Clinical Study Protocol

Title:	A Multicenter, Double-blind, Placebo-controlled, Randomized Withdrawal, Parallel Group Study of Patiromer for the Management of Hyperkalemia in Subjects Receiving Renin-Angiotensin-Aldosterone System Inhibitor (RAASi) Medications for the Treatment of Heart Failure (DIAMOND)
Clinical Protocol Number:	PAT-CR-302
Version Date:	23 June 2021
Version Number:	4.0
Prior Version/ Amendments:	Version 1.0, 14 September 2018 Version 1.1, 26 February 2019 Version 1.2 (UK only), 28 November 2019 Version 1.3 (Germany only), 24 January 2020 Version 1.4 (Germany only), 8 July 2020 Version 2.0, 19 October 2020 Version 3.0, 9 April 2021 (FDA only, not implemented)
Phase:	Phase 3b
Investigational Drug:	Patiromer for Oral Suspension (Veltassa®)
IND Number:	075615
EudraCT Number:	2018-005030-38
Sponsor Contact:	Peter Szecsödy, MD VP Global Clinical Development [redacted]
Sponsor Address:	Vifor Pharma, Inc. 200 Cardinal Way Redwood City, CA 94063, USA [redacted]

SIGNATURE PAGE

Declaration of Sponsor

Title: A Multicenter, Double-blind, Placebo-controlled, Randomized Withdrawal, Parallel Group Study of Patiromer for the Management of Hyperkalemia in Subjects Receiving Renin-Angiotensin-Aldosterone System Inhibitor (RAASi) Medications for the Treatment of Heart Failure (DIAMOND)

Clinical Protocol Number: PAT-CR-302

Version/Amendment Number/Date: Version 4.0, 23 June 2021

This study protocol was subject to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational product, as well as with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline for Good Clinical Practice as amended.

Sponsor Medical Expert Peter Szecsödy, MD VP Global Clinical Development Vifor Pharma Ltd. [redacted] Vifor Pharma, Inc. 200 Cardinal Way Redwood City, CA 94063 USA	Date (day month year)

EXECUTIVE SUMMARY OF CHANGES (PROTOCOL AMENDMENT VERSION 3.0 TO 4.0)

The study design was updated to reflect strategic changes made by the Sponsor in collaboration with the study Executive Steering Committee.

- The following changes proposed in Protocol Amendment Version 3.0, which were never implemented, have been reverted to the prior wording as per Protocol Amendment Version 2.0. All other minor changes have been kept:
  - Inclusion Criterion 6 has been reverted to the prior wording as in Protocol Amendment 2.0.
  - Inclusion Criterion 7 has been reverted to the prior wording as in Protocol Amendment 2.0.
  - Exclusion Criterion 20 was added in Protocol Amendment 3.0; in the current Protocol Amendment 4.0, Exclusion Criterion 20 has been removed.
  - Randomization Criterion 1 has been reverted to the prior wording as in Protocol Amendment 2.0.
- The objective of the study was updated to assess the effects of patiromer compared with placebo on serum potassium (K^+) in heart failure (HF) patients.
  - Primary endpoint was changed to:
    - Changes in serum K^+ levels from Baseline
  - Key secondary endpoints (hierarchically ordered) were changed to:
    1. Hyperkalemia events with a serum K^+ value >5.5 mEq/L
    2. Durable enablement to stay on the MRA target dose (as assessed by the between treatment group difference of the cumulative frequency of patients not staying on the target dose)
    3. Investigator-reported events of hyperkalemia (first and recurrent events)
    4. Hyperkalemia-related hard outcome endpoints (Win Ratio)
       a. Time to cardiovascular (CV) death
       b. Total number of CV hospitalizations
       c. Total number of hyperkalemia toxicity events with serum K^+ >6.5 mEq/L

d. Total number of hyperkalemia events with serum K+ >6.0-6.5 mEq/L

e. Total number of hyperkalemia events with serum K^+ >5.0 mEq/L

5. RAASi Use Score (Win Ratio)

a. All-cause death

b. Occurrence of a CV hospitalization

c. HF medication use and dose for i) an angiotensin-converting enzyme inhibitor (ACEi)/angiotensin II receptor blocker (ARB)/angiotensin receptor/neprilysin inhibitor (ARNi), ii) an MRA, and iii) a beta-blocker

- The following endpoints were added as Other Secondary Endpoints:
  - Durable enablement to stay on the target dose of ACEi/ARB or ARNi
  - Durable hyperkalemia-free enablement to stay on the MRA target dose
  - Total number of hyperkalemia toxicity events with serum K^+ >6.5 mEq/L
  - Total number of hyperkalemia events with serum K^+ >6.0-6.5 mEq/L
  - Total number of other hyperkalemia events with serum K^+ >5.0 mEq/L
- The following were added as Other Endpoints:
  - CV death
  - First and recurrent CV hospitalizations
  - First and recurrent HF hospitalizations (or equivalent in outpatient clinic)
  - Time to first occurrence of HF hospitalization (or equivalent in outpatient clinic)
  - Changes in serum K^+ from Baseline to individual visits
- The following endpoints were moved from Primary or Secondary to Other Endpoints:
  - Proportion of subjects on ≥50% of target dose of ACEi, ARB, or ARNi and ≥50% of target dose of MRA at the End of Study (EoS) Visit
  - Total HF hospitalizations (or equivalent in outpatient clinic)
  - Kansas City Cardiomyopathy Questionnaire (KCCQ) – changes in overall summary score (OSS), clinical summary score (CSS), and total symptom score (TSS) (combined with earlier endpoints)

- The following safety endpoint was changed:
  - Laboratory parameters other than those defined as efficacy endpoints

For the full list of changes see Section 19.

INVESTIGATOR AGREEMENT AND SIGNATURE PAGE

Title: A Multicenter, Double-blind, Placebo-controlled, Randomized Withdrawal, Parallel Group Study of Patiromer for the Management of Hyperkalemia in Subjects Receiving Renin-Angiotensin-Aldosterone System Inhibitor (RAASi) Medications for the Treatment of Heart Failure (DIAMOND)

Clinical Protocol Number: PAT-CR-302

Version/Amendment Number/Date: Version 4.0, 23 June 2021

I have read the attached protocol as specified on this page and agree to abide by all provisions set forth therein.

I agree to comply with the current International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guideline for Good Clinical Practice as amended, and applicable local regulations and guidelines.

I agree to ensure that financial disclosure statements will be completed by:

- Me (including, if applicable, my spouse (or legal partner) and dependent children)
- My Sub-investigators

before the start of the study and to report any changes that affect my financial disclosure status for up to 1 year after the study is completed.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

Signature by the Investigator on this Protocol Signature Page documents review, agreement and approval of the requirements contained within this protocol.

Signature of Principal Investigator	Date (day month year)

Name, Title, Address, Telephone Number and Email of Principal Investigator

SYNOPSIS

Protocol Number PAT-CR-302

Title:	A Multicenter, Double-blind, Placebo-controlled, Randomized Withdrawal, Parallel Group Study of Patiromer for the Management of Hyperkalemia in Subjects Receiving Renin-Angiotensin-Aldosterone System Inhibitor (RAASi) Medications for the Treatment of Heart Failure
Short Title:	DIAMOND
Study Product(s):	Patiromer (RLY5016) and placebo
Study Population:	Subjects with HF with reduced ejection fraction (HFrEF) who are hyperkalemic (serum K^+ >5.0 mEq/L) while receiving treatment with RAASi medications or who are normokalemic (serum K^+ ≥4.0–≤5.0 mEq/L) but have a history of hyperkalemia prior to Screening with subsequent reduction or discontinuation of a RAASi medication.
Phase:	Phase 3b
Sponsor:	Vifor Pharma, Inc.
Protocol Number:	PAT-CR-302
Objectives:	Primary Objective: To assess the effects of patiromer compared with placebo on serum K^+ in HF patients.
Design:	Prospective Phase 3b multinational, multicenter, double-blind, placebo-controlled, randomized withdrawal, parallel group study that includes Screening, an up to 12 weeks Run-in Phase (all subjects will have patiromer initiated and RAASi medications, including MRA, optimized) and a randomized withdrawal Blinded Treatment Phase.
Duration:	Each subject's participation includes a Run-in Phase (single-blinded, up to 12 weeks) followed by the Treatment Phase (double-blinded, variable per subject). Study duration for individual subjects will vary, depending on their individual enrollment date. Subjects who prematurely discontinue patiromer/placebo will remain in the study for the collection of clinical events data, up to and including the common EoS, and will receive usual care during the study phase.
Study Treatments:	Patiromer or Placebo: During the Run-in Phase, subjects who meet all eligibility criteria will initiate patiromer, single-blinded, at an oral dose of 1 packet/day (8.4 g/day). The dose will be adjusted based on local serum K^+ levels in accordance with the patiromer treatment algorithm (see Section 6.7.1.1). During the Treatment Phase (double-blinded), subjects will be randomized to receive patiromer or placebo and will initially continue on the same number of packets as established for patiromer during the Run-in Phase but may be up- or down-titrated depending on local serum K^+ levels (see Treatment Phase and Section 6.7.1.2).

HF Treatments:	**RAAS Inhibitors:** Since subjects who enter this study will either have hyperkalemia or a previous history of hyperkalemia due to the use of RAASi medications, the Run-in Phase is intended for the management of serum K^+ with patiromer to allow optimization of RAASi HF treatments (i.e., ACEi/ARB or ARNi and MRA (spironolactone or eplerenone)). The Investigator should evaluate the RAASi treatment(s) that subjects are receiving for HF against recommendations from professional society HF guidelines and make adjustments in accordance with guideline recommendations; see Study Manual for additional details on guideline recommendations and the study-specific target doses [1]. For a subject to be eligible for randomization into the Treatment Phase, the subject must be on ≥50% of the target dose of an ACEi/ARB/ARNi, and ≥50% of the target dose of MRA (spironolactone or eplerenone only, see Study Manual [1] for information on the study-specific target dose of individual RAASi medications and Section 6.7.2). During the Treatment Phase, subjects randomized to either patiromer or placebo will initially continue on the doses of RAASi medications (ACEi/ARB/ARNi and/or MRA) optimized during the Run-in Phase (see the Procedures section below and Section 6.7.1.2 in the protocol for details on the management of hyperkalemia during this period). **Usual Care:** Whether subjects are treated with patiromer or placebo during the Blinded Treatment Phase, usual care in accordance with guideline recommendations will be provided for all subjects. Usual care includes recommendations for all aspects of care for HFrEF patients (i.e., dietary and exercise recommendations, implantable devices, and procedures and medications for the management of HF). Usual care may also include patient education. See Section 6.8.4 for additional details regarding concomitant medication use. **Management of K^+:** Serum K^+ levels will be monitored and managed throughout the study. The management of K^+ is different during the Run-in Phase from the Treatment Phase. Urgent treatment of hyperkalemia is in accordance with usual care and the Investigator's judgment. See Procedures section of the synopsis for further details.
Inclusion Criteria:	The following criteria must be met for each subject prior to entry into the Run-in Phase: 1. Subject provides written informed consent prior to study participation. 2. Age at least 18 years or greater. 3. Current New York Heart Association (NYHA) Class II–IV. 4. Left ventricular ejection fraction ≤40%, measured by any echocardiographic, radionuclide, magnetic resonance imaging (MRI), angiographic, or computerized tomography method in the last 12 months (without subsequent measured ejection fraction >40% during this interval). 5. Receiving any dose of a beta-blocker for the treatment of HF or unable to tolerate beta-blocker (reason documented). 6. eGFR ≥30 mL/min/1.73 m^2 at Screening (based on a single local laboratory analysis of serum creatinine and calculation using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation; see Section 9.2).

	7. Hyperkalemia at Screening (defined by 2 local serum K^+ values of >5.0 mEq/L, each obtained from a separate venipuncture, e.g., one in each arm or 2 separate venipunctures in the same arm) while receiving ACEi/ARB/ARNi, and/or MRA, OR Normokalemia at Screening (defined by 2 local serum K^+ ≥4.0–≤5.0 mEq/L each obtained from a separate venipuncture, e.g., one in each arm or two separate venipunctures in the same arm) with a history of hyperkalemia documented by a usual care serum K^+ measurement >5.0 mEq/L while on RAASi treatment in the 12 months prior to Screening leading to a subsequent and permanent dose decrease or discontinuation of one or more RAASi medications. 8. Females of child-bearing potential must be non-lactating, must have a negative pregnancy test at Screening, and must agree to continue using contraception (see Section 9.8) throughout the study and for 4 weeks after study completion. 9. With hospitalization for HF or equivalent (e.g., emergency room or outpatient visit for worsening HF during which the subject received intravenous medications for the treatment of HF) within the last 12 months before Screening. a) Without atrial fibrillation at Screening, brain natriuretic peptide (BNP*) level must be greater than 150 pcg/mL (18 pmol/L) or N-terminal pro b-type BNP (NT-proBNP) must be greater than 600 pcg/mL (71 pmol/L) b) With atrial fibrillation at Screening, BNP* level must be greater than 300 pcg/mL (35 pmol/L) or NT-proBNP must be greater than 1,200 pcg/mL (142 pmol/L) OR Without hospitalization for HF or equivalent (e.g., emergency room or outpatient visit for worsening HF during which the subject received intravenous medications for the treatment of HF) within the last 12 months before Screening. a) Without atrial fibrillation at Screening, BNP* level must be greater than 300 pcg/mL (35 pmol/L) or NT-proBNP must be greater than 1,200 pcg/mL (142 pmol/L). b) With atrial fibrillation at Screening, BNP* level must be greater than 600 pcg/mL (71 pmol/L) or NT-proBNP must be greater than 2,400 pcg/mL (284 pmol/L). *For subjects treated with ARNi (sacubitril/valsartan) in the previous 4 weeks before Screening, only NT-proBNP values are to be considered. Note: The following table provides the same information of Inclusion Criterion 9 as described above.

	BNP and NT-proBNP Threshold Levels (Based on Local Laboratory), Comorbidities, and Previous Hospitalizations

	Subjects with hospitalization for HF or equivalent[1] within last 12 months	**Subjects with no hospitalization for HF or equivalent[1] within last 12 months**
Subjects presenting without atrial fibrillation when the blood sample was collected	BNP[2] >150 pcg/mL (18 pmol/L) or NT-proBNP >600 pcg/mL (71 pmol/L)	BNP[2] >300 pcg/mL (35 pmol/L) or NT-proBNP >1,200 pcg/mL (142 pmol/L)
Subjects presenting with atrial fibrillation when the blood sample was collected	BNP[2] >300 pcg/mL (35 pmol/L) or NT-proBNP >1,200 pcg/mL (142 pmol/L)	BNP[2] >600 pcg/mL (71 pmol/L) or NT-proBNP >2,400 pcg/mL (284 pmol/L)

1 E.g., emergency room or outpatient visit for worsening HF during which the subject received intravenous medications for the treatment of HF.
2 For subjects treated with ARNi (sacubitril/valsartan) in the previous 4 weeks before Screening only NT-proBNP values are to be considered.
Notes: ARNi=Angiotensin receptor/neprilysin inhibitor; BNP=Brain natriuretic peptide; HF=Heart failure; NT-proBNP=N-terminal pro b-type brain natriuretic peptide.

