha = 0.05$.

9.1.1 Interim Analysis

An interim analysis has been planned after approximately 50% of the subjects have completed Week 12 to evaluate the assumptions used to determine the sample size. The DSMC will determine if additional subjects are required to meet the primary endpoint. Relypsa will determine if the protocol will be amended to allow additional subject enrollment. The study will not be stopped early based on the interim analysis.

9.2 Randomization

Eligible subjects will be randomized 1:1 to either spironolactone + patiromer or spironolactone + placebo. The randomization will be stratified by the Visit S4 locally measured potassium at baseline (4.3 to < 4.7 mEq/L or 4.7 to 5.1 mEq/L) and history of Type 1 or 2 diabetes mellitus (Yes or No).

Treatment group assignments will be kept blinded until database lock. The blind will be maintained for subjects, site personnel, and all Relypsa and vendor staff, with the exception of unblinded staff required for the development of the final randomization schedule, for production of unblinded materials for the DSMC, and Relypsa Drug Safety staff in situations where unblinding is necessary to comply with Regulatory requirements. The Relypsa staff who may be unblinded will be identified prior to the start of study enrollment.

The study populations planned for analysis are described below.

- *Safety Population:* The Safety Population consists of all subjects who have received at least one dose of spironolactone, patiromer or placebo.
- *Intent-to-Treat Population (ITT)*: The ITT Population consists of all subjects who have been randomized and have received at least one dose of spironolactone and at least one dose of blinded study medication (patiromer or placebo).
- *Blood Pressure Analysis Population (BPA Population):* The BPA Population consists of all subjects who have non-missing Baseline and Week 12 AOBP-assessed SBP.

Additional study populations may be defined in the SAP if needed.

9.3 General Considerations

Local potassium values will be used for randomization/stratification, titration of the blinded study medication (patiromer/placebo), and discontinuation of spironolactone. Central serum potassium values will be used for the analysis of change in potassium over time.

Subjects will be screened for eligibility at Screening Visits 1 – 4 (S1, S2, S3, and S4). If a subject meets all eligibility criteria at Visits S1 – S4, the subject will be randomized at the S4/Baseline (Day 0) Visit (Appendix A). The subject will take his or her first dose of spironolactone and first dose of blinded study medication (patiromer/placebo) on the day after this visit (Day 1).

Tables will be presented by treatment group and overall, unless otherwise specified in the SAP.

9.4 Subject Disposition

Summaries will be presented for the number and percentage of subjects who were randomized, received study drug, completed Week 12, and participated in the scheduled Follow-up Visit. For subjects who terminated early, a summary of reasons will be provided.

Counts of subjects will be presented for each analysis population, by study site and overall.

A listing of subject disposition will be provided, including membership in each analysis population.

9.5 Demography and Baseline Characteristics

Demographic and baseline characteristics will be summarized for the ITT Population, the Safety Population (if it differs from the ITT Population), and the BPA Population.

Demographic and baseline characteristics to be summarized include, but are not limited to: age, gender, race, ethnicity, vital signs, height, weight and BMI, baseline concomitant medications of special interest, and relevant comorbidities.

Summaries of continuous variables will include the mean, standard deviation (SD), standard error (SE), median, 25th and 75th percentiles, and the maximum and minimum. Summaries of categorical variables will include counts and percentages.

Listings for demographics and baseline characteristics will be provided.

9.6 Efficacy Analyses

9.6.1 Primary Efficacy

The proportion of subjects remaining on spironolactone at Week 12 will be compared between treatment groups (spironolactone/patiromer versus spironolactone/placebo) using the Cochran-Mantel-Haenszel test, stratified by baseline potassium category (4.3 to < 4.7 mEq/L or 4.7 to 5.1 mEq/L). Additionally, a sensitivity analysis will include stratification by study site (small sites will be pooled).

The primary efficacy analysis will be performed using the ITT Population.

Subjects who terminate from the study early or discontinue study spironolactone early, for any reason, will be considered as not having remained on spironolactone.

9.6.2 Secondary Efficacy

The secondary efficacy variable for this study is change from Baseline in AOBP SBP at Week 12 or last available assessment prior to addition of any new BP medications or changes to any baseline BP medications.

The secondary efficacy endpoint will be analyzed using an analysis of covariance (ANCOVA) model, with baseline AOBP SBP as a covariate and baseline serum potassium as a categorical factor (K^+ 4.3 – < 4.7 or 4.7 – 5.1 mEq/L). The analysis will use the ITT Population.

9.6.3 Other Endpoints

Additional end-points will be compared between treatment groups including (please refer to the statistical analysis plan for further information):

- Change in AOBP SBP from Baseline to Week 12
- Potassium levels over time (measured both centrally and locally)

- Proportion of subjects with serum $K^+ \geq 5.5$ mEq/L
- Average daily dose and cumulative dose of spironolactone
- Time to discontinuation of spironolactone
- Change from baseline to Week 12 in albuminuria (ACR)
- EQ-5D-5L questionnaire results at Baseline and at Week 12/ET

Change in AOBP at Week 12 will be analyzed with an ANCOVA model using the BPA Population. Additionally, change at Week 12 will be analyzed using a repeated measures mixed model that will include all ITT subjects with at least one measurement of AOBP SBP at Week 1 or later. Models will include baseline AOBP SBP as a covariate and baseline serum potassium as a categorical factor (K^+ 4.3 – < 4.7 or 4.7 – 5.1 mEq/L).

Potassium levels will be summarized for local and central values at each time point. Counts (%) of subjects who have experienced no potassium measurement ≥ 5.5 mEq/L will be presented at each time point.

Kaplan-Meier methods will be used to analyze the time to discontinuation of spironolactone. Treatment groups will be compared using the log-rank test.