Exclusion Criteria:

Subjects who meet any of the following criteria during Screening will be excluded:

1. Current acute decompensated HF within 4 weeks before Screening. Subjects with a discharge from a hospitalization for acute decompensation of HF longer than 4 weeks before Screening may be included.
2. Symptomatic hypotension or systolic blood pressure <90 mmHg.
3. Significant primary aortic or mitral valvular heart disease (except secondary mitral regurgitation due to left ventricular dilatation).
4. Heart transplantation or planned heart transplantation (i.e., currently on a heart transplant waiting list) during the study period.
5. Diagnosis of peripartum or chemotherapy-induced cardiomyopathy or acute myocarditis in the previous 12 months.
6. Implantation of a cardiac resynchronization therapy device in the previous 4 weeks before Screening.
7. Restrictive, constrictive, hypertrophic, or obstructive cardiomyopathy.
8. Untreated ventricular arrhythmia with syncope in the previous 4 weeks.
9. History of, or current diagnosis of, a severe swallowing disorder, moderate-to-severe gastroparesis, or major gastrointestinal (GI) surgery (e.g., bariatric surgery or large bowel resection).
10. A major CV event within 4 weeks prior to Screening, including acute myocardial infarction, stroke (or transient ischemic attack), a life-threatening atrial or ventricular arrhythmia, or resuscitated cardiac arrest.
11. Note: This exclusion criterion is included in the new Inclusion Criterion 9.
12. Liver enzymes (alanine aminotransferase, aspartate aminotransferase) >5 times upper limit of normal at Screening based on the local laboratory.

	13. Diagnosis or treatment of a malignancy in the past 2 years, excluding non-melanoma skin cancer and carcinoma in situ of the cervix, prostate cancer with Gleason score <7, or a condition highly likely to transform into a malignancy during the study. 14. Presence of any condition (e.g., drug/alcohol abuse; acute illness), in the opinion of the Investigator, that places the subject at undue risk, or prevents complete participation in the trial procedures, or potentially jeopardizes the quality of the study data. 15. Use of any investigational product for an unapproved indication within 4 weeks prior to Screening or currently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study. 16. Known hypersensitivity to patiromer (RLY5016) or its components. 17. Note: This exclusion criterion is modified and partially incorporated in the Exclusion Criterion 18. 18. Subjects currently being treated with or having taken any one of the following medications in the 7 days prior to Screening: sodium or calcium polystyrene sulfonate or sodium zirconium cyclosilicate, or patiromer. 19. An employee, spouse, or family member of the Sponsor (Vifor Pharma), investigational site or the Contract Research Organization (CRO).
Randomization Criteria:	The following randomization criteria must be met during the up to 12-week Run-in Phase to be randomized into the Treatment Phase: 1. Current MRA dose is at least the target dose* (e.g., spironolactone 50 mg/day, eplerenone 50 mg/day) and has been stable for at least 1 week. 2. Current ACEi/ARB/ARNi is ≥50% of the target dose* and has been stable for at least 1 week. 3. Current patiromer dose is at least 1 packet daily. 4. Current local serum K^+ level is ≥4.0–≤5.0 mEq/L. * Study-specific target doses as per Table 4 in the Study Manual.
Primary and Secondary Endpoints:	Primary Endpoint: • Changes in serum K^+ levels from Baseline Key Secondary Endpoints (Hierarchically Ordered): 1. Hyperkalemia events with a serum K^+ value >5.5 mEq/L. 2. Durable enablement to stay on the MRA target dose (of 50 mg daily spironolactone or eplerenone, respectively) as assessed by the between treatment group difference of the cumulative frequency of patients not staying on that target dose. Note: Discontinuation of the target dose for at least 14 days (or less if at the EoS) is required to confirm this endpoint. 3. Investigator reported events of hyperkalemia (first and recurrent events). 4. Hyperkalemia-related hard outcomes endpoints (Win Ratio). a. Time to CV death

b. Total number of CV hospitalizations

c. Total number of hyperkalemia toxicity events with serum K+ >6.5 mEq/L

d. Total number of hyperkalemia events with serum K+ >6.0-6.5 mEq/L

e. Total number of hyperkalemia events with serum K^+ >5.0 mEq/L

5. RAASi Use Score (Win Ratio).

   Note: This score (of 0–8 points) will be analyzed at the respective time points for each subject in each comparison, and it consists of the following components:

   a. All-cause death

   b. Occurrence of a CV hospitalization

   c. HF medication use and dose for i) an ACEi/ARB/ARNi, ii) an MRA, and iii) a beta-blocker

<u>Other Secondary Endpoints:</u>

- Durable enablement to stay on the target dose of ACE/ARB/ARNi

  Note: Discontinuation of the target dose for at least 14 days (or less if at the EoS) is required to confirm this endpoint

- Durable hyperkalemia-free enablement to stay on the MRA target dose (days on 50mg MRA without presence of hyperkalemia)
- Total number of hyperkalemia toxicity events with serum K^+ >6.5 mEq/L
- Total number of hyperkalemia events with serum K^+ >6.0-6.5 mEq/L
- Emergency treatment for hyperkalemia (hospitalization or emergency room)
- Total number of hyperkalemia events with serum K^+ >5.0 mEq/L
- KCCQ questionnaire, changes in OSS, CSS and TSS
- Investigator reported events of hyperkalemia (first events)
- Proportion of subjects on ≥50% of target dose of ACEi, ARB, or ARNi and ≥50% of target dose of MRA at the EoS Visit
- Time to first occurrence of CV death or CV hospitalization

<u>Other Endpoints:</u>

- CV death
- First and recurrent CV hospitalizations
- First and recurrent HF hospitalizations (or equivalent in outpatient clinic)
- Patient-reported outcome: EQ-5D-5L questionnaire
- Proportion of subjects on any dose of MRA at the EoS Visit
- Proportion of subjects on any dose of ACEi, ARB, or ARNi at the EoS Visit
- Change in proteinuria from Screening
- Change in NT-proBNP from Screening
- Change in high sensitivity troponin from Baseline

	• Functional status by NYHA class • 30-day HF re-hospitalization after a prior HF hospitalization • Health Economics and Outcomes Research (HEOR) analyses • Changes in serum K^+ from Baseline to individual visits <u>Safety Endpoints:</u> • Adverse events (AEs), including all-cause mortality • All-cause mortality • Slope of eGFR change during the study • Decline in eGFR >50% or end-stage renal disease (ESRD), renal death, or need for dialysis • Laboratory parameters other than those defined as efficacy endpoints
Procedures:	See Study Schema for an overview of the study design. The study consists of: • Screening Phase (the Screening Phase may last up to 10 calendar days) • Run-in Phase (single-blinded), up to 12 weeks; weekly visits recommended but are at the Investigator's discretion • Treatment Phase (double-blinded); the scheduled visits are listed below: – Day 1/Baseline – Day 3 (±1 day) – Week 1 (±3 days) – Week 2 (±3 days) – Week 6 (±14 days) – Week 18 (-30 days), first Every 3 Months visit – Visits every 3 months (-30 days) thereafter through the end of the study – EoS Visit • Potassium Assessment Visit (occurs within 2 weeks after patiromer/placebo is discontinued) Note: Subjects who prematurely discontinue patiromer/placebo during the Blinded Treatment Phase remain in the study. • Follow-up Phone Call (at least 2 weeks after the EoS for the assessment of safety; for subjects who discontinue patiromer at the EoS Visit, and attend the Potassium Assessment Visit 2 weeks later, a Follow-up Phone Call will not be needed) • Unscheduled Visit (during the Treatment Period, anytime there are changes to ACEi, ARB, ARNi and/or MRA dose or interventions for serum K^+ outside the desired range, additional Unscheduled Visits should occur weekly until the ACEi, ARB, ARNi and/or MRA dose or serum K^+ has been stable for at least 2 consecutive visits)

Screening Phase and Run-in Phase (Single-Blinded, Up to 12 Weeks):

At the end of the Screening Phase, subjects who satisfy the eligibility criteria will be enrolled into the Run-in Phase. The purpose of the Run-in Phase is to select subjects who will potentially benefit from treatment and not unnecessarily expose those who will not. In addition, the Run-in Phase is for management of serum K^+ with patiromer to allow optimization of RAASi medications and their dosage (including initiation of MRA if not already receiving an MRA).

All subjects who meet the eligibility criteria for the Run-in Phase (single-blinded) will initiate patiromer (1 packet/day).

Subjects with 2 screening K^+ values >5.0 mEq/L are considered hyperkalemic; these subjects begin patiromer when they qualify for the Run-in Phase, i.e., on the same day Run-in qualification is met or the next day.

Note: If one screening K^+ value is >5.0 mEq/L and one value is ≤5.0 mEq/L, then a third peripheral venipuncture is performed within 1 day to obtain clarity, whether subject is hyperkalemic or normokalemic (local serum K^+ ≥4.0-≤5.0 mEq/L).

All other subjects are considered normokalemic and serum K^+ will be measured again latest after the first week during the Run-in Phase. Patiromer will be started at this first Run-in Visit only if subjects are still normokalemic or have progressed to hyperkalemia; in case of newly observed hypokalemia (local serum K^+ <4.0 mEq/L) during the first Run-in Week, patiromer must not be given. In subjects with hypokalemia serum K^+ must be controlled after 3 days.

During the first week of the Run-in Phase, ACEi/ARB/ARNi and/or MRA doses ideally remain unchanged, if clinically indicated. On or after the Run-in Week 1 Visit, up-titration of ACEi/ARB/ARNi and/or MRA may be initiated.

Patiromer is titrated during the Run-in Phase to achieve target local serum K^+ level of ≥4.0–≤5.0 mEq/L (see below).

Note: Depending on the actual local serum K^+ value this could include patiromer 0 g/day (i.e., 0 packets/day) during the Run-in Phase.

- If local serum K^+ is >5.0 mEq/L, up-titrate patiromer in at least (≥) 1-week intervals by 1 packet/day (maximum dose is 3 packets/day)
  - If subject is taking maximum dose patiromer (3 packets/day) and local serum K^+ remains >5.0 mEq/L during the Run-in Phase, then subject is Run-in failed
- If local serum K^+ is >5.0–≤5.5 mEq/L and the reduction in serum K^+ from the previous visit was ≥0.4 mEq/L, at the Investigator's discretion, a dose increase of patiromer may not be required
- If local serum K^+ is ≥4.3–≤5.0 mEq/L at the first week during the Run-in Phase, patiromer must be started at 1 packet/day
- If local serum K^+ is ≥4.0–<4.3 mEq/L at the first week during the Run-in Phase, patiromer may be started at 1 packet/day; initiation or increase of patiromer dose should be made with caution when local serum K^+ is ≥4.0–<4.3 mEq/L to avoid inducing hypokalemia
- If local serum K^+ decreases from >4.3 mEq/L to values <4.3 mEq/L, remaining ≥4.0 mEq/L, patiromer may be down-titrated by 1 packet/day (minimum dose is 0 packets/day); in case of a reversal of this decrease from <4.3 mEq/L but

remaining ≥4.0 mEq/L to values ≥4.3 mEq/L at following visits, patiromer may be up-titrated by 1 packet/day; subjects must receive at least 1 packet/day at serum K^+ ≥4.3–≤5.0 mEq/L

  - If 1 week after reducing patiromer to 0 packets/day local serum K^+ remains stable ≥4.0–≤4.3 mEq/L, optimize RAASi dose and resume patiromer at 1 packet/day before considering these subjects as Run-in failed; initiation or increase of patiromer dose should be made with caution when local serum K^+ is ≥4.0–≤4.3 mEq/L to avoid inducing hypokalemia

- If local serum K^+ is <4.0 mEq/L, patiromer must be down-titrated to 0 g/day (i.e., 0 packets/day), with confirmation of hypokalemia within 3 days and follow-up in at least 1-week intervals until serum K^+ is ≥4.0 mEq/L. Resume patiromer only when local serum K^+ rises to >5.0 mEq/L

  - If 2 weeks after taking the minimum 0 packets/day, local serum K^+ remains <4.0 mEq/L during the Run-in Phase, then subject is Run-in failed

Optimization of ACEi/ARB/ARNi or MRA During Run-in Phase:

The Investigator should manage ACEi/ARB/ARNi or MRA dose initiation, escalation and maintenance with the aim to achieve 100% of target doses as per the Study Manual, using clinical judgment to customize ACEi/ARB/ARNi or MRA addition or dose escalation based on subject response; see Section 6.7.2, Section 6.8.2, and Study Manual [1] for a summary of practice guideline recommendations.

Initiation or escalation of ACEi/ARB/ARNi or MRA dose should be made with caution when local serum K^+ is >5.0 mEq/L. Assessment of serum K^+ will occur at each visit. The patiromer dose is titrated based on the subject's K^+ level as presented above.

Subjects may be randomized anytime (but no later than 12 weeks) during the Run-in Phase when they meet all of the following randomization criteria:

- Current MRA dose is at least the target dose* (e.g., spironolactone 50 mg/day, eplerenone 50 mg/day) and has been stable for at least 1 week
- Current ACEi/ARB/ARNi is ≥50% of the target dose* and has been stable for at least 1 week
- Current patiromer dose is at least 1 packet daily

Current local serum K^+ level is ≥4.0–≤5.0 mEq/L

* Study-specific target doses as per Table 4 in the Study Manual.

Subjects are Run-in failed from the study if:

- After completing 12 weeks of Run-in do not meet the randomization criteria
- 1 week after taking the maximum 3 packets/day dose of patiromer, local serum K^+ remains >5.0 mEq/L
- 2 weeks after taking the minimum 0 packets/day, local serum K^+ remains <4.0 mEq/L

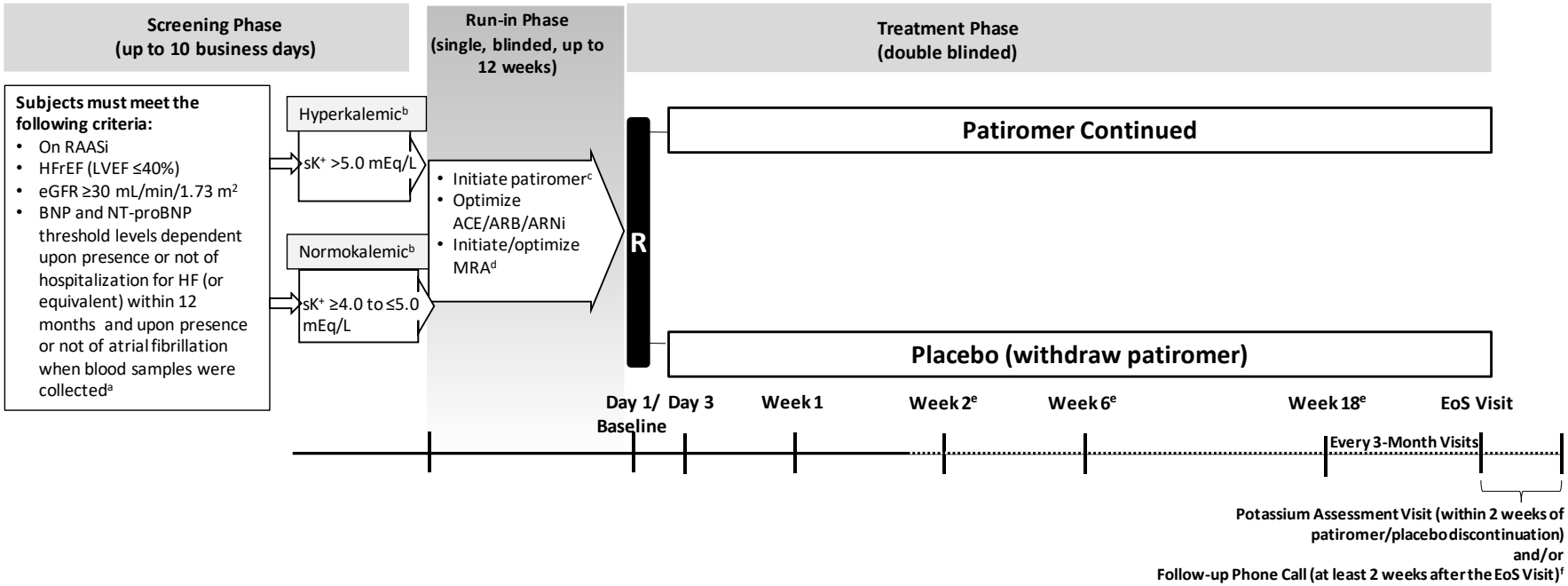
Run-in failed subjects cannot be randomized but may be rescreened once, after 3 months (Section 8.1.1.1).