Average daily dose and cumulative dose of spironolactone, and change in albuminuria (ACR) from Baseline to Week 12, will be analyzed using ANCOVA methods.

The EQ-5D-5L questionnaire results will be summarized at Baseline and Week 12/ET.

9.6.4 Subgroups of Interest

Primary and secondary efficacy analyses will be produced for the subgroups specified below. Subgroup analyses will also be done for selected efficacy or safety endpoints, as appropriate.

Subgroups to be analyzed include:

- Gender
- Age < 65 versus ≥ 65 years
- Type 1 or Type 2 diabetes mellitus (presence versus absence at baseline)
- Any additional subgroups of interest will be described in the SAP

9.6.5 Safety Analysis

9.6.5.1 Adverse Events

A treatment-emergent adverse event (TEAE) is defined as any AE that begins or worsens at the time of or after the first dose of any study medication (spironolactone, patiromer, or placebo).

All AEs and serious AEs (SAEs) will be coded using MedDRA (version will be specified in the SAP).

Summaries will be provided by SOC, PT and severity for:

- All TEAEs
- TEAEs related to study medication (separately for spironolactone and for patiromer/placebo)
- TEAEs leading to study medication discontinuation (separately for spironolactone and for patiromer/placebo
- SAEs
- TEAEs of special interest (e.g. allergic reactions, gastrointestinal events, renal events)

A listing of AEs will be provided, to include verbatim term, PT, SOC, severity, relationship to study medications, whether serious, onset/end date, action taken and outcome of event.

9.6.5.2 Deaths

A listing of deaths will be provided.

9.6.5.3 Laboratory Assessments

Laboratory parameters will be summarized at each visit at which the parameter is scheduled to be collected. Summaries will also be provided for the change from baseline at each of these visits.

Tables will be provided to summarize counts and percentages of subjects experiencing clinically significant levels of, or change in, serum potassium (< 3.0, < 3.5, and > 5.1 mEq/L), calcium, magnesium and phosphorus.

Shift tables will be provided for change from baseline to end of treatment in serum potassium, serum calcium, and serum magnesium, and for change in CKD stage as defined by eGFR level.

9.6.5.4 Concomitant Medications

Summaries will be provided of concomitant medication use during the study, by ATC4 and preferred drug name.

9.6.5.5 Vital Signs

Clinic assessments of SBP, DBP, resting heart rate, and weight will be summarized at each scheduled visit at which they are assessed. Summaries will also be provided for change from baseline at each of these visits.

Height is collected only at Screening Visit 1. Height will be provided in the listing of vital signs, but will not otherwise be summarized.

9.7 Handling of Missing Data

Missing central serum potassium laboratory values may be imputed using local laboratory values collected on the same day. Details regarding imputation methods will be provided in the SAP.

Procedures for managing any other missing data will be provided in the SAP.

10 DATA HANDLING AND RECORDKEEPING

Source documents are original documents, data, and records (e.g., case histories, progress notes of the physician, nurses' notes, medical records, hospital records, clinical and office charts, laboratory notes, memoranda, or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, records kept at the pharmacy or laboratories, and subject logs). Source data are contained in source documents and must be adequate to reconstruct all data transcribed onto the eCRFs and to evaluate the study. Examples of source data include clinical findings, observations, enrollment summary information and ICF procedures, assessment of clinical significance for laboratory results, AE severity and seriousness, and Investigator's opinion of AE relatedness to patiromer.

The Investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation for all subjects.

Source documentation should be available at monitoring visits to verify entries made on eCRFs, as needed. Source documentation should also be available for verification by auditors and/or inspectors, as needed.

10.1 Case Report Forms / Electronic Data Record

An eCRF is designed to record all of the protocol-required information to be reported to Relypsa on each trial subject. The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported on subjects' eCRFs. Data reported on the eCRF, which are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. An explanation should be given for all missing data.

All eCRF data and query resolutions must be completed only by the clinical trial personnel designated by the Investigator. All site staff will have proper training prior to accessing the EDC system.

Any change or correction to an eCRF will be tracked via an audit trail within the EDC system. The audit trail will contain the original data value, new data value, date changed, the user who made the change, and the reason(s) for the change.

CRFs should be completed in a timely manner to support the study timeline (i.e., the site should not wait for a monitoring visit before entering data into the eCRF).

Data from the eCRFs and queries will be tracked and entered into a 21 CFR Part 11 compliant clinical database. The database system will be a secured, password-protected system with full audit trail utility.

Subject data will be reviewed via programmed quality checks and manually via data listings review by Relypsa and its designee. Data that appear inconsistent, incomplete, or inaccurate will be queried for site clarification. Data corrections will be updated to the database and tracked in the audit trail. AEs and concomitant medications will be coded using industry standard dictionaries (e.g., Medical Dictionary for Regulatory Activities [MedDRA] and World Health Organization [WHO] Drug dictionary).

The Investigator is responsible for reviewing, verifying, and approving all subject data (i.e., eCRFs and resolved queries).

10.2 Record Retention

The Investigator must maintain adequate records for the study including completed eCRFs, medical records, laboratory reports, signed ICFs, drug disposition records, adverse experience reports, information regarding subjects who discontinued, all correspondence with the IRB/IEC and Relypsa, and other pertinent data.

The Investigator is to retain all records until notified by Relypsa. The Investigator will notify Relypsa in writing of the relocation of any study records away from the research facility after study closure. The Investigator must contact Relypsa in writing prior to the destruction of any study records, or in the event of loss of any study records.

11 QUALITY CONTROL AND QUALITY ASSURANCE

The integrity and quality of subject data will be ensured by providing training and process instructions for the completion of the eCRFs, performing quality control checks, conducting ongoing clinical data review (including medical and safety reviews), and performing source data verification and data reconciliation.

Relypsa employees or designee will conduct site monitoring visits at regular intervals in accordance with FDA and International Conference on Harmonisation (ICH) guidelines. The Investigator will permit Relypsa or designee monitors to review and inspect facilities, and all records relevant to this study.

The Investigator will also permit Relypsa or designee auditors, the IRB/IEC, FDA or other Regulatory Authority inspectors to review and inspect facilities, procedures, and all records relevant to this study. These records include, but are not limited to: subject signed ICFs, source documentation, regulatory and essential documents, CRFs, and drug accountability records. If the FDA or other regulatory agency should schedule an inspection, the Investigator should notify the Medical Monitor immediately.

The following steps will be taken to ensure that the trial is conducted by the investigational site in compliance with the study protocol, Good Clinical Practices (GCP), and other applicable regulatory requirements:

- Investigator meeting and/or Investigator site initiation
- Routine site monitoring
- Documented protocol and GCP training
- eCRF and query review against source documents
- Collection of local laboratory normal ranges

12 ETHICS

The study will be conducted in accordance with US FDA regulations, the ICH E6 guidelines for GCP, the Declaration of Helsinki, and IRB or IEC requirements. The study will also be conducted in accordance with the European Union Clinical Trials Directive 2001/20/EC (EUCTD) for sites in the EU and all other applicable local and national laws and regulations governing the conduct of human clinical studies.

12.1 Institutional Review Board / Independent Ethics Committee

All Investigators participating in this study must be governed under an appropriate IRB or IEC. The applicable IRB or IEC should review and approve this protocol, the ICF, the Investigator's Brochure and any information to be given to the subject before a site can begin conducting any study-related activities. A copy of the IRB/IEC approval letter for the protocol and the ICF must be provided to Relypsa prior to investigational product shipment. The IRB/EC must approve any subject recruitment materials before the material is used for subject recruitment.

Subsequently, the Investigator is responsible for obtaining re-approval by the IRB/IEC annually or more frequently in accordance with the regulatory requirements and policies and procedures established by the IRB/IEC. Copies of the Investigator's annual report and other required reports to the IRB/IEC and copies of the IRB/IEC continuance of approval must be furnished to Relypsa. The Investigator must also inform the IRB/IEC of any protocol changes or amendments, changes to the Investigator's Brochure, expedited reports of SAEs submitted to regulatory authorities, and other significant safety concerns according to the IRB/IEC policy. Written documentation of IRB approval of protocol amendments must be received before the amendment is implemented. After completion or termination of the study, Investigators will notify their IRB/IECs. The Investigator will comply with all IRB/IEC policies throughout the duration of the study.

12.2 Ethical Conduct of the Trial

The Investigator is responsible for assuring that the study is conducted in accordance with current local and national regulations, ICH GCP guidelines, and other applicable requirements governing the conduct of human clinical trials.

The Investigator will not deviate from the protocol without prior written approval from Relypsa, except in medical emergencies. In the event of a medical emergency, the Investigator must notify the Medical Monitor as soon as possible. Any other change to the protocol must be implemented as an amendment to the protocol and must be approved by the IRB/IEC prior to implementation.

The Investigator must inform the governing IRB/IEC of all protocol changes in accordance with the IRB/IEC's established procedure. No deviation from the protocol of any type will be permitted without complying with the established IRB/IEC procedures.

If an Investigator chooses to advertise for subjects, whether in professional or consumer publications, radio, or television, all advertising must be approved by Relypsa and the IRB/IEC prior to initiation.

Financing and insurance are covered in the Clinical Trial Agreement and Clinical Trial Insurance Policy.

12.3 Subject's Information and Informed Consent

Individual subject's medical information obtained as a result of this study is considered confidential and disclosure to unauthorized parties is prohibited. Subject's confidentiality will be assured by utilizing subject identification code numbers and/or initials, instead of names. If results of this study are reported in medical journals or at meetings, the subject's identity will not be disclosed.

With the subject's authorization, medical information may be provided to the subject's personal physician or to other appropriate medical personnel responsible for the subject's welfare.

In compliance with GCP guidelines, all subjects will be informed of the purpose of the research, the possible risks, and their right to withdraw at any time from the study without prejudice and without jeopardy to their future medical care at the center. Each subject must agree to cooperate in all aspects of the study and must give informed written acknowledgment (signed ICF) to the Investigator prior to participation in the study. If the ICF is revised during the study, active subjects must sign the new version in order to continue participating in the study. For any updated or revised ICF, the subject record should state that written informed consent was obtained for the updated/revised consent form for continued participation in the trial. The ICF should be revised whenever there are changes to procedures in the amended protocol associated with procedures in the ICF or when new information becomes available that may affect the willingness of the subject to participate. Every subject will be given a copy of each version of the form that he/she signs before and during the study. In the United States, each ICF may also include authorization allowing the institution, Investigator and Relypsa to use and disclose personal health information in compliance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

No subject is to participate in study activities until informed consent has been obtained. Documentation of the informed consent process and subject information discussion must appear in the subject's medical record, and include a statement that informed consent was obtained prior to participation in the study. Signed acknowledgments (ICFs) must remain in the subjects' files and be available for verification by monitors, auditors, and/or regulatory agency inspectors at any time. The final IRB/IEC-approved ICF must be provided to Relypsa for regulatory purposes.

13 RELYPSA DISCONTINUATION CRITERIA

Based on their data review, the DSMC may provide recommendations to stop the study as per guidance within the DSMC Charter. Relypsa will determine whether the study should be stopped early.

14 PUBLICATION OF TRIAL RESULTS

The Clinical Trial Agreement describes Relypsa's publication terms.