Treatment Phase (Double-Blinded):

	After the Run-in Phase (single-blinded), eligible subjects will be randomized in a 1:1 ratio, to treatment with patiromer or placebo double-blinded; see Study Schema. Randomized subjects will begin their assigned treatment (patiromer or placebo), double-blinded, using the same number of packets established for patiromer at the end of the Run-in Phase and will continue the ACEi/ARB/ARNi and MRA regimen being administered at the end of the Run-in Phase. Anytime during the Treatment Phase when subjects are on less than the target dose of either ACEi/ARB/ARNi or MRA, up-titration should be attempted if serum K^+ remains in the normokalemic range (serum K^+ 4.0–5.0 mEq/L) and no other contravening conditions are present. After randomization, serum K^+ will be measured prior to initiation of assigned patiromer/placebo, double-blinded, on Treatment Day 1/Baseline (if not already obtained that day), and at each subsequent scheduled and unscheduled visit during the Treatment Phase. Protocol allowed interventions for the management of hyperkalemia during the Treatment Phase include the following: • Up-titration of patiromer/placebo if on <3 packets per day • Down-titration or discontinuation of ACEi, ARB, ARNi and/or MRA • Initiate or increase diuretics • Dietary K^+ restriction If local K^+ is >5.5 mEq/L one or more of these interventions must be initiated either individually or in combination following the recommendations by practice guidelines. Repeat the K^+ measurement within 7 days; if local K^+ remains >5.5 mEq/L consider repeating the intervention or using other interventions in the order described above. If local K^+ is between ≥5.0 mEq/L and ≤5.5 mEq/L one or more of these interventions may be initiated per Investigator discretion. Urgent treatment of hyperkalemia should be in accordance with usual care and the Investigator's judgment. As described in Section 6.8.4.1, the only K^+ binding medications permitted for use during the study are temporary use of sodium or calcium polystyrene sulfonate as well as sodium zirconium cyclosilicate for up to 7 days or until local serum K^+ <5.0 mEq/L, whichever occurs first. Patiromer/placebo must be withheld during temporary use of permitted K^+ binding medications. If hypokalemia develops during the Treatment Phase, study drug should be down-titrated (lowest acceptable dose is 0 packets/day) until local serum K^+ ≥4.0 mEq/L. Samples will be collected at each scheduled visit, at minimum, for the measurement of serum K^+ and creatinine (for calculation of eGFR). Subject reported outcome will be assessed using the KCCQ and EQ-5D-5L questionnaire. See Schedule of Events for full details of protocol required procedures and laboratory assessments at the applicable visits (and timings of each visit).

	Monitoring Changes in Renal Function: Throughout the study, creatinine will be measured at each study visit (and may be measured at unscheduled visits). Subjects must be monitored for changes in renal function (eGFR and creatinine), especially during periods of medication changes or adjustments and when the subject has a change in clinical status. See Section 6.7.4 for suggested guidance on medication adjustments based on changes in renal function.
Sample Size:	The sample size of 410 subjects per treatment arm (total of 820 subjects) has been calculated to provide 90% power to detect a difference between the control group (placebo) and the active group (patiromer) on the mean change in K^+ levels from Baseline. This sample size calculation was based upon the following assumptions: alpha level of 5% (2-sided), a difference between group means of 0.116 a standard deviation (SD) of 0.5 and a 5% rate of loss to follow-up
Study Sites:	Approximately 375 sites
Statistical Methods:	The mean change in serum K^+ levels from Baseline is analyzed by means of a mixed model for repeated measures (MMRM) approach including all available follow-up data. A Gaussian linear model for repeated measures with treatment, geographic region, sex, baseline Type 2 diabetes mellitus (T2DM) status, and visit as factors, and baseline K^+ level, baseline eGFR as covariates. The error terms are assumed to follow a multivariate normal distribution with unstructured covariance. Sensitivity analyses for the primary endpoint will explore changes in treatment effect over follow-up time by including treatment by visit interactions in the above-mentioned model. In addition, sensitivity analyses accounting for potentially informative missingness will be based upon a Win Ratio approach. Secondary efficacy endpoints will be tested in the order listed (i.e., fixed-sequence method to preserve the family-wise error rate) and summarized descriptively through the calculation of point estimates by treatment group along with 95% ICIs for the treatment differences. Other endpoints will be summarized using the calculation of point estimates by treatment group along with 95% CIs for the treatment differences and descriptive methods as appropriate. Safety evaluations include AEs and serious adverse events (SAEs) (including all-cause mortality); slope of eGFR change during the study; decline in eGFR >50% or ESRD, renal death, or need for dialysis; and serum K^+ level. Safety variables will be summarized using the safety set. No interim analysis is planned. See Section 12 for additional information.

STUDY SCHEMA



R = Randomized (see Section 5.4 for the Randomization Criteria); the assigned patiromer or placebo treatment begins and RAASi medication continues from the Run-in Phase

ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNi = angiotensin receptor/neprilysin inhibitor; BNP=brain natriuretic peptide; EoS = end of study; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NT-proBNP=N-terminal pro b-type brain natriuretic peptide; RAASi = renin-angiotensin-aldosterone system inhibitor; sK^+ = serum potassium

a. For BNP and NT-proBNP inclusion criteria in relation to the presence or not of hospitalization for HF within 12 months and the presence or not of atrial fibrillation when blood samples were collected see Section 5.2.
b. Hyperkalemia or normokalemia defined by 2 local serum K^+ values each obtained from a separate veni puncture, e.g., one in each arm. If 1 serum potassium value is hyperkalemic (>5.0 mEq/L) and 1 value is normokalemic (≤5.0 mEq/L), then a third peripheral venipuncture is performed within 1 day to obtain clarity whether a subject is hyperkalemic or normokalemic.
c. Start at 8.4 g/day and up-titrate as necessary up to 25.2 g/day. Hyperkalemic subjects start patiromer immediately; normokalemic subjects start at Week 1 or later. Subject must return within 1 week (3 days) after patiromer initiation or dose adjustments to assess potassium levels.
d. Initiate/optimize selected MRA; up-titrate to 50 mg/day. For subjects not on an MRA, the Investigator determines which MRA to initiate, and also determines the starting dose. For subjects who are on <50 mg/day of MRA, double their current dose up to 50 mg/day. Assess tolerance to the 50 mg target dose
e. If there are changes to ACEi, ARB, ARNi and/or MRA dose or serum potassium varies outside the intended range, unscheduled weekly or monthly visits should occur until stability returns.
f. If the Potassium Assessment Visit is at 2 weeks after the EoS Visit, then Follow-up phone call is not required.

SCHEDULE OF EVENTS

Procedures	Screening Phase	Run-in Phase (Single-Blinded)	Treatment Phase (Double-Blinded)										
	Screening Visits[1]	Run-in Visits[2] (Up To 12 wks)	Day 1/ Baseline	Day 3 (±1 D)	Week 1 (±3 D)	Week 2 (±3 D)	Week 6 (±14 D)	Week 18 (-30 D), First Every 3 Months Visit	Every 3 Months Visits After Week 18 Until EoS (-30 D)	EoS/ET Visit	PA Visit[3] (Up to 2 Wks)	Follow-up Phone Call (at Least 2 Wks After EoS)[4]	U Visit[5]
Informed consent	X												
IWRS entry	X	X	X	X	X	X	X	X	X	X	X	X	X[24]
Eligibility criteria	X	X[6]	X[6]										
Demographics	X												
NYHA class	X		X					X	X	X	X		
Medical/surgical history	X												
Physical examination	X									X			X[7]
Height	X												
Weight	X	X	X	X	X	X	X	X	X	X	X		X
BP and heart rate	X	X	X	X	X	X	X	X	X	X	X		X
12-lead ECG[22]	X												
K^{+}[8]	L[9]	L	L&C	L	L	L	L	L&C	L&C	L&C	L&C		L
Serum chemistry	L[10]&C[11]	L[12,13]	C	L[13]	L[13]	L[13]	L[13]	C	C	C	C		L
Hematology	C							C	C	C	C		C[7]
Urinalysis	C		C							C			
Urine ACR		C[14]		C[15]		C[15]		C[15]	C[15]	C[15]			
Urine or serum pregnancy test[16]	X		X							X			
BNP/NT-proBNP[22,23]	L&C[11]							C	C	C			
High sensitivity troponin			C							C			
MRA levels[17]			C		C			C[18]	C[18]	C			
Adverse events/special situations	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications and procedures	X	X	X	X	X	X	X	X	X	X	X	X	X
KCCQ and EQ-5D-5L[19]	X		X					X[18]	X[18]	X			

Procedures	Screening Phase	Run-in Phase (Single-Blinded)	Treatment Phase (Double-Blinded)										
	Screening Visits[1]	Run-in Visits[2] (Up To 12 wks)	Day 1/ Baseline	Day 3 (±1 D)	Week 1 (±3 D)	Week 2 (±3 D)	Week 6 (±14 D)	Week 18 (-30 D), First Every 3 Months Visit	Every 3 Months Visits After Week 18 Until EoS (-30 D)	EoS/ET Visit	PA Visit[3] (Up to 2 Wks)	Follow-up Phone Call (at Least 2 Wks After EoS)[4]	U Visit[5]
Randomization			X										
Drug accountability		X	X	X	X	X	X	X	X	X			X[24]
Dispense patiromer/placebo[20]		X	X	X	X	X	X	X	X				X[24]
Reimburse MRA[21]		X		X	X	X	X	X	X				X

1 Screening activities may take place over different calendar days if needed, but not exceeding 10 calendar days.
2 Subjects with 2 screening K^+ values >5.0 mEq/L are considered hyperkalemic; these patients begin patiromer when they qualify for the Run-in Phase (i.e., on the same day Run-in qualification is met or the next day). All other subjects are considered normokalemic and will begin patiromer latest by the end of the first week during the Run-in Phase only if they are still normokalemic or progressed to hyperkalemia. Note: Depending on the actual local serum K^+ value this could include patiromer 0 g/day (i.e., 0 packets/day). During the Run-in Phase, after any adjustments of patiromer (up or down) subjects must return within 1 week ±3 days to assess their serum K^+ level. See Section 6.7.1.1 for details.
3 Occurs after discontinuation of patiromer during the Run-in Phase (Run-in Phase failed) and after discontinuation from patiromer/placebo during Treatment Phase; see Section 8.6.
4 If the PA Visit is 2 weeks after the EoS Visit, then the Follow-up Phone Call is not required.
5 Any other study assessments (see Section 8.8) may be performed at the discretion of the Investigator during an unscheduled visit.
6 See Section 5.4 for the assessment of the randomization criteria.
7 Assessment is optional.
8 If hemolysis of the local sample is detected or is suspected (see Section 9.1.1), or the initial 2 screening blood samples reveal inconsistent values not allowing to clearly define hyperkalemia or normokalemia, a repeat (third) K^+ measurement from a separate blood draw will be performed within 1 day.
9 Collect 2 local samples at Screening, each obtained from a separate venipuncture (e.g., one in each arm or 2 separate venipunctures in the same arm) to determine normokalemia or hyperkalemia in both blood samples; in case of deviant results, another blood sample is to be taken within 1 day to confirm normokalemia or hyperkalemia.
10 Only locally measured creatinine for the calculation of eGFR for assessment of Inclusion Criterion 6 and alanine aminotransferase and aspartate aminotransferase for assessment of Exclusion Criterion 12.
11 Central laboratory values only to be collected when subject meets all other eligibility criteria.
12 Locally measured magnesium level at 1 week after starting patiromer, followed by periodic measurements during Run-in Phase to early detect rare cases of hypomagnesemia.
13 Only locally measured serum creatinine for the calculation of eGFR.
14 Urine sample containers will be dispensed at Screening to subjects who qualify for entry into the Run-in Phase and subjects will be provided proper training and instructions on the use of the containers. Urine ACR is collected and measured latest at the end of the initial week during the Run-in Phase only and not assessed at other Run-in Phase Visits.
15 Urine sample containers will be dispensed at the prior visit and subjects will be provided proper training and instructions on the use of the containers. See Section 9.6.
16 Only for women of child-bearing potential. Serum pregnancy tests will be locally measured.
17 MRA must be taken in the morning before blood withdrawal for analysis of MRA levels.
18 Performed at 3 months (i.e., Week 18), 6 months, 12 months, and then every 12 months thereafter.
19 Subjects will complete the KCCQ and EQ-5D-5L questionnaire before study staff performs any clinic or study assessments.
20 During Run-in Phase, only patiromer is dispensed. After randomization, patiromer/placebo dose on Day 1/Baseline will be the same number of packets established for patiromer at the end of the Run-in Phase. Throughout the study patiromer or patiromer/placebo will be dispensed as needed.
21 Only if needed for subjects who initiate spironolactone or eplerenone during the Run-in Phase; see Section 6.7.2 and Section 6.8.2.
22 Screening 12-lead ECG and BNP/NT-proBNP needs to be assessed on the same day.
23 For subjects treated with ARNi (sacubitril/valsartan) in the previous 4 weeks before Screening only NT-proBNP values are to be considered.
24 Applicable only if IMP is dispensed at an unscheduled visit.

Notes: ACEi=Angiotensin-converting enzyme inhibitor; ACR=Albumin-to-creatinine ratio; ARB=Angiotensin II receptor blocker; ARNi=Angiotensin receptor/neprilysin inhibitor; BNP=Brain natriuretic peptide; BP=Blood pressure; C=Central laboratory; D=Day(s); ECG=Electrocardiogram; eGFR=Estimated glomerular filtration rate; EoS=End of study; ET=Early termination; IMP=Investigational medicinal Product; IWRS=Interactive web response system; K^+=Potassium; KCCQ=Kansas City Cardiomyopathy Questionnaire; L=Local; MRA=Mineralocorticoid receptor antagonist; NT-proBNP=N-terminal pro b-type brain natriuretic peptide; NYHA=New York Heart Association; PA=Potassium assessment; U=Unscheduled.