15 REFERENCES

1. Aldactone PI. Aldactone (Spironolactone) [Package Insert], Revised Oct-2014. G.D. Searle LLC, 2008.
2. Bianchi S, Batini V, Bigazzi R. The Renal Effects of Mineralocorticoid Receptor Antagonists. Int J Cardiol, 200, 20-24, 2015.
3. Bolignano D, Palmer SC, Navaneethan SD, Strippoli GF. Aldosterone Antagonists for Preventing the Progression of Chronic Kidney Disease. Cochrane Database Syst Rev, 4, CD007004, 2014.
4. Bomback AS, Klemmer PJ. The Incidence and Implications of Aldosterone Breakthrough. Nat Clin Pract Nephrol, 3[9], 486-492, 2007.
5. Calhoun DA, Jones D, Textor S, et al. Resistant Hypertension: Diagnosis, Evaluation, and Treatment: a Scientific Statement From the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. Circulation, 117[25], e510-e526, 2008.
6. De la Sierra A, Segura J, Banegas JR, et al. Clinical Features of 8295 Patients With Resistant Hypertension Classified on the Basis of Ambulatory Blood Pressure Monitoring. Hypertension, 57[5], 898-902, 2011.
7. Horowitz B, Miskulin D, Zager P. Epidemiology of Hypertension in CKD. Adv Chronic Kidney Dis, 22[2], 88-95, 2015.
8. Judd E, Calhoun DA. Management of Hypertension in CKD: Beyond the Guidelines. Adv Chronic Kidney Dis, 22[2], 116-122, 2015.
9. KDIGO. Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group. KDIGO Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease. Kidney Inter Suppl, 2[5], 337-414, 2012.
10. Khosla N, Kalaitzidis R, Bakris GL. Predictors of Hyperkalemia Risk Following Hypertension Control With Aldosterone Blockade. Am J Nephrol, 30[5], 418-424, 2009.
11. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC Practice Guidelines for the Management of Arterial Hypertension. Eur Heart J, 2013[34], 2159-2219, 2013.
12. Muntner P, Anderson A, Charleston J, et al. Hypertension Awareness, Treatment, and Control in Adults With CKD: Results From the Chronic Renal Insufficiency Cohort (CRIC) Study. Am J Kidney Dis, 55[3], 441-451, 2010.

13. Narayan H, Webb DJ. New Evidence Supporting the Use of Mineralocorticoid Receptor Blockers in Drug-Resistant Hypertension. Curr Hypertens Rep, 18[5], 34, 2016.

14. NKF. KDOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease. Guideline 11: Use of Angiotensin-Converting Enzyme Inhibitors and Angiotensin Recptor Blockers in CKD. 2004 [Accessed on: 6-29-2016]; Available from: URL: http://www2.kidney.org/professionals/KDOQI/guidelines_bp/guide_11.htm.

15. Patiromer for oral suspension. Investigator's Brochure. Relypsa, Inc. Version 9. July 2015.

16. Pitt B, Anker SD, Bushinsky DA, et al. 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. Eur Heart J, 32[7], 820-828, 2011.

17. Robles, N. R. Home Blood Pressure Monitoring, Reproducibility and Prognostic Aspects - Third in Series. 2015 [Accessed on: 7-7-2016]; Available from: URL: https://www.escardio.org/Guidelines-&-Education/Journals-and-publications/ESC-journals-family/E-journal-of-Cardiology-Practice/Volume-13/Home-blood-pressure-monitoring-reproducibility-and-prognostic-aspects-third-i.

18. Rossi GP, Bernini G, Caliumi C, et al. A Prospective Study of the Prevalence of Primary Aldosteronism in 1,125 Hypertensive Patients. J Am Coll Cardiol, 48[11], 2293-2300, 2006.

19. Rossignol P, Massy ZA, Azizi M, et al. The Double Challenge of Resistant Hypertension and Chronic Kidney Disease. Lancet, 386[10003], 1588-1598, 2015.

20. Tamargo J, Solini A, Ruilope LM. Comparison of Agents That Affect Aldosterone Action. Semin Nephrol, 34[3], 285-306, 2014.

21. Tanner RM, Calhoun DA, Bell EK, et al. Prevalence of Apparent Treatment-Resistant Hypertension Among Individuals With CKD. Clin J Am Soc Nephrol, 8[9], 1583-1590, 2013.

22. Vasan RS, Evans JC, Larson MG, et al. Serum Aldosterone and the Incidence of Hypertension in Nonhypertensive Persons. N Engl J Med, 351[1], 33-41, 2004.

23. Veltassa PI. Veltassa (Patiromer) [Package Insert], Revised May-2016. Relypsa, Inc., 2016.

24. 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, 386[10008], 2059-2068, 2015.

25. Wolley MJ, Stowasser M. Resistant Hypertension and Chronic Kidney Disease: a Dangerous Liaison. Curr Hypertens Rep, 18[5], 36, 2016.

Appendix A: Schedule of Events

Study Period	**Screening/Run-in Period**			**Screening/ Randomization**	**Double-Blind Treatment**								**Follow-Up[a]**	**Unscheduled Visit**
Visit/Day/Week	S1	S2	S3	S4/BL(D0)[b]	W1	W2	W3	W4	W6	W8	W10	W12 or ET Visit	2W after W12 or ET Visit	
Window	1 week (≥ 4 d but ≤ 10 d) apart				±3 d	±3 d	±3 d	±3 d	±7 d	±7 d	±7 d	±7 d	+7 d	
Study Activity														
Informed Consent	X													
IWRS Entry	X	X	X	X[c]	X	X	X	X	X	X	X	X	X	X
Inclusion Exclusion Criteria	X			X[d]										
Demographics	X													
Medical History	X													
Heart Rate (resting for 5 minutes)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X													
Weight	X			X[d]								X		X, optional
Physical Examination	X											X		X, optional
12-lead Electrocardiogram	X											X		X, optional
AOBP performed onsite (triplicate measurements)[e]	X	X	X	X	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X	X	X
SMBP performed onsite and HBP training, as necessary (triplicate measurements)[g]	X	X	X	X	X	X	X	X	X	X	X	X		X, if available
SMBP performed at home (triplicate measurements)[h]		X	X	X	X	X	X	X	X	X	X	X		X, if available
Potassium[i]	L&C		L&C	L&C[d]	L[j]&C	L[j]&C	L[j]&C	L[j]&C	L[j]&C	L[j]&C	L[j]&C	L&C	L&C	L&C
Serum Chemistry (including creatinine, eGFR)	C		C	C[d]	C	C	C	C	C	C	C	C	C	C, optional
Hematology	C			C[d]				C				C		C, optional
Serum Pregnancy	C											C		
NT-proBNP				C[d]								C		