TABLE OF CONTENTS

Page

LIST OF TABLES

Page

LIST OF ABBREVIATIONS

ACEi	Angiotensin-converting enzyme inhibitor
ACR	Albumin-to-creatinine ratio
ADR	Adverse drug reactions
AE	Adverse event
ARB	Angiotensin II receptor blocker
ARNi	Angiotensin receptor/neprilysin inhibitor
BNP	Brain natriuretic peptide
BP	Blood pressure
CI	Confidence interval
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
COX-2	Cyclooxygenase-2
CRO	Contract Research Organization
CV	Cardiovascular
DSMB	Data and Safety Monitoring Board
EAC	Event Adjudication Committee
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
EoS	End of study
ESRD	End-stage renal disease
ET	Early termination
GCP	Good Clinical Practice
GI	Gastrointestinal
GWTG-HF	Get With The Guidelines-Heart Failure
HEOR	Health Economics and Outcomes Research
HF	Heart failure
HFrEF	Heart failure with reduced ejection fraction

HR	Hazard ratio
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP(s)	Investigational medicinal product(s)
IRB	Institutional Review Board
IWRS	Interactive web response system
KCCQ	Kansas City Cardiomyopathy Questionnaire
KDOQI	Kidney Disease Outcomes Quality Initiative
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measures
MRA	Mineralocorticoid receptor antagonist
MRI	Magnetic resonance imaging
NSAIDs	Nonsteroidal anti-inflammatory drugs
NT-proBNP	N-terminal pro b-type brain natriuretic peptide
NYHA	New York Heart Association
PT	Preferred term
RAASi	Renin-angiotensin-aldosterone system inhibitor
RSI	Reference Safety Information
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SE	Standard error
SOC	System organ class
SS	Safety set
SUSAR	Suspected unexpected serious adverse reaction
T2DM	Type 2 diabetes mellitus
TEAE(s)	Treatment-emergent adverse event(s)
US	United States
WBC	White blood cell count

1. INTRODUCTION AND BACKGROUND

1.1 Background of the Disease and Treatment Options

Twenty-six (26) million people worldwide have a diagnosis of HF [5]. In their Heart Disease and Stroke Statistics—2017 Update, the American Heart Association (AHA) reported data from National Health and Nutrition Examination Survey 2011–2014, which estimates that 6.5 million Americans ≥20 years of age have HF. Projections show that with improved survival and the aging of the population, the prevalence of HF in the US will increase 46% from 2012 to 2030, resulting in more than 8 million people ≥18 years of age with HF. Currently, HF accounts for nearly 1 million annual hospitalizations in the US and more than 3 million physician office visits. By 2030, 1 in every 33 US citizens will have a diagnosis of HF. Accordingly, it is in the public interest that therapies which have shown reductions in CV mortality, reductions in HF hospitalizations, and improvements in patient quality of life be used and optimally implemented [6,7,8]. Renal insufficiency is common in HF and is independently associated with increased all-cause and CV mortality [9]. However, in patients with advanced chronic kidney disease (CKD) (eGFR <30 mL/min/1.73 m^2) evidence-based strategies for improving CV outcomes remain almost unavailable [10].

HF mortality remains high. Approximately 50% of people diagnosed with HF will die within 5 years, but mortality rates have improved in the past 20 years, and this has been primarily because of evidence-based approaches to treating HF risk factors and comorbidities, as well as use of ACEi, beta-blocker, MRA, coronary revascularization, implantable cardioverter-defibrillators, and cardiac resynchronization therapeutic strategies [6].

However, evidence suggests that these treatments are not being implemented as recommended in HF treatment guidelines. Data from the Get With The Guidelines-Heart Failure (GWTG-HF) registry suggests that approximately 47% of individuals admitted to the hospital with HF should have had initiation of at least 1 new medication on discharge. The GWTG-HF registry 2008–2013 collected prescribing, indications, and contraindications for ACEi or ARB, beta-blocker, MRA, hydralazine/isosorbide dinitrate, and anticoagulants. The difference between a patient's medication regimen at hospital admission and that which was recommended by HF quality measures at discharge was calculated. Among 158,922 patients from 271 hospitals with a primary discharge diagnosis of HF, initiation of ACEi/ARB was indicated in 18.1% of all patients, 55.5% of whom had not been receiving ACEi/ARB at admission. Beta-blockers were indicated in 20.3%, 50.5% of whom had not been receiving beta-blockers at admission, and initiation of MRA was indicated in 24.1%, 87.4% of whom had not been receiving MRA at admission. A quarter of patients hospitalized with HF needed to start more than 1 medication to meet HF quality measures, and a significant proportion of these patients were not taking these medications at admission, excluding them from the mortality and morbidity benefits attributed to these treatments which have earned Class I recommendations in the HF treatment guidelines [7-11].

Similar findings have been seen in the European Society of Cardiology Heart Failure Long-Term Registry. In patients with chronic HFrEF, renin-angiotensin system blockers, beta-blockers, and MRA were used in 92.2, 92.7, and 67.0% of patients, respectively. About 70% of patients did not receive the target dosage of these drugs [14]. Among reasons for non-adherence or not achieving the target dose with ACEi, ARB, or MRA were contraindication or lack of tolerance, most often due to worsening renal function, symptomatic hypotension, or hyperkalemia. The reduction in renal function associated with HF, older age, and comorbidities such as diabetes mellitus hampers K^+ excretion and so makes patients with HF more likely to develop hyperkalemia. Additionally, the guideline-recommended pharmacologic treatments, which include multiple neurohormonal antagonists of the renin-angiotensin-aldosterone system (RAAS), increase the risk of hyperkalemia, especially when used in combination [15].

Despite advances in treatment of CV diseases, evidence-based strategies for improving CV outcomes in patients with advanced CKD remain almost unavailable [10]. This is in part because the efficacy and safety studies that support drug approval typically exclude patients with more advanced CKD; although criteria vary, typically patients with Stages 4 and 5 CKD are excluded from CV outcome studies. As a consequence, very few adequately powered CV outcome trials that focus specifically on patients with advanced CKD have been done [16].

Patients with severe renal insufficiency have generally been excluded from the RAASi outcomes trials. Thus, eGFR <30 mL/min/1.73 m^2, i.e., CKD Stages 4 and 5 (Europe), constitutes contraindications or cautions when initiating RAASi medication [17]. For example, cautious use or avoidance of MRAs is recommended in HFrEF patients with eGFR <30 mL/min/1.73 m^2 or serum K^+ >5 mEq/L [12,13].

New K^+ binders might also enable study of patients that have been excluded or underrepresented in RAASi clinical trials, e.g., those with eGFR <30 mL/min/1.73 m^2 or serum K^+ >5.0–5.5 mEq/L [18]. K^+ binders may be used to study the potential benefit of RAASi in populations not studied in the past due to the risk of hyperkalemia, for example, in patients with eGFR <30 mL/min/1.73 m^2. Also, K^+ binders may enable investigating the benefit of higher doses MRA therapy [19].

Epstein et al, 2015 examined renin-angiotensin-aldosterone-system inhibitor (RAASi) dose levels in a US patient population. They investigated the impact of hyperkalemia on RAASi dose and the association between dose levels and clinical outcomes [20]. Patients were classified by comorbidities CKD, HF, or diabetes and RAASi dose level at index date, as determined by prescription information (supramaximal = above labeled dose; maximal = labeled dose; submaximal = less than labeled dose; or discontinued). One-third (32.8%) of all qualifying subjects experienced at least 1 hyperkalemic event (serum K^+ >5.0 mEq/L). Among subjects with HF and Stage 3–4 CKD, maximum doses were prescribed in 19% of subjects; 64% of subjects were prescribed submaximal doses, and 16% of patients discontinued treatment with RAASi medications as of the index date. Analysis of RAASi dosing before and after hyperkalemia events revealed that a substantial proportion of

subjects had changes in their dose following an episode of elevated serum K^+, with dose changes occurring more frequently after moderate-to-severe hyperkalemia events (serum K^+ >5.5 mEq/L). Patients on a maximum dose of a RAASi were down-titrated to a submaximal dose or discontinued the RAASi nearly half the time (47%) after moderate-to-severe hyperkalemia events and 38% of the time after mild events. Among patients on submaximal doses of RAASi, moderate-to-severe hyperkalemia events were followed by submaximal dose maintenance in 55% of patients and discontinuation in 27% of patients, compared with dose maintenance in 61% after mild hyperkalemia events and discontinuation in 24% after mild events. Nearly 60% of subjects with HF who discontinued RAASi experienced an adverse outcome or mortality compared with 52.3% of patients on submaximal doses and 44.3% of patients on maximum doses (all comparisons $p<0.05$). Patients on submaximal doses or who discontinued RAASi therapy showed consistently worse outcomes compared with patients on maximum doses, irrespective of comorbidity status (CKD, HF, diabetes mellitus) or patient age [20], suggesting that patients may benefit from continuing maximal, guideline-directed doses of medications, if hyperkalemia can be managed.

Although these data are taken from a retrospective database analysis with many limitations, they are consistent with other observational and retrospective studies [11,14,21,22,23] that have reported a meaningful gap between recommendations in guidelines and real-world practice. Closing this gap between the number of guideline-RAASi-eligible patients with HFrEF and the actual number receiving RAASi may provide an opportunity to further reduce CV mortality, hospitalizations for CV events (including HF), and healthcare costs.

New treatments for hyperkalemia may offer a solution to intolerance or contraindication due to hyperkalemia while on RAASi medications and may help close this gap. Veltassa® (patiromer) for Oral Suspension is a non-absorbed, polymeric K^+ binder that is approved for the treatment of hyperkalemia [24].

1.2 Summary of Clinical Data

In a Phase 3 study (RLY5016-301) CKD patients on RAASi with serum K^+ levels ≥5.1-<6.5 mEq/L (n=243) received patiromer (8.4 g daily initially) for 4 weeks (Initial Treatment Phase); the primary efficacy endpoint was mean change in serum K^+ from Baseline to Week 4. Eligible patients (those with Baseline K^+ ≥5.5-<6.5 mEq/L and levels ≥3.8–<5.1 mEq/L at the end of Week 4) entered an 8-week randomized withdrawal phase and were randomly assigned to continue patiromer or switch to placebo; the primary efficacy endpoint was the change in the serum K^+ over the first 4 weeks of that phase. One hundred two (102) patients (42%) had HF (per the Investigator's assessment). A prespecified analysis of these subjects demonstrated a mean (±standard error (SE)) change in serum K^+ from Baseline to Week 4 of -1.06±0.05 mEq/L (95% confidence interval (CI), -1.16, -0.95; $p<0.001$); 76% (95% CI, 69, 84) achieved target serum K^+ (3.8-<5.1 mEq/L). In the randomized withdrawal phase, the median increase in serum K^+ from Baseline of that phase was greater with placebo (n=22) than patiromer (n=27) ($p<0.001$); recurrent hyperkalemia (serum K^+ ≥5.5 mEq/L) occurred in 52% on placebo and 8% on patiromer

($p<0.001$). By the end of the randomized withdrawal phase, 55% of HF patients on placebo and 100% of HF patients on patiromer were still receiving RAASi [25]. These findings support the use of patiromer to manage hyperkalemia in HF patients.

In addition, the effect of treatment with patiromer for up to 52 weeks was evaluated in an open-label study of 304 hyperkalemic patients with CKD and Type 2 diabetes mellitus on RAASi therapy (Study RLY5016-205). This study demonstrated that the treatment effect on serum K^+ was maintained during continued therapy. Patiromer was well tolerated over this longer treatment period, supporting its use in the management of more chronic hyperkalemia seen with RAASi treatment of HF in some subjects [26].

2. RATIONALE

Patients with HF and CKD are among those at the highest risk of severe outcomes of COVID-19 infection. Treatment practices for this patient population have been adapted to reduce risks of exposure to infection during hospital visits, disrupting clinical care and impacting the conduct of randomized clinical trials such as the DIAMOND study. Priority has been to protect the safety of the patients in the trial, and to respect the need of the healthcare system to prioritize efforts to contain the pandemic. This has led to fewer patients enrolled in the trial than anticipated.

Due to the changing treatment landscape in HFrEF, the lower-than-expected recruitment rate due to the COVID-19 pandemic and the consecutively lower-than-expected event rates, the Sponsor with recommendations from the Executive Steering Committee of the study decided to change the study objectives and the primary and secondary endpoints. The decision was made to maximize the scientific value of the data already collected in DIAMOND, while at the same time ensuring the safety and wellbeing of patients. It also took into account the way the unprecedented demands of the COVID-19 pandemic had altered clinical care during this period.

It is therefore hypothesized that patiromer can be used to treat hyperkalemia that develops in high-risk HFrEF patients while receiving treatment with RAASi. This is expected to result in improved adherence to guideline RAASi treatment, and less hyperkalemic events are expected compared with the current standard of care in these patients, which includes RAASi dose reduction or discontinuation.

We hypothesize that patiromer can be used to treat hyperkalemia that develops in high-risk HFrEF patients while receiving treatment with RAASi. This is expected to result in improved adherence to guideline RAASi treatment, and we expect reductions in CV mortality and hospitalizations for CV events compared with current standard of care to manage hyperkalemia in these patients, which includes RAASi dose reduction or discontinuation.

Therefore, the present multinational, multicenter, double-blind, placebo-controlled, randomized withdrawal, parallel group study of subjects with HFrEF who have developed hyperkalemia (serum K^+ >5.0 mEq/L) while being treated with RAASi medications is re-designed to determine if patiromer treatment will result in better K^+ control compared with placebo treatment.

The selection criteria for the present study will provide a cohort of subjects who have risk factors for hyperkalemia (e.g., CKD, diabetes mellitus, older age), who have demonstrated hyperkalemia and who pose the greatest therapeutic dilemma to clinicians, since they have the highest risk of developing hyperkalemia but stand to benefit most from these RAASi therapies [27].

The study includes a single-blinded Run-in Phase and a double-blinded Treatment Phase. During the Run-in Phase, doses of RAASi medications will be adjusted consistent with guideline therapy, including initiation and up-titration of an MRA. Serum K^+ will be managed through treatment with patiromer in all subjects during the Run-in Phase. Doses of patiromer will be adjusted according to a Sponsor-provided algorithm to maintain serum K^+ 4.0–5.0 mEq/L. Mortality is increased on the lower end of the serum K^+ "normal range" with K^+ values as high as 4.1 mEq/L, so a lower limit of 4.0 mEq/L was chosen for the target range [8,28,29]. The 4.0–5.0 mEq/L target range will allow optimization of HF treatment while managing serum K^+ in all subjects before randomization. After the Run-in Phase, subjects are randomized 1:1 to either continued patiromer treatment (patiromer group) or the withdrawal of patiromer (placebo group); subjects and site study personnel will be blinded to treatment assignment.