Appendix A: Schedule of Events (Cont'd)

Study Period	Screening/Run-in Period			Screening/ Randomization	Double-Blind Treatment								Follow-Up[a]	Unscheduled Visit
Visit/Day/Week	S1	S2	S3	S4/BL(D0)[b]	W1	W2	W3	W4	W6	W8	W10	W12 or ET Visit	2W after W12 or ET Visit	
Window	1 week (≥ 4 d but ≤ 10 d) apart				±3 d	±3 d	±3 d	±3 d	±7 d	±7 d	±7 d	±7 d	+7 d	
Study Activity														
Aldosterone and plasma renin activity				C[d]										
Spironolactone Level					C			C		C		C		
Urinalysis	C			C[d]								C		
24 hr urine collection container (dispense and train)			X											
24 hr urine for sodium, potassium, creatinine, albumin (for ACR)				C[d]										
ACR urine sample collection cups (dispense and train)			X				X		X		X			
Urine ACR (3 first morning void samples)				C[d,k]				C		C		C		
Urine pregnancy test				X[d]										
EQ-5D-5L Questionnaire[l]				X[d]								X		
IWRS Randomization to Patiromer / Placebo				X[d]										
Patiromer/placebo Dispensing[m]				X[d]	X	X	X	X	X	X	X			X, optional
Spironolactone Dispensing[n]				X[d]	X	X	X	X	X	X	X			X, optional
Drug Accountability					X	X	X	X	X	X	X	X		X, optional
Dietary Counselling	X	X	X	X[d]	X	X	X	X	X	X	X	X		X

Appendix A: Schedule of Events (Cont'd)

Study Period	Screening/Run-in Period			Screening/ Randomization	Double-Blind Treatment								Follow-Up[a]	Unscheduled Visit
Visit/Day/Week	S1	S2	S3	S4/BL(D0)[b]	W1	W2	W3	W4	W6	W8	W10	W12 or ET Visit	2W after W12 or ET Visit	
Window	1 week (≥ 4 d but ≤ 10 d) apart				±3 d	±3 d	±3 d	±3 d	±7 d	±7 d	±7 d	±7 d	+7 d	
Study Activity														
AE Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Record Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X

AOBP = automated office blood pressure; ACR = albumin to creatinine ratio; AE = adverse event; BP = blood pressure; C = central laboratory; D (or d) = day; D0 = Day 0; ET = Early Termination Visit; hr = hour; IWRS = Interactive Web Response System; L = local; R = Randomization; S = Screening Visit; SMBP = subject-measured blood pressure.

[a] If a subject completes the Follow-up Visit prior to 2 Weeks, the subject will receive a Follow-up Phone Call at 2 weeks after Week 12 or ET Visit (+ up to 7 days) (Section 6.3.1).

[b] If hemolysis of the local sample is detected or is suspected (see Section 7.1.1), subject is not randomized at S4, and a repeat of the potassium measurement from a separate blood draw will be performed within 1 day. If subject qualifies they will be randomized and this Visit will be the Randomization/Baseline (Day0) Visit. All assessments at S4, aside from the repeat potassium level, will be considered the baseline.

[c] For subjects who meet all inclusion criteria, this Visit becomes the Randomization/Baseline Visit (Day0). For subjects who screen fail at this visit, this is Visit S4.

[d] Assessment or event will occur only if subject meets all inclusion criteria (Section 4.1).

[e] Measured automatically using office device (while unobserved by the study staff) after 5 minutes of quiet seating prior to triplicate measures (Section 7.3.2.2).

[f] Review AOBP results and adjust study medications according to Section 3.1.2 and Appendix C, and Appendix D.

[g] HBP device issued on Visit S1 and measured by subject using their issued HBP device (while unobserved by the study staff) after 5 minutes of quiet seating prior to triplicate measures (Section 7.3.2.2). HBP monitors are collected from subjects at the Visit Week-12.

[h] HBP will be measured by subject twice daily (Section 7.3.2.1) (e.g., at approximately 08:00 hrs and 20:00 hrs) after sitting quietly for at least 5 minutes. The subject will perform triplicate measures, 1 minute apart. HBP training will be performed at the first screening visit and retraining can be performed at any Visit, as needed. HBP monitors are collected from subjects at the Visit Week-12.

[i] If hemolysis of the local sample is detected or is suspected (see Section 7.1.1), the sample must repeated within 1 .day for reassessment of potassium.

[j] Review potassium results and adjust study medications according to Section 3.1.2 and Appendix B.

[k] One of the ACR measurements will be from the 24-hour urine collection (see Section 7.7).

[l] Subjects will complete the EQ-5D-5L questionnaire before study staff performs any clinic or study assessments to avoid biasing the subjects' responses.

[m] On Day1 patiromer/placebo two packets QD will be taken at home with food and at least 3 hours before or 3 hours after other oral medications including spironolactone. See Appendix B for dosing/titration algorithm.

[n] On Day 1 spironolactone (25 mg QD) will be taken at home and increased to 50 mg at Week 3 for subjects with blood pressure ≥ 120 mmHg See Appendix C for dosing instructions.

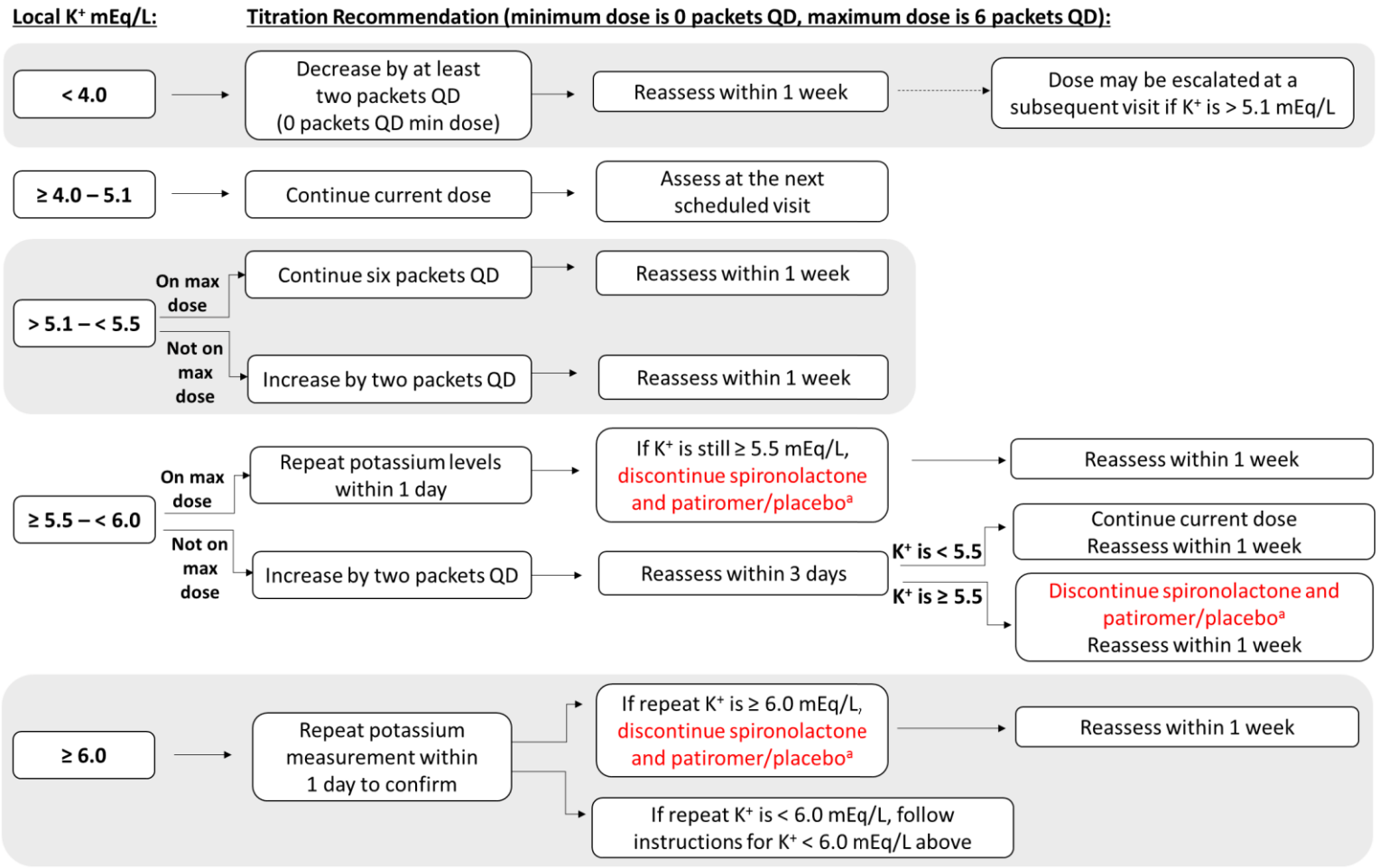
Appendix B: Patiromer/Placebo Titration

Patiromer/placebo will be taken at a starting dose of two packets once daily (QD). Based upon the treatment algorithm, patiromer/placebo will be increased in two-packet per day increments for local $K^+ > 5.1$ mEq/L in intervals of at least 1 week up to a maximum dose of six packets QD. For subjects with $K^+ < 4.0$ mEq/L, patiromer/placebo dose will be decreased by at least two packets. The minimum dose of patiromer/placebo is 0 packets.

Throughout the Double-Blind Treatment Period, subjects who develop $K^+ \geq 5.5$ mEq/L that cannot be managed with blinded patiromer/placebo escalation according to the treatment algorithm (refer to Figure 2) will discontinue spironolactone and patiromer/placebo, but will remain in the study (refer to Appendix C, Spironolactone Dosing) and complete all remaining scheduled visits. After discontinuation of spironolactone and patiromer/placebo, hyperkalemia may be treated using standard of care per the Investigator's judgment.

Figure 2 describes patiromer/placebo dosing adjustments by Visit and level of potassium.

Figure 2: Patiromer/Placebo Titration



K^+ = potassium; max = maximum; QD = once daily.

[a] After discontinuation of spironolactone and patiromer/placebo, hyperkalemia may be treated using standard of care per the Investigator's judgment.