We hypothesize that the ability of patiromer to treat hyperkalemia will allow better adherence to HF guidelines in the patiromer arm than in the placebo arm and that this difference will lead to a difference in the serum K^+ changes from Baseline compared with placebo.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1 Primary Objective

- To assess the effects of patiromer on serum K^+ in HF patients compared with placebo

3.2 Primary Endpoint

- Changes in serum K^+ levels from Baseline

  Note: All analyses will be restricted to serum K^+ levels and not substituted by plasma values as they are known to be systematically lower. Both central laboratory and local laboratory values will be used at all visits; however, if both values are available at one visit, then central laboratory values will be used.

3.3 Key Secondary Endpoints (Hierarchically Ordered)

1. Hyperkalemia events with a serum K^+ value >5.5 mEq/L

2. Durable enablement to stay on the MRA target dose (of 50 mg daily spironolactone or eplerenone, respectively) as assessed by the between treatment group difference of the cumulative frequency of patients not staying on that target dose

   Note: Discontinuation of the target dose for at least 14 days (or less if at the EoS) is required to confirm this endpoint.

3. Investigator reported events of hyperkalemia (first and recurrent events)

4. Hyperkalemia-related hard outcomes endpoints (Win Ratio)

   a. Time to CV death

   b. Total number of CV hospitalizations

   c. Total number of hyperkalemia toxicity events with serum K^+ >6.5 mEq/L

   d. Total number of hyperkalemia events with serum K+ >6.0-6.5 mEq/L

   e. Total number of hyperkalemia events with serum K^+ >5.0 mEq/L

5. RAASi Use Score (Win Ratio)

   Note: This score (of 0–8 points) will be analyzed at the respective time points for each patient in each comparison, and it consists of the following components:

   a. All-cause death

   b. Occurrence of a CV hospitalization

c. HF medication use and dose for i) an ACEi/ARB/ARNi, ii) an MRA, and ii) a beta-blocker

3.4 Other Secondary Endpoints

- Durable enablement to stay on the target dose of ACE/ARB/ARNi

  Note: Discontinuation of the target dose for at least 14 days (or less if at the EoS) is required to confirm this endpoint

- Durable hyperkalemia-free enablement to stay on the MRA target dose (days on 50mg MRA without presence of hyperkalemia)
- Total number of hyperkalemia toxicity events with serum K^+ >6.5 mEq/L
- Total number of hyperkalemia events with serum K^+ >6.0-6.5 mEq/L
- Emergency treatment for hyperkalemia (hospitalization or emergency room)
- Total number of hyperkalemia events with serum K+ >5.0 mEq/L
- KCCQ questionnaire, changes in OSS, CSS and TSS
- Investigator reported events of hyperkalemia (first events)
- Proportion of subjects on ≥50% of target dose of ACEi, ARB, or ARNi and ≥50% of target dose of MRA at the EoS Visit
- Time to first occurrence of CV death or CV hospitalization

3.5 Other Endpoints

- CV death
- First and recurrent CV hospitalizations
- First and recurrent HF hospitalizations (or equivalent in outpatient clinic)
- Patient-reported outcome: EQ-5D-5L questionnaire
- Proportion of subjects on any dose of MRA at the EoS Visit
- Proportion of subjects on any dose of ACEi, ARB, or ARNi at the EoS Visit
- Change in proteinuria from Screening
- Change in NT-proBNP from Screening

- Change in high sensitivity troponin from Baseline
- Functional status by NYHA class
- 30-day HF re-hospitalization after a prior HF hospitalization
- HEOR analyses
- Changes in serum K^+ from Baseline to individual visits

3.6 Safety Endpoints

- AEs, including all-cause mortality
- All-cause mortality
- Slope of eGFR change during the study
- Decline in eGFR >50% or ESRD, renal death, or need for dialysis
- Laboratory parameters other than those defined as efficacy endpoints

4. INVESTIGATIONAL PLAN

4.1 Overall Study Design

See Study Schema for an overview of the study design. The study consists of:

- Screening Phase (the Screening Phase may last up to 10 calendar days)
- Run-in Phase (single-blinded), up to 12 weeks; weekly visits recommended but are at the Investigator's discretion
- Treatment Phase (double-blinded); the scheduled visits are listed below:
  - Day 1/Baseline
  - Day 3 (±1 day)
  - Week 1 (±3 days)
  - Week 2 (±3 days)
  - Week 6 (±14 days)
  - Week 18 (−30 days), first Every 3 Months visit
  - Visits every 3 months (−30 days) thereafter through the end of the study
  - EoS Visit
- Potassium Assessment Visit (occurs within 2 weeks after patiromer or placebo is discontinued)

  Note: Subjects who prematurely discontinue patiromer/placebo during the Blinded Treatment Phase remain in the study.
- Follow-up Phone Call (at least 2 weeks after the EoS for the assessment of safety; for subjects who discontinue patiromer at the EoS Visit, and attend the Potassium Assessment Visit 2 weeks later, a Follow-up Phone Call will not be needed)
- Unscheduled Visit (during the Treatment Period, anytime there are changes to ACEi, ARB, ARNi and/or MRA dose or interventions for serum K^+ outside the desired range, additional Unscheduled Visits should occur weekly until the ACEi, ARB, ARNi and/or MRA dose or serum K^+ has been stable for at least 2 consecutive visits)

Screening Phase and Run-in Phase (Single-Blinded, Up to 12 Weeks):

At the end of the Screening Phase, subjects who satisfy the eligibility criteria will be enrolled into the Run-in Phase. The purpose of the Run-in Phase is to select subjects who

will potentially benefit from treatment and not unnecessarily expose those who will not. In addition, the Run-in Phase is for management of serum K^+ with patiromer to allow optimization of RAASi medications and their dosage (including initiation of MRA if not already receiving an MRA).

All subjects who meet the eligibility criteria for the Run-in Phase will initiate patiromer (1 packet/day), single-blinded.

Subjects with 2 Screening K^+ values >5.0 mEq/L are considered hyperkalemic; these patients begin patiromer when they qualify for the Run-in Phase, i.e., on the same day Run-in qualification is met or the next day.

Note: If one screening K^+ value is >5.0 mEq/L and one value is ≤5.0 mEq/L, then a third peripheral venipuncture is performed within 1 day to obtain clarity, whether subject is hyperkalemic or normokalemic (local serum K^+ ≥4.0–≤5.0 mEq/L).

All other subjects are considered normokalemic and serum K^+ will be measured again latest after the first week during the Run-in Phase. Patiromer will be started at this first Run-in Visit only if subjects are still normokalemic or have progressed to hyperkalemia; in case of newly observed hypokalemia (local serum K^+ <4.0 mEq/L) during the first Run-in Week, patiromer must not be given. In subjects with hypokalemia serum K+ must be controlled after 3 days. During the first week of Run-in, ACEi/ARB/ARNi and/or MRA doses ideally remain unchanged, if clinically indicated. On or after the Run-in Week 1 Visit, up-titration of ACEi/ARB/ARNi and/or MRA may be initiated.

Patiromer is titrated during Run-in Phase to achieve target local serum K^+ level of ≥4.0-≤5.0 mEq/L; see Section 6.7.1.1 for patiromer titration algorithm. Note: Depending on the actual local serum K^+ value this could include patiromer 0 g/day (i.e., 0 packets/day) during the Run-in Phase.

Optimization of ACEi/ARB/ARNi or MRA During Run-in Phase:

The Investigator should manage ACEi/ARB/ARNi or MRA dose initiation, escalation and maintenance with the aim to achieve 100% of target doses as per the Study Manual, using clinical judgment to customize ACEi/ARB/ARNi or MRA addition or dose escalation based on subject response; see Section 6.7.2, Section 6.8.2, and Study Manual [1] for a summary of practice guideline recommendations.

Initiation or escalation of ACEi/ARB/ARNi or MRA dose should be made with caution when local serum K^+ is >5.0 mEq/L. Assessment of serum K^+ will occur at each visit. The patiromer dose is titrated based on the subject's K^+ level.

Subjects may be randomized anytime (but no later than 12 weeks) during the Run-in Phase when they meet all of the randomization criteria; see Section 5.4.

Treatment Phase (Double-Blinded):

After the Run-in Phase (single-blinded), eligible subjects will be randomized in a 1:1 ratio, to treatment with patiromer or placebo double-blinded; see Study Schema.

Randomized subjects will begin their assigned treatment (patiromer or placebo) using the same number of packets established for patiromer at the end of the Run-in Phase and will continue the ACEi/ARB/ARNi and MRA regimen being administered at the end of the Run-in Phase.

Anytime during the Treatment Phase when subjects are on less than the target dose of either ACEi/ARB/ARNi or MRA, up-titration should be attempted if serum K^+ remains in the normokalemic range (serum K^+ ≥4.0–≤5.0 mEq/L) and no other contravening conditions are present.

After randomization, serum K^+ will be measured prior to initiation of assigned patiromer/placebo, double-blinded, on Treatment Day 1/Baseline (if not already obtained that day), and at each subsequent scheduled and unscheduled visit during the Treatment Phase. See Table 1 for the allowed interventions for the management of hyperkalemia during the Treatment Phase.

Table 1 Protocol Allowed Interventions for the Management of Hyperkalemia During the Blinded Treatment Phase

1. Up-titration of patiromer/placebo if on <3 packets per day
2. Down-titration or discontinuation of ACEi, ARB, ARNi and/or MRA
3. Initiate or increase diuretics
4. Dietary K^+ restriction

Notes: ACEi=Angiotensin-converting enzyme inhibitor; ARB=Angiotensin II receptor blocker; ARNi=Angiotensin receptor/neprilysin inhibitor; K^+=Potassium; MRA=Mineralocorticoid receptor antagonist.

If local K^+ is >5.5 mEq/L, one or more of these interventions must be initiated either individually or in combination following the recommendations by practice guidelines. Repeat the K^+ measurement within 7 days; if local K^+ remains >5.5 mEq/L consider repeating the intervention or using other interventions in the order presented in Table 1.

If local K^+ is between >5.0 mEq/L and 5.5 mEq/L, one or more of these interventions may be initiated per Investigator discretion.

Urgent treatment of hyperkalemia should be in accordance with usual care and the Investigator's judgment. As described in Section 6.8.4.1, the only K^+ binding medications permitted for use during the study are temporary use of sodium or calcium polystyrene sulfonate as well as sodium zirconium cyclosilicate for up to 7 days or until local serum K^+

<5.0 mEq/L, whichever occurs first. Patiromer/placebo must be withheld during temporary use of permitted K^+ binding medications.

If hypokalemia develops during the Treatment Phase, study drug should be down-titrated (lowest acceptable dose is 0 packets/day) until local serum K^+ ≥4.0 mEq/L.

Samples will be collected at each scheduled visit, at minimum, for the measurement of serum K^+ and creatinine (for calculation of eGFR). Subject reported outcome will be assessed using the KCCQ and EQ-5Q-5L. See Schedule of Events for full details of protocol required procedures and laboratory assessments at the applicable visits (and timings of each visit).

4.2 Duration of Subject Participation and Study

Each eligible subject's participation includes a Screening Phase (within a maximum of 10 calendar days), Run-in Phase (single-blinded, up to 12 weeks) followed by the Treatment Phase (double-blinded, variable per subject). Study duration for individual subjects will vary, depending on their individual enrollment date. The common EoS will occur when 820 subjects have completed the Week 6 visit. Recruitment will be stopped when it is projected that a sufficient number of subjects have been enrolled in order for 820 subjects to reach the Week 6 visit. Sites will be notified of the common EoS date prior to study closure and should advise ongoing study subjects of the study termination date thereafter; see Section 8.4 for detailed description of the EoS procedures.

Patients who prematurely discontinue patiromer/placebo will remain in the study for the collection of composite endpoint event data up to and including the common EoS and will receive usual care during the study phase.

5. SELECTION AND WITHDRAWAL OF SUBJECTS

5.1 Number of Subjects

For detailed justification of the sample size please refer to Section 12.2.

5.2 Inclusion Criteria

The following criteria must be met for each subject prior to entry in the Run-in Phase:

1. Subject provides written informed consent prior to study participation

2. Age at least 18 years or greater

3. Current NYHA Class II–IV

4. Left ventricular ejection fraction ≤40%, measured by any echocardiographic, radionuclide, MRI, angiographic, or computerized tomography method in the last 12 months (without subsequent measured ejection fraction >40% during this interval)

5. Receiving any dose of a beta-blocker for the treatment of HF or unable to tolerate beta-blockers (reason documented)

6. eGFR ≥30 mL/min/1.73 m^2 at Screening (based on a single local laboratory analysis of serum creatinine and calculation using the CKD-EPI equation; see Section 9.2)

7. Hyperkalemia at Screening (defined by 2 local serum K^+ values of >5.0 mEq/L, each obtained from a separate venipuncture, e.g., one in each arm or two separate venipunctures in the same arm) while receiving an ACEi/ARB/ARNi, and/or an MRA

   OR

   Normokalemia at Screening (defined by 2 local serum K^+ ≥4.0–≤5.0 mEq/L, each obtained from a separate venipuncture, e.g., one in each arm or two separate venipunctures in the same arm) with a history of hyperkalemia documented by a usual care serum K^+ measurement >5.0 mEq/L while on RAASi treatment in the 12 months prior to Screening leading to a subsequent and permanent dose decrease or discontinuation of one or more RAASi medications

8. Females of child-bearing potential must be non-lactating, must have a negative pregnancy test at Screening, and must agree to continue using contraception (see Section 9.8) throughout the study and for 4 weeks after study completion

9. With hospitalization for HF or equivalent (e.g., emergency room or outpatient visit for worsening HF during which the patient received intravenous medications for the treatment of HF) within the last 12 months before Screening

   a) Without atrial fibrillation at Screening, BNP level must be greater than 150 pcg/mL (18 pmol/L) or NT-proBNP must be greater than 600 pcg/mL (71 pmol/L)

   b) With atrial fibrillation at Screening, BNP level must be greater than 300 pcg/mL (35 pmol/L) or NT-proBNP must be greater than 1,200 pcg/mL (142 pmol/L)

   OR

   Without hospitalization for HF or equivalent (e.g., emergency room or outpatient visit for worsening HF during which the subject received intravenous medications for the treatment of HF) within the last 12 months before Screening

   a) Without atrial fibrillation at Screening, BNP level must be greater than 300 pcg/mL (35 pmol/L) or NT-proBNP must be greater than 1,200 pcg/mL (142 pmol/L)

   b) With atrial fibrillation at Screening, BNP level must be greater than 600 pcg/mL (71 pmol/L) or NT-proBNP must be greater than 2,400 pcg/mL (284 pmol/L)

Note: Table 2 provides the same information of Inclusion Criterion 9 as described in the text above.

Table 2 BNP and NT-proBNP Threshold Levels (Based on Local Laboratory), Comorbidities, and Previous Hospitalizations

	Subjects with hospitalization for HF or equivalent[1] within last 12 months	**Subjects with no hospitalization for HF or equivalent[1] within last 12 months**
Subjects presenting without atrial fibrillation when the blood sample was collected	BNP[2] >150 pcg/mL (18 pmol/L) or NT-proBNP >600 pcg/mL (71 pmol/L)	BNP[2] >300 pcg/mL (35 pmol/L) or NT-proBNP >1,200 pcg/mL (142 pmol/L)
Subjects presenting with atrial fibrillation when the blood sample was collected	BNP[2] >300 pcg/mL (35 pmol/L) or NT-proBNP >1,200 pcg/mL (142 pmol/L)	BNP[2] >600 pcg/mL (71 pmol/L) or NT-proBNP >2,400 pcg/mL (284 pmol/L)

1 E.g., urgent emergency room or outpatient visit for worsening HF during which the subject received intravenous medications for the treatment of HF.
2 For subjects treated with ARNi (sacubitril/valsartan) in the previous 4 weeks before Screening only NT-proBNP values are to be considered.
Notes: ARNi=Angiotensin receptor/neprilysin inhibitor; BNP=Brain natriuretic peptide; HF=Heart failure; NT-proBNP=N-terminal pro b-type brain natriuretic peptide.

5.3 Exclusion Criteria

Subjects who meet any of the following criteria during Screening will be excluded:

1. Current acute decompensated HF within 4 weeks before Screening. Subjects with a discharge from a hospitalization for acute decompensation of HF longer than 4 weeks before Screening may be included

2. Symptomatic hypotension or systolic blood pressure <90 mmHg

3. Significant primary aortic or mitral valvular heart disease unrelated to HF (except secondary mitral regurgitation due to left ventricular dilatation)

4. Heart transplantation or planned heart transplantation (i.e., currently on a heart transplant waiting list) during the study period

5. Diagnosis of peripartum or chemotherapy-induced cardiomyopathy or acute myocarditis in the previous 12 months

6. Implantation of a cardiac resynchronization therapy device in the previous 4 weeks before Screening

7. Restrictive, constrictive, hypertrophic, or obstructive cardiomyopathy

8. Untreated ventricular arrhythmia with syncope in the previous 4 weeks before Screening

9. History of, or current diagnosis of, a severe swallowing disorder, moderate-to-severe gastroparesis, or major GI surgery (e.g., bariatric surgery or large bowel resection)

10. A major CV event within 4 weeks prior to Screening, including acute myocardial infarction, stroke (or transient ischemic attack), a life-threatening atrial or ventricular arrhythmia, or resuscitated cardiac arrest

11. Note: This exclusion criterion is included in the new Inclusion Criterion 9

12. Liver enzymes (alanine aminotransferase, aspartate aminotransferase) >5 times upper limit of normal at Screening based on the local laboratory

13. Diagnosis or treatment of a malignancy in the past 2 years, excluding non-melanoma skin cancer and carcinoma in situ of the cervix, prostate cancer with Gleason score <7, or a condition highly likely to transform into a malignancy during the study

14. Presence of any condition (e.g., drug/alcohol abuse; acute illness), in the opinion of the Investigator, that places the subject at undue risk, or prevents complete participation in the trial procedures, or potentially jeopardizes the quality of the study data

15. Use of any investigational product for an unapproved indication within 4 weeks before Screening or currently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study

16. Known hypersensitivity to patiromer (RLY5016) or its components

17. Note: This exclusion criterion is modified and partially incorporated in the Exclusion Criterion 18

18. Subjects currently being treated with or having taken any one of the following medications in the 7 days prior to Screening: sodium or calcium polystyrene sulfonate or sodium zirconium cyclosilicate, or patiromer

19. An employee, spouse, or family member of the Sponsor (Vifor Pharma), investigational site or the CRO

5.4 Randomization Criteria

Subject may be randomized anytime (but no later than 12 weeks) during the Run-in Phase when they meet all of the following criteria:

1. Current MRA dose is at least the target dose* (e.g., spironolactone 50 mg/day, eplerenone 50 mg/day) and has been stable for at least 1 week.

2. Current ACEi/ARB/ARNi is ≥50% of the target dose* and has been stable for at least 1 week.

3. Current patiromer dose is at least 1 packet daily.

4. Current local serum K^+ level is ≥4.0–≤5.0 mEq/L.

* Study-specific target doses as per Table 4 in the Study Manual.

5.5 Discontinuing Patiromer/Placebo or Withdrawal of Subjects

5.5.1 Discontinuation from Patiromer/Placebo

The management of ACEi/ARB/ARNi and/or MRA are at the discretion of the Investigator during the Blinded Treatment Phase. If one or more ACEi/ARB/ARNi and/or MRA are adjusted, patiromer/placebo may be adjusted accordingly, based on changes in local serum K^+ levels. The lowest dose of patiromer/placebo is 0 packets/day. It is recommended to discuss with the subject a study treatment interruption (dose level 0 packets/day) rather than a permanent patiromer/placebo discontinuation, which should only occur when it is requested by the Investigator or the subject.

Subjects who discontinue from patiromer/placebo treatment after randomization and prior to completion of the study will be encouraged to return within 2 weeks, or as soon as possible thereafter, for a Potassium Assessment Visit (see Section 8.6). Subjects who

discontinue from patiromer/placebo treatment after randomization and prior to the common EoS will continue in the study for collection of composite endpoint events. These subjects will be treated in accordance with the standard of care per the Investigator's judgment.
Note: Subjects who discontinue from patiromer during the Run-in Phase will also be encouraged to return for a Potassium Assessment Visit within 2 weeks, or as soon as possible thereafter.

5.5.2 Withdrawal from Study

5.5.2.1 Withdrawal of Consent

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 Treatment Phase and the Potassium Assessment Visit after discontinuation of patiromer/placebo. 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 use best efforts 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 eCRF, and every effort should be made by the site to ensure that the subject completes the procedures described for early termination (ET) (Section 8.5). Every effort will be made to contact a subject who fails to attend a study visit, in order to ensure that the subject is in satisfactory health.

The subject who wishes to withdraw consent will be offered the opportunity to withdraw consent only partially and to accept any or all of the following:

- Providing information about his/her own health status by telephone or other means until the common EoS date
- Allowing Primary Care physicians or family to be contacted to provide information about the subject's health status
- Allowing 1 final contact at the end of the study (at or after the EoS)

5.5.2.2 Investigator-Withdrawn Subject

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, related to e.g., subject's non-adherence to the study protocol, subject's non-compliance to study medication, any medical condition that the Investigator or Sponsor determines may jeopardize the subject's safety if he or she continues in the study, subject's excessive drug/alcohol abuse. The Investigator may also terminate a subject's participation due to any condition preventing complete participation in the trial procedures, or potentially jeopardizing the quality of the study data. The Investigator will immediately inform the Medical Monitor of plans for early

withdrawal of a subject from the study. Investigator-withdrawn subjects will also be offered the opportunity to consent to the 3 options described above. All subjects withdrawn early from the study for any reason will complete the procedures described for ET (Section 8.5) and be followed for safety after receiving the last dose of study medications. Randomized subjects withdrawn from the study for any reason will not be replaced.

5.5.2.3 All Early Withdrawal Subjects

For any subject who early terminates from the study (including subjects who withdraw their consent), survival information may be ascertained via public database search at the end of the study.

6. STUDY TREATMENTS

6.1 Treatment Blinding

The Run-in Phase is single-blinded for the subject.

To minimize the potential for bias during the Treatment Phase, treatment randomization information will be kept confidential by an 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, Sponsor and vendor staff, except for unblinded staff required for the development of the final randomization schedule and for production of unblinded materials for the Data and Safety Monitoring Board (DSMB) and Sponsor's Drug Safety staff in situations where unblinding is necessary to comply with regulatory requirements.

Clinical Trial Supply Management will have access to overall patiromer/placebo usage for management of patiromer/placebo packaging and distribution activities and oversight of patiromer/placebo stock levels at drug depots and study sites.

If the Investigator or site study staff 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 caregivers. Blinded Sponsor staff will also remain blinded to treatment assignment.

The Investigational Pharmacist or the qualified designee as assigned by the Principal Investigator will exclusively be responsible for investigational medicinal product (IMP) handling and should not be involved in any other study procedures (see Section 6.5 for more details).

Subjects will be instructed to refrain from discussion of their study drugs with the site staff (except with the Investigational Pharmacist or the qualified designee as assigned by the Principal Investigator) or other subjects, and that any questions regarding the study drug should be directed to the Investigational Pharmacist or the qualified designee as assigned by the Principal Investigator only.

6.1.1 Unblinding

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 interactive web response system (IWRS). The Investigator should make every reasonable attempt to notify study Medical Monitor before breaking the blind. The Investigator may inform the subject and/or his/her treating physician of the treatment assignment.

Other situations where unblinding may be necessary are for study-specific suspected unexpected serious adverse reaction (SUSAR) and aggregate safety reporting to health

authorities. In these cases, Sponsor's Drug Safety personnel must know the subject's treatment allocation to ensure compliance with reporting requirements.

6.2 Dosage Forms/Formulation

6.2.1 Patiromer for Oral Suspension (Patiromer) or Placebo (Microcrystalline Cellulose)

Patiromer or placebo (microcrystalline cellulose) will be provided to the subject blinded, as a powder for oral suspension in packets.

Information on patiromer is provided below:

Active Ingredient:	Patiromer sorbitex calcium
Chemical Name:	Calcium, hydrolyzed divinylbenzene-Me 2-fluoro-2-propenoate-1,7-octadiene polymer sorbitol complexes
Generic Name:	Patiromer sorbitex calcium, powder for oral suspension
Trade Name:	Veltassa
Strength:	Each packet contains 8.4 g patiromer
Excipients:	Xanthan gum
Dosage Form:	Powder for oral suspension
Manufacturer:	Patheon Inc. or OM Pharma S.A.
Labeling:	Almac or Catalent
Storage:	2–8ºC (see the Pharmacy Manual for additional details)

All IMPs used in this study have been manufactured in accordance with current Good Manufacturing Practice.

6.3 Drug Dosage and Administration

6.3.1 Treatment Arms

All enrolled subjects will be treated with patiromer single-blinded during the Run-in Phase. After the Run-in Phase, eligible subjects will be randomized in a 1:1 ratio to treatment with patiromer or placebo in a double-blinded fashion.

6.3.2 Dosing and Administration Guidelines

6.3.2.1 Patiromer/Placebo

The starting dose will be 1 packet/day and may be taken either with food or without food. Based upon the K^+ management algorithms (Section 6.7.1.1 and Section 6.7.1.2),

patiromer/placebo may be increased by 1 packet per day in intervals of at least 1 week (±3 days). For subjects who become hypokalemic (K^+ <4.0 mEq/L), patiromer/placebo must be decreased to a minimum of 0 packets/day (see Section 6.7.1.1). If serum K^+ increases from <4.0–≥4.0 mEq/L and remains between ≥4.0–≤5.0 mEq/L, patiromer/placebo must not be resumed yet. Resume patiromer/placebo only when K^+ >5.0 mEq/L to prevent re-inducing or aggravating hypokalemia. Doses of patiromer/placebo will be 0 packets/day, 1 packet/day, 2 packets/day, and 3 packets/day (maximum dose).

Patiromer/placebo are for oral administration only. Each dose must be prepared immediately prior to administration. Patiromer/placebo should be taken at least 3 hours before or 3 hours after administration of other orally administered medications. Patiromer/placebo should be taken once daily, and preferably at the same time of day, consistently. An accidentally missed dose can be taken later on the same day but shall not be taken the next day. At the discretion of the Investigator, the following drugs may be co-administered with patiromer/placebo: allopurinol, amlodipine, amoxicillin, apixaban, aspirin, atorvastatin, cephalexin, cinacalcet, clopidogrel, digoxin, furosemide, glipizide, lisinopril, lithium, metoprolol, phenytoin, rivaroxaban, spironolactone, trimethoprim, valsartan, verapamil, and warfarin (see the Investigator's Brochure (IB), Version 13.0, dated 15 July 2020, for additional information [30]).

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

- Measure 1/3 cup (approximately 80 mL) of water. Pour half of the water into a glass, then add the contents of the prescribed number of patiromer/placebo packets 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

6.4 Package and Labeling

Patiromer powder for oral suspension or placebo will be provided by the Sponsor in a blinded manner as kits labeled for clinical trial use only. Each Run-in kit contains packets of patiromer, and these kits are only dispensed during the Run-in Phase (single-blinded for the subject). Each Treatment kit contains packets of either patiromer or placebo, and these kits are only dispensed in during the Treatment Phase (double-blinded). Additional details are provided in the Pharmacy Manual.

All packaging and labeling will be performed according to Good Manufacturing Practice guidelines. The study drug will be labeled in accordance with local regulations for investigational products.

6.5 Study Treatment Allocation

Each eligible subject will be assigned (blinded) to 1 of the 2 treatment groups via IWRS:

- Patiromer
- Placebo

Upon enrollment into the Run-in Phase of the study, each subject will be provided with instructions on proper dosing of patiromer and individualized instructions on when to take patiromer and other concomitant medications after considering the subject's current medication regimen, patiromer instructions regarding administration, and subject preference; see Section 7.1. 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 study drug dosing instruction requires changes at each visit and any changes will be communicated to the subject.

For subjects who qualify for the Blinded Treatment Phase, subjects will be randomized to either patiromer or placebo on Day 1/Baseline via IWRS. The study drug will be dispensed to subjects by the Investigational Pharmacist, or the qualified designee as assigned by the Principal Investigator.

Subjects will also be instructed to discard all used/empty packets but to bring back any unopened packets to the next visit for compliance assessment during both the Run-in and Blinded Treatment Phases. Subjects will be instructed to return the unopened (unused) patiromer/placebo packets in the outer packaging (boxes) in which they were originally provided. The Investigational Pharmacist or the qualified designee as assigned by the Principal Investigator will assess compliance based on returned unopened packets during the entire study to confirm that the subject is taking patiromer/placebo according to the protocol instructions.

Compliance will be documented and assessed on the basis of the prescribed number of patiromer/placebo packets, the duration of treatment, and the quantity of dispensed and returned unused packets. The Investigational Pharmacist or the qualified designee as assigned by the Principal Investigator will inform the study personnel if any compliance issues (e.g., <80% of expected usage) are identified so that the subject can be retrained on proper dosing and administration.

6.6 Site Supply, Storage, Accountability

6.6.1 Site Supply

Once a site has been approved to receive study drug, the site will be supplied with an initial shipment of patiromer/placebo sufficient for 1 to 2 subjects. The need for drug resupply will be assessed on a regular basis taking into account the number of subjects enrolled, the number of subjects in Screening at the site, and the overall enrollment into the study.

6.6.2 Storage

The Investigational Pharmacist or qualified designee as assigned by the Principal Investigator will verify and acknowledge receipt of each shipment of patiromer/placebo. Patiromer/placebo will be shipped and stored under refrigeration (2–8 degrees Celsius); see the Pharmacy Manual for additional details. Upon dispensation to a subject, patiromer/placebo should ideally be kept refrigerated at 2°C to 8°C (36°F to 46°F) if possible, but if stored at ambient room temperature (<25°C (<77°F)) patiromer/placebo must be used within 3 months of being taken out of the refrigerator [24]. All study drugs will be stored in a secure location. No subject other than those enrolled in this specific clinical study are allowed to take patiromer/placebo provided for this study. Patiromer/placebo provided for this study must not be utilized for any laboratory or animal research.