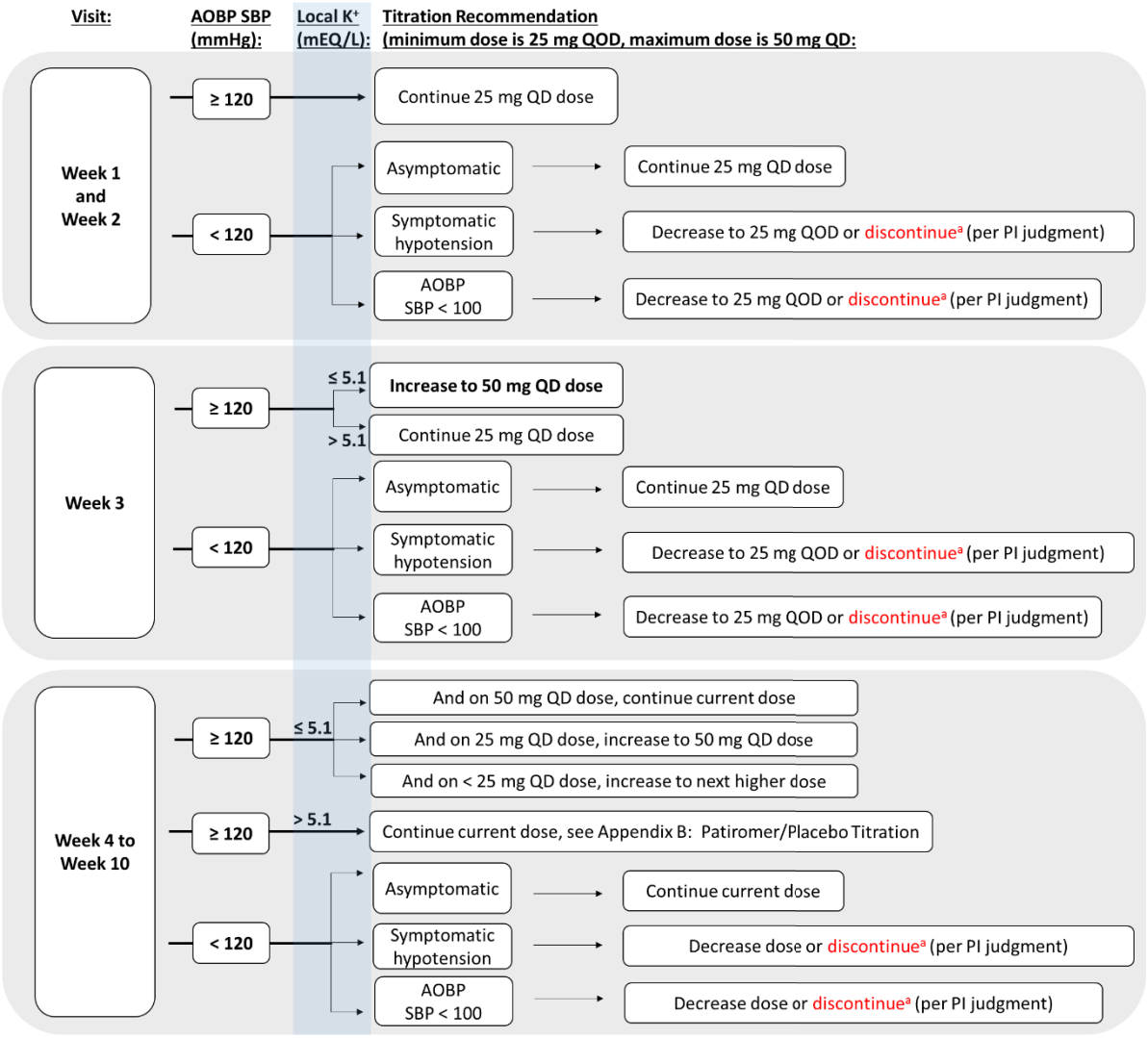
NOTE: All patiromer/placebo dose increases should be made no less than 1 week apart. At Week 12 all study treatments (patiromer/placebo and spironolactone) will be discontinued.

Appendix C: Spironolactone Dosing

Spironolactone will be initiated for all randomized subjects on Day 1, at a dose of 25 mg taken orally QD. At Week 3, for subjects with AOBP SBP ≥ 120 mmHg and K^+ ≤ 5.1 mEq/L, spironolactone will be increased to 50 mg QD. For subjects with K^+ > 5.1 mEq/L, 25 mg daily dose of spironolactone will be continued until the first subsequent visit when K^+ is ≤ 5.1 mEq/L (and AOBP SBP ≥ 120 mmHg), at which time spironolactone will be increased to 50 mg QD.

Subjects with AOBP SBP < 120 mmHg at the Week 3 Visit will continue their 25 mg daily dose, unless symptoms of hypotension are present in which case the spironolactone dose may be reduced to 25 mg every other day or discontinued altogether, at the discretion of the Investigator. Spironolactone may be reduced or discontinued for AOBP SBP < 100 mmHg. If spironolactone is discontinued, patiromer/placebo must be discontinued at the same time. These subjects will remain in the study and be followed per protocol. Note: At any study visit spironolactone dose may be reduced or discontinued for AOBP SBP < 120 mmHg with symptoms of hypotension, or for AOBP SBP < 100 mmHg at the direction of the investigator. Figure 3 describes spironolactone dosing adjustments by Visit and level of SBP (AOBP).

Figure 3: Spironolactone Titration



AOBP = automated office blood pressure; K^+ = potassium; PI = Investigator; QD = once daily; QOD = once every other day; SBP = systolic blood pressure.

[a] If spironolactone is discontinued, patiromer/placebo must be discontinued at the same time. These subjects will remain in the study and be followed per protocol. After study drug discontinuation, the treatment of hypertension should proceed in accordance with the standard of care for BP management and the Investigator's judgment.

NOTE: At Week 12 all subjects will discontinue all study medications (spironolactone and patiromer/placebo).

Changes in Spironolactone Dosing Based on eGFR

Throughout the treatment period, creatinine will be measured at each study visit (and may be measured at Unscheduled Visits). Subjects should be monitored for changes in renal function, especially during periods of medication changes or adjustments. Acute reductions in GFR have been seen with the initiation of spironolactone, similar to those seen with initiation of ACE inhibitors and ARBs that have been attributed to transient changes in glomerular hemodynamics (Bianchi, 2015, KDIGO, 2012). These changes typically do not impact long-term renal function. In this study, use of the KDOQI recommendations for the detection and management of early decrease in GFR (when initiating ACE inhibitors/ARBs) for monitoring the initiation of spironolactone (NKF, 2004) should be considered.

Based on KDOQI guidelines:

- An early decline in GFR is defined as > 15% reduction from baseline within 4 weeks of initiation of spironolactone
- For decreases in eGFR up to 30%, no changes to spironolactone dosing need to be made, and eGFR may be followed routinely
- Decreases in eGFR > 30%, however, should prompt a search for other etiologies of abrupt renal function decline, including prerenal and postrenal causes, toxic reactions, and renal artery disease
- For a decline in eGFR from 30 to 50%, the spironolactone dose should be decreased and the eGFR followed weekly. If the eGFR does not return to within 30% of baseline within 4 weeks, spironolactone should be discontinued
- Spironolactone should be discontinued for a decline in eGFR > 50% and eGFR should be followed at least weekly until eGFR has returned to within 15% of the baseline value, and biweekly thereafter through the end of the study

Appendix D: Blood Pressure Management and Additional BP Medication Suggestions

Prior to addition of new antihypertensive blood pressure medications please consider:

- The degree of blood pressure elevation
- Whether or not the subject is still receiving spironolactone
- The time since last spironolactone dose adjustment
- The level of urgency to lower blood pressure

The following are recommendations, but the investigator's best clinical judgment should guide the final decision. Baseline medication doses should not be changed except for AE-related reasons where changes to baseline medications can be justified by the Investigator (e.g., increases in loop diuretics for new edematous states or discontinuation of baseline medication for drug-related AEs) or for AOBP ≥ 200 mmHg, where possible.

AOBP SBP ≥ 200 mmHg

Baseline antihypertensive medication doses may be increased and new ACE inhibitors or ARB medications may be initiated during the study only for management of AOBP SBP ≥ 200 mmHg (whether or not on spironolactone). These subjects may continue spironolactone if discontinuation reasons (see Appendix B and Appendix C) have not been met, but spironolactone may not be reinitiated if it has been discontinued during the study. Treatment of hypertension in these subjects should be standard of care, in accordance with the clinical judgment of the Investigator.

AOBP SBP ≥ 165 mmHg and < 200 mmHg and Spironolactone has been Discontinued

At any time after spironolactone discontinuation, alternative BP medications may be added to control persistent SBP ≥ 165 mmHg (assessed by AOBP) through the end of the treatment period (Week 12).

Subjects may be treated with additional BP medication (excluding ACE inhibitors and ARBs) selected by the Investigator, according to standard of care practices. Doses of baseline antihypertensive medications may not be increased and spironolactone may not be reinitiated if it has been discontinued during the study.

Baseline antihypertensive medication doses should not be changed except for AE-related reasons where changes to baseline medications can be justified by the Investigator (e.g., increases in loop diuretics for new edematous states or discontinuation of baseline medication for drug-related AEs).

AOBP SBP ≥ 165 mmHg and < 200 mmHg and Spironolactone Ongoing

For subjects on spironolactone 25 mg QD (before Week 3) and $K^+ \leq 5.1$ mEq/L, spironolactone may be increased to 50 mg before the Week 3 visit for persistent SBP ≥ 180 mmHg (assessed by AOBP), at the investigator's discretion.

For subjects on spironolactone 50 mg QD (for most subjects will usually be after Week 3) or on spironolactone < 50 mg QD and $K^+ > 5.1$ mEq/L, additional BP medication may be added to control persistent SBP ≥ 165 mmHg (assessed by AOBP) at the discretion of the investigator. This decision may reflect the degree of blood pressure elevation, the time since last spironolactone dose adjustment and the level of urgency to lower blood pressure, in the investigator's judgment. Baseline medication doses should not be changed except for AE-related reasons where changes to baseline medications can be justified by the Investigator (e.g., increases in loop diuretics for new edematous states or discontinuation of baseline medication for drug-related AEs.

Suggestions for BP medications which may be added are listed below (Rossignol, 2015):

- β blockers, preferably one with an hepatic elimination route (i.e., metoprolol, carvedilol, nebivolol, and propranolol) to avoid drug accumulation, which could lead to an increased risk of bradyarrhythmias
- α blockers (e.g., doxazosin)
- Centrally acting α agonists that do not require dose adjustments (e.g., clonidine)
- Direct vasodilators (i.e., hydralazine or minoxidil) may sometimes be used, but could induce severe fluid retention and tachycardia (especially minoxidil, which has other side effects such as hirsutism and pericardial effusion).

Appendix E: List of Central Laboratory Assays

Serum Chemistry Panel:	**Hematology:**
Alanine aminotransferase	White blood cell count (WBC)
Albumin	Red blood cell count
Alkaline phosphatase	Hemoglobin
Amylase	Hematocrit (Packed Cell Volume)
Aspartate aminotransferase	Mean cell volume
Bicarbonate	Mean cell hemoglobin
Bilirubin (total)	Mean cell hemoglobin concentration
Blood Urea Nitrogen	Platelet count
Calcium	Differential WBC
Creatine kinase	**Urine:**
Creatinine (with eGFR)	Specific gravity
Glucose	pH
Inorganic phosphate	Protein
Iron	Glucose
Lactate dehydrogenase	Creatinine
Magnesium	Ketones
Potassium	Blood
Sodium	Urobilinogen
Total cholesterol	Leukocytes
Total protein	Leukocyte esterase
Uric acid	Nitrites
Other:	Bilirubin
Serum pregnancy	24-hour urine collection for sodium, creatinine, albumin (for ACR)
NT-proBNP	Spot urine for albumin and creatinine (for ACR)
Aldosterone and plasma renin activity	Urine pregnancy
Spironolactone level	