6.6.3 Accountability

All investigational product dispensed to subjects must be accurately recorded on the Investigational Product Accountability Records maintained at the Study Site by the Investigational Pharmacist or the qualified designee as assigned by the Principal Investigator. Subjects will be instructed to return all containers of investigational product dispensed to them (including unused packets and all containers) at each scheduled visit. All used containers will be retained at the site by the Investigational Pharmacist/qualified designee as assigned by the Principal Investigator for the Study Monitor's verification. Investigational product accountability and compliance for all investigational products will be performed by the Investigational Pharmacist or the qualified designee as assigned by the Principal Investigator at each scheduled study visit.

6.7 Drug Dose Modification

6.7.1 Management of Serum K^+

6.7.1.1 Management of Serum K^+ in the Run-in Phase (Single-Blinded)

During the Screening Phase, subjects who satisfy the eligibility criteria will be enrolled into the Run-in Phase. The purpose of the Run-in Phase is for management of serum K^+ with patiromer to allow optimization of RAASi medications (including initiation of MRA if not already receiving an MRA).

All subjects who meet the eligibility criteria for the Run-in Phase (single-blinded) will initiate patiromer (1 packet/day).

Subjects with 2 Screening K^+ values >5.0 mEq/L are considered hyperkalemic; these subjects begin patiromer when they qualify for the Run-in Phase, i.e., on the same day Run-in qualification is met or the next day.

All other subjects are considered normokalemic and serum K^+ will be measured again latest after the first week during the Run-in Phase. Patiromer will be started at this Week 1 Run-in Visit only if subjects are still normokalemic or have progressed to hyperkalemia; in case of newly observed hypokalemia (local serum K^+ <4.0 mEq/L) during the first Run-in Week, patiromer must not be given. In subjects with hypokalemia serum K^+ must be controlled after 3 days.

Note: If one screening K^+ value is >5.0 mEq/L and one value is ≤5.0 mEq/L, then a third peripheral venipuncture is performed within 1 day to obtain clarity, whether subject is hyperkalemic or normokalemic (local serum K^+ ≥4.0-≤5.0 mEq/L).

During the first Run-in Week, ACEi/ARB/ARNi and/or MRA doses ideally remain unchanged, if clinically indicated. On or after the initial first week visit during the Run-in Phase, up-titration of ACEi/ARB/ARNi and/or MRA may be initiated.

Patiromer is titrated during Run-in Phase to achieve target local serum K^+ level of ≥4.0-≤5.0 mEq/L (see below).

Note: Depending on the actual local serum K^+ value this could include patiromer 0 g/day (i.e., 0 packets/day) during the Run-in Phase.

- If local serum K^+ is >5.0 mEq/L, up-titrate patiromer in at least (≥) 1-week intervals by 1 packet/day (maximum dose is 3 packets/day)
  - If subject is taking maximum dose patiromer (3 packets/day) and local serum K^+ remains >5.0 mEq/L during the Run-in Phase, then subject is Run-in failed
- If local serum K^+ is >5.0–≤5.5 mEq/L and the reduction in serum K^+ from the previous visit was ≥0.4 mEq/L, at the Investigator's discretion, a dose increase may not be required
- If local serum K^+ is ≥4.3–≤5.0 mEq/L at the first week during the Run-in Phase, patiromer must be started at 1 packet/day
- If local serum K^+ is ≥4.0–<4.3 mEq/L at the first week during the Run-in Phase, patiromer may be started at 1 packet/day; initiation or increase of patiromer dose should be made with caution when local serum K^+ is ≥4.0–<4.3 mEq/L to avoid inducing hypokalemia

- If local serum K^+ decreases from >4.3 mEq/L to values <4.3 mEq/L, remaining ≥4.0 mEq/L, patiromer may be down-titrated by 1 packet/day (minimum dose is 0 packets/day); in case of a reversal of this decrease from <4.3 mEq/L but remaining ≥4.0 mEq/L to values ≥4.3 mEq/L at following visits, patiromer may be up-titrated by 1 packet/day; subjects must receive at least 1 packet/day at serum K^+ ≥4.3–≤5.0 mEq/L

  - If 1 week after reducing patiromer to 0 packets/day local serum K^+ remains stable ≥4.0–≤4.3 mEq/L, optimize RAASi dose and resume patiromer at 1 packet/day before considering these subjects as Run-in failed; initiation or increase of patiromer dose should be made with caution when local serum K^+ is ≥4.0-≤4.3 mEq/L to avoid inducing hypokalemia

- If local serum K^+ is <4.0 mEq/L, patiromer must be down-titrated to 0 g/day (i.e., 0 packets/day), with confirmation of hypokalemia within 3 days and follow-up in at least (≥) 1-week intervals until serum K^+ is ≥4.0 mEq/L. Resume patiromer only when local serum K^+ rises to >5.0 mEq/L

  - If 2 weeks after taking the minimum 0 packets/day, local serum K^+ remains <4.0 mEq/L during the Run-in Phase, then subject is Run-in failed

Once a subject meets all randomization criteria (see Section 5.4), they may be randomized into the Treatment Phase (double-blinded).

6.7.1.2 Management of Serum K^+ in the Treatment Phase (Double-Blinded)

After the Run-in Phase (single-blinded), eligible subjects will be randomized in a 1:1 ratio, to treatment with patiromer or placebo (double-blinded); see Study Schema.

Randomized subjects will begin their assigned treatment (patiromer or placebo), double-blinded, using the same number of packets established for patiromer at the end of the Run-in Phase and will continue the ACEi/ARB/ARNi and MRA regimen being administered at the end of the Run-in Phase.

For subjects who are on less than the target dose of either ACEi/ARB/ARNi or MRA, up-titration should continue if serum K^+ remains in the normokalemic range (serum K^+ ≥4.0–≤5.0 mEq/L).

After randomization, serum K^+ will be measured prior to initiation of assigned patiromer/placebo, double-blinded, on Treatment Day 1/Baseline, and at each subsequent visit during the Treatment Phase.

The Investigator may initiate an unscheduled visit at their discretion throughout the Treatment Phase.

Protocol allowed interventions for the management of hyperkalemia during the Treatment Phase include the following:

1. Up-titration of patiromer/placebo if on <3 packets per day

2. Down-titration or discontinuation of ACEi, ARB, ARNi and/or MRA

3. Initiate or increase diuretics

4. Dietary K^+ restriction

If local K^+ is >5.5 mEq/L, one or more of these interventions must be initiated either individually or in combination following the recommendations by practice guidelines. Repeat the K^+ measurement within 7 days; if local K^+ remains >5.5 mEq/L consider repeating the intervention or using other interventions in the order described above.

If local K^+ is between >5.0 mEq/L and ≤5.5 mEq/L, one or more of these interventions may be initiated per Investigator discretion.

Urgent treatment of hyperkalemia is in accordance with usual care and the Investigator's judgment. As described in Section 6.8.4.1, the only K^+ binding medications permitted for use during the study are temporary use of sodium or calcium polystyrene sulfonate and sodium zirconium cyclosilicate for up to 7 days or until serum K^+ is <5.0 mEq/L, or whichever occurs first. Patiromer/placebo must be withheld during temporary use of permitted K^+ binding medications.

If hypokalemia develops during the Treatment Phase, study drug should be down-titrated (lowest acceptable dose is 0 packets/day) until local serum K^+ ≥4.0 mEq/L.

The Investigator reinitiates patiromer/placebo treatment after a temporary interruption of dosing per treatment algorithm described in Section 6.7.1.1.

6.7.2 Optimization of ACEi/ARB/ARNi or MRA Medications During Run-in Phase

Because subjects will enter the Run-in Phase on a variety of different ACEi/ARB/ARNi and/or MRA medications, the Investigator will determine how to optimize each subject's ACEi/ARB/ARNi and/or MRA with the goal of achieving the best guideline-recommended HF treatment regimen for the subject and meeting the randomization criteria. The Investigator should manage ACEi/ARB/ARNi or MRA dose initiation or escalation to achieve 100% of target doses as recommended by the Study Manual [1] using clinical judgment to customize ACEi/ARB/ARNi or MRA addition or dose escalation based on subject response; see Study Manual for summary of practice guideline recommendations and the study-specific target doses.

Initiation or escalation of ACEi/ARB/ARNi or MRA dose should be made with caution when local serum K^+ is >5.0 mEq/L. Assessment of serum K^+ will occur at each visit. Patiromer dose will be titrated as described in Section 6.7.1.1 to achieve and/or maintain local serum K^+ within the range of ≥4.0–≤5.0 mEq/L during the Run-in Phase.

Subjects may be randomized anytime (but no later than 12 weeks) during the Run-in Phase when they meet all of the randomization criteria; see Section 5.4. Subjects who do not meet all of the Randomization criteria within 12 weeks are Run-in failures and may be rescreened after 3 months (Section 8.1.1.1).

Note: For the purpose of this study, maximum tolerated dose of ACEi/ARB/ARNi or MRA is not defined by hyperkalemia, but one that is limited by other health considerations, such as renal function decline or symptoms of hypotension. If intolerance of ACEi/ARB/ARNi or MRA is due to K^+ level, patiromer should be titrated as described in Section 6.7.1.1 and ACEi/ARB/ARNi or MRA dose increase should be attempted.

Table 3 describes an example of how ACEi/ARB/ARNi or MRA could be optimized during the Run-in Phase of the study.

Table 3 Example of ACEi/ARB/ARNi or MRA Optimization During Run-in Phase

Optimization of ACEi/ARB/ARNi:

For subjects initiating an ACEi/ARB/ARNi, the Investigator decides which ACEi/ARB/ARNi will be started and its dose.

ACEi/ARB/ARNi can be up-titrated by 50% of the prior dose to achieve target doses(1) in 1-week intervals, as tolerated.

If the local serum K^+ is >5.0 mEq/L to ≤5.5 mEq/L, increase the patiromer dose by 1 packet/day (if on <3 packets/day); the ACEi/ARB/ARNi dose may be escalated and the patient evaluated at the next scheduled visit. If local serum K^+ is >5.5 mEq/L, the patiromer dose must be increased by 1 packet/day (if on <3 packets/day) and optionally maintaining the same ACEi/ARB/ARNi dose or decreasing ACEi/ARB/ARNi dose. When patiromer titration results in local serum K^+ ≤5.0–≥4.0 mEq/L, ACEi/ARB/ARNi dose may be escalated if needed. See Section 6.7.1.1 for titration of patiromer during Run-in Phase.

Optimization of MRA:

For subjects who are not on an MRA at study entry, the Investigator determines which MRA to initiate, e.g., spironolactone and at which starting dose; 25 mg/day, or 25 mg/every other day, or 12.5 mg/day, at the Investigator's discretion.

For subjects who are on <50 mg/day of MRA, double their current dose up to 50 mg/day. Assess tolerance to the 50 mg target dose.Patiromer dose is titrated based on the subject's serum K^+ level as described in Section 6.7.1.1.

The subject can be randomized when:

- MRA dose is at least 50 mg/day and has been stable for at least 1 week
- ACEi/ARB/ARNi dose is ≥50% of target dose(1) and has been stable for at least 1 week
- Local serum K^+ is ≥4.0–≤5.0 mEq/L
- Patiromer dose is at least 1 packet/day

1 Study-specific target doses as per Table 4 in the Study Manual.

Notes: ACEi=Angiotensin-converting enzyme inhibitor; ARB=Angiotensin II receptor blocker; ARNi=Angiotensin receptor/neprilysin inhibitor; MRA=Mineralocorticoid receptor antagonist.

6.7.3 Temporary Interruption or Dose Reduction of HF Medications

During the Treatment Phase, temporary interruption or dose reduction of HF medications is allowed, with documentation of the reason for the change. HF medications may be reinitiated at the time that is deemed appropriate by the Investigator, and HF medications may be titrated as needed.

6.7.4 Management of eGFR Level

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 glomerular filtration rate have been seen with the initiation of MRA, similar to those seen with initiation of ACEi and ARB that have been attributed to transient changes in glomerular hemodynamics [31,32]. These changes typically do not impact long-term renal function. In this study, use of the Kidney Disease Outcomes Quality Initiative (KDOQI) recommendations for the detection and management of decreases in eGFR when initiating or up-titrating ACEi/ARB/ARNi or MRA [33] should be considered.

Based on KDOQI guidelines:

- An early decline in eGFR is defined as >15% reduction from Baseline (Screening) within 4 weeks of initiation of ACEi/ARB/ARNi or MRA.

- For decreases in eGFR up to 30%, no changes to ACEi/ARB/ARNi or MRA 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 ≥31–50%, the ACEi/ARB/ARNi or MRA dose should be decreased and the eGFR followed weekly. If the eGFR does not return to within 30% of Baseline within 4 weeks, ACEi/ARB/ARNi or MRA should be discontinued.

- ACEi/ARB/ARNi or MRA 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 until stabilized.

- An eGFR decline >50% must be reported as an AE; see Section 10.5 for reporting of AEs.

6.7.5 Usual Care

During the Treatment Phase, all subjects will receive usual care in accordance with guideline recommendations; see Study Manual. Usual care includes recommendations for all aspects of care for HFrEF patients (i.e., dietary and exercise recommendations,

implantable devices, and procedures and medications for the management of HF and blood pressure). Usual care may also include patient education. See Section 6.8.4 for additional details regarding concomitant medication use.

6.8 Prohibited Therapy, Special Considerations, and Concomitant Treatment

6.8.1 Prohibited Medications

During the entire study, the following medications will be prohibited while being treated with patiromer/placebo as these drugs may increase the risk of constipation and/or hyperkalemia:

- Colesevelam (increased risk of constipation)
- Colestipol (increased risk of constipation)
- Cholestyramine (increased risk of constipation)
- Drospirenone (increased risk of hyperkalemia)
- Aliskiren or any direct renin inhibitor (increased risk of hyperkalemia)
- K^+ sparing diuretics such as triamterene and amiloride (increased risk of hyperkalemia)
- K^+ supplements (increased risk of hyperkalemia)

6.8.2 MRA

In the study only 2 MRAs are allowed — spironolactone and eplerenone. For subjects who are already taking MRA at entry into the Run-in Phase, the MRA dose will be managed by the Investigator; see Section 6.7.2. In case subjects enter the Run-in Phase with spironolactone or eplerenone (any brand), subjects should stay on their initially prescribed MRA as long as they follow the guideline recommendations. In case subjects enter the Run-in Phase with an MRA other than spironolactone or eplerenone (any brand), subjects will have to switch to either of the 2 allowed MRAs to qualify for the Treatment Phase (see Randomization Criteria Section 5.4). A change from spironolactone to eplerenone is allowed if indicated due to medical reasons. For subjects who are not taking an MRA at entry into the Run-in Phase, and the Investigator prescribes spironolactone as the MRA, spironolactone may be reimbursed by the Sponsor, but only for these subjects who initiated spironolactone during the Run-in Phase.
Reimbursement of eplerenone might be considered by the Sponsor only in medically indicated cases (e.g., male subjects who develop breast discomfort or gynecomastia).

6.8.2.1 Potential Interactions with Spironolactone

For subjects receiving spironolactone, the following interactions described in the spironolactone prescribing information must be considered:

Digoxin:

The half-life of digoxin has been shown to be increased by spironolactone, which may result in increased serum levels of digoxin and may lead to subsequent digitalis toxicity. To avoid over- or under-digitalization, subjects taking digoxin should be carefully monitored when also taking spironolactone.

Lithium:

The renal clearance of lithium is reduced by diuretic agents, which can lead to a high risk of lithium toxicity. Generally, lithium should not be taken with diuretics [34].

6.8.2.2 Potential Interactions with Eplerenone

Because eplerenone metabolism is predominantly mediated via CYP3A4, eplerenone is contraindicated in all patients with concomitant administration of strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, nefazodone, troleandomycin, clarithromycin, ritonavir, and nelfinavir).

Digoxin:

The systemic exposure of digoxin has been shown to be increased by 16% when co-administered with eplerenone, which may lead to subsequent digitalis toxicity. Caution is recommended when digoxin is dosed near the upper limit of the therapeutic window.

Lithium

No interaction study has been performed with eplerenone and lithium. If this treatment combination is considered necessary, then plasma lithium concentrations should be monitored.

6.8.3 Caution Regarding the Use of NSAIDs or COX-2 Inhibitors

Nonsteroidal anti-inflammatory drugs (NSAIDs) or cyclooxygenase-2 (COX-2) inhibitors are not recommended by treatment guidelines for patients with HF, as they increase the risk of HF worsening and HF hospitalization. If new medications for mild to moderate pain relief are required, NSAIDs and COX-2 inhibitors (except low dose aspirin) should be avoided and alternatives such as acetaminophen should be used.

6.8.4 Concomitant Medications

Information on concomitant medication (prescription, over-the-counter, herbal and naturopathic remedies, etc.) will be collected beginning at Screening and continuing for the duration of the study (including EoS/ET Visit, Follow-up Phone Call, and Potassium Assessment Visit; see Section 8.5 and Section 8.6).

In general, subjects should continue on the same medications and regimens that were ongoing at the study entry with the exception of ACEi/ARB/ARNi and MRA medications (see Section 6.7.2). Doses of these concomitant 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.

6.8.4.1 Permitted K^+ Binding Medications

Only temporary use of sodium or calcium polystyrene sulfonate as well as sodium zirconium cyclosilicate is permitted for up to 7 days or until K^+ is <5.0 mEq/L, whichever occurs first. During this period patiromer/placebo must be withheld. During the study, the Medical Monitor should be notified when a subject has been treated with K^+ binding medications other than patiromer/placebo.

6.8.4.2 Magnesium Supplements

The use of magnesium supplementation is allowed during the study and should be considered for subjects whose serum magnesium is near or below the lower limit of normal based on the Investigator's decision and per standard of care.

7. RISKS/PRECAUTIONS

7.1 Precautions

Patiromer should be taken 3 hours before or 3 hours after administration of other concomitant medications. At the discretion of the Investigator, the following drugs may be co-administered with patiromer: allopurinol, amlodipine, amoxicillin, apixaban, aspirin, atorvastatin, cephalexin, cinacalcet, clopidogrel, digoxin, furosemide, glipizide, lisinopril, lithium, metoprolol, phenytoin, rivaroxaban, spironolactone, eplerenone, trimethoprim, valsartan, verapamil, and warfarin.

Patiromer binds K^+ and other cations. In conducted clinical trials with patiromer, magnesium was the only other cation with mean decreases in serum levels. Serum magnesium values <1.4 mg/dL (0.58 mmol/L) occurred in 9% of subjects treated with patiromer. Mean decreases in serum magnesium were 0.17 mg/dL (0.070 mmol/L) or less. Serum magnesium levels should be monitored in all subjects according to this protocol, and magnesium supplementation should be considered in those with low serum magnesium levels at the Investigator's discretion and per standard of care.

Studies in healthy adults on K^+-controlled diets demonstrated that about 73 mg of calcium is absorbed from a maximal 25.2 g daily dose of patiromer. Patiromer at 25.2 g/day increased urinary calcium levels by 72.9±23.4 mg/day in healthy individuals who are on a 1,000 mg/day calcium diet. Based on these findings, Investigators should evaluate the benefit/risk of continued supplemental calcium in addition to patiromer in each subject in the overall context of the subject's calcium intake, calcium balance, vitamin D status and bone health and adjust accordingly [35].

7.2 Adverse Reactions

The majority of the adverse reactions reported from clinical trials conducted with patiromer were GI disorders, with the most frequently reported adverse reactions being constipation (5.9%), diarrhea (4.9%), nausea (2.1%), flatulence (2.1%), and hypomagnesemia (4.1%) [30]. GI disorder reactions were generally mild to moderate in nature, did not appear to be dose related, generally resolved spontaneously or with treatment, and none were reported as serious. Hypomagnesemia was mild to moderate, with no subject developing a serum magnesium level <1.0 mg/dL (0.41 mmol/L).

8. STUDY PROCEDURES

For a detailed schedule of assessments (including all protocol required assessments, visits and visit windows) please refer to the Study Schema.

8.1 Screening and Run-in Phase Procedures (Single-Blinded, Up to 12 Weeks)

8.1.1 Screening Procedures

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) or equivalent Ethics Committee (EC) (see Section 13.2 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. Due to the expected waiting period of certain assessments (e.g., central laboratory parameters), screening activities can be held over different calendar days, but not exceeding 10 calendar days.

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 K^+ level by the local laboratory. At the Screening Visit, subjects will be assigned a unique subject number, which will be generated during Screening Visit registration in IWRS.

Subjects are first screened to identify those who satisfy the eligibility criteria (see Section 5.2 and Section 5.3, and Screening activities below). Once a subject meets all eligibility criteria, they will begin the Run-in Phase (see Section 8.1.2).

The following activities will be performed at Screening:

- Subject signs ICF
- Completion of the KCCQ and EQ-5D-5L questionnaire (must be performed by subjects after signing of the ICF but before all other assessments)
- IWRS registration
- Review inclusion and exclusion criteria
- Collect demographic information
- Assess NYHA class
- Review medical/surgical history
- Perform physical examination

- Measure weight and height
- Measure resting heart rate (pulse) after the subject has been sitting quietly for 5 minutes
- Measure blood pressure after the subject has been sitting quietly for 5 minutes (see Section 9.3.2)
- Perform 12-lead ECG
- Collect blood samples (measured locally and/or by central laboratory; see Table 5):
  - The following serum chemistry assessments will be measured locally; only when the subject meets all eligibility criteria will serum chemistry samples be sent to the central laboratory:
- Creatinine, eGFR
- Alanine aminotransferase, aspartate aminotransferase
- BNP or NT-proBNP
  - K^+ level (measured locally)
- 2 samples, each obtained from a separate venipuncture (e.g., one in each arm)
  - Hematology (central laboratory only)
- Collect urine samples for the evaluation of (see Table 5):
  - Urinalysis
  - Urine or serum pregnancy test
- Dispense urine sample containers for the visit at Week 1 during the Run-in Phase and provide proper training/instructions on use (see Section 9.6)
- Assess AEs/special situations
- Record concomitant medications and procedures

8.1.1.1 Rescreening of Subjects

Subjects who screen failed may be rescreened twice. The first rescreening must be at least 2 weeks after initial screen failure. If the subject also fails on the second attempt (first rescreening), another screening attempt is allowed but must be at least 6 months after the first rescreening. All Screening procedures described in Section 8.1.1 will be repeated. If a subject screen fails three times, they are no longer eligible to be screened again.

Subjects who Run-in failed may be rescreened once, earliest after 3 months from the date of Run-in failure. All screening procedures described in Section 8.1.1 will be repeated.

Subjects can be screened maximum three times in total as shown in Table 4.

Table 4 Rescreening of Subjects

Scenario #	1st Screen	2nd Screen	3rd Screen
1	Screen Fail	Screen Fail	
2	Screen Fail	Run-in Fail	
3	Screen Fail	Randomized	
4	Run-in Fail	Screen Fail	
5	Run-in Fail	Run-in Fail	
6	Run-in Fail	Randomized	
7	Screen Fail	Screen Fail	Screen Fail
8	Screen Fail	Screen Fail	Run-in Fail
9	Screen Fail	Screen Fail	Randomized
10	Screen Fail	Run-in Fail	Screen Fail
11	Screen Fail	Run-in Fail	Run-in Fail
12	Screen Fail	Run-in Fail	Randomized

8.1.2 Run-in Phase (Single-Blinded) Procedures

The purpose of the Run-in Phase is intended for the management of serum K^+ with patiromer (see Section 6.7.1.1) to allow optimization of ACEi/ARB/ARNi and MRA as tolerated (see Section 6.7.2). The frequency of subject weekly visits during the Run-in Phase is at the discretion of the Investigator.

Subjects with 2 Screening K^+ values >5.0 mEq/L are considered hyperkalemic; these patients begin patiromer (single-blinded) when they qualify for the Run-in Phase (i.e., on the same day Run-in qualification is met or the next day).

All other subjects are considered normokalemic and serum K^+ will be measured again latest at 1 week during the Run-in Phase. Patiromer will be started at the first week during the Run-in Phase only if subjects are still normokalemic or have progressed to hyperkalemia; in case of newly observed hypokalemia during the first week of the Run-in Phase, patiromer must not be given.

In subjects with hypokalemia serum K^+ must be controlled after 3 days to evaluate the effects of up-titrated ACEi/ARB/ARNi and/or MRA. Note: Depending on the actual local serum K^+ value this could include patiromer 0 g/day (i.e., 0 packets/day) during the Run-in Phase.

Except where noted, the following activities will be performed during all visits during the Run-in Phase:

- IWRS entry
- Measure resting heart rate (pulse) after the subject has been sitting quietly for 5 minutes
- Measure blood pressure after the subject has been sitting quietly for 5 minutes (see Section 9.3.2)
- Measure weight
- Collect blood samples for evaluation of:
  - K^+ level (measured locally)
- Review local laboratory K^+ results and adjust study medications according to Section 6.7.1.1
  - Magnesium level (measured locally) starting at 1 week after initiating the use of patiromer; consider periodic measurements of serum magnesium levels based on your clinical assessment of clinical signs of hypomagnesemia
  - Serum creatinine, eGFR (measured locally)
- Collect and measure urine albumin-to-creatinine ratio (ACR) (at first week during Run-in Phase only, not assessed at other Run-in Phase Visits; see Section 9.6)
- Assess AEs/special situations
- Assess ACEi/ARB/ARNi and MRA doses and determine if titration is needed (see Section 6.7.2)
- Record concomitant medications and procedures
- Investigational Pharmacist or qualified designee as assigned by the Principal Investigator performs the following:
  - Perform drug accountability
  - Dispense patiromer based on kit number(s) assigned by IWRS, if needed

- Reimburse MRA (only for subjects who are initiating spironolactone or eplerenone; see Section 6.7.2 and Section 6.8.2) if needed

- Assess if subject meets randomization criteria; if yes, the visit becomes the Day 1/Baseline Visit; see Section 8.2

- For subjects who Run-in fail a follow-up (K^+ assessment) visit needs to be completed; see Section 8.6

8.2 Treatment Phase (Double-Blinded) Procedures

Subjects who meet all randomization criteria (see Section 5.4) within the 12 weeks of the Run-in Phase (single-blinded) may be randomized on the same day in which they qualify, and all assessments performed at the visit in the Run-in Phase when they qualified will be considered the Baseline assessments and will not be repeated. The qualifying Run-in Phase visit will become the Day 1/Baseline Visit.

If a subject cannot be randomized on the same day the randomization criteria were met, then the subject should be randomized within 1 week and all assessments described in Section 8.2.1 will be repeated on the day of randomization.

8.2.1 Day 1/Baseline Visit

The following activities will be performed at the Day 1/Baseline Visit:

- Confirm subject meets all randomization criteria

- IWRS randomization to patiromer or placebo (assignment blinded)

- Perform KCCQ and EQ-5D-5L questionnaire (see Section 9.7)

- Assess NYHA class

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

- Measure blood pressure after the subject has been sitting quietly for 5 minutes (see Section 9.3.2)

- Measure weight

- Collect blood samples for evaluation of (see Table 5):

  - K+ level (measured locally and by central laboratory)

  - Serum chemistry including creatinine, eGFR (central laboratory)

  - MRA level (see Section 9.2.1)

- High sensitivity troponin

- Collect urine samples for the evaluation of
  - Urinalysis
  - Urine or serum pregnancy test
- Dispense urine sample containers for Day 3 Visit and provide proper training/instructions on use (see Section 9.6)
- Assess AEs/special situations
- Record concomitant medications and procedures
- Investigational Pharmacist or qualified designee as assigned by the Principal Investigator performs the following:
  - Perform drug accountability
  - Dispense patiromer/placebo based on kit number(s) assigned by IWRS and collect all packets or kits dispensed during the Run-in Phase

8.2.2 Day 3 Visit (±1 Day)

The following activities will be performed at the Day 3 Visit:

- IWRS entry
- Measure resting heart rate (pulse) after the subject has been sitting quietly for 5 minutes
- Measure blood pressure after the subject has been sitting quietly for 5 minutes (see Section 9.3.2)
- Measure weight
- Collect blood samples for evaluation of:
  - K^+ level (measured locally)
    - Review local K^+ results and adjust study medications according to Section 6.7.1.2
  - Serum creatinine, eGFR (measured locally)
- Collect and measure urine ACR (see Section 9.6)
- Assess AEs/special situations

- Record concomitant medications and procedures
- Investigational Pharmacist or qualified designee as assigned by the Principal Investigator performs the following:
  - Perform drug accountability
  - Dispense patiromer/placebo based on kit number(s) assigned by IWRS as needed
- Reimburse MRA (only for subjects who are initiating spironolactone or eplerenone; see Section 6.7.2 and Section 6.8.2) if needed

8.2.3 Week 1 Visit (±3 Days)

The following activities will be performed at the Week 1 Visit:

- IWRS entry
- Measure resting heart rate (pulse) after the subject has been sitting quietly for 5 minutes
- Measure blood pressure after the subject has been sitting quietly for 5 minutes (see Section 9.3.2)
- Measure weight
- Collect blood samples for evaluation of (see Table 5):
  - K^+ level (measured locally)
    - Review K^+ results and adjust study medications according to Section 6.7.1.2
  - Serum creatinine, eGFR (measured locally)
  - MRA level (see Section 9.2.1)
- Dispense urine sample containers and provide proper training/instructions on use (see Section 9.6)
- Assess AEs/special situations
- Record concomitant medications and procedures
- Investigational Pharmacist or qualified designee as assigned by the Principal Investigator performs the following:
  - Perform drug accountability
  - Dispense patiromer/placebo based on kit number(s) assigned by IWRS as needed

- Reimburse MRA (only for subjects who are initiating spironolactone or eplerenone; see Section 6.7.2 and Section 6.8.2) if needed

8.2.4 Week 2 Visit (±3 Days)

If at Week 2 there are changes to ACEi, ARB, ARNi and/or MRA dose or serum K^+ varies outside the intended range, unscheduled weekly visits should occur until stability (i.e., at 2 consecutive visits) returns.

The following activities will be performed at the Week 2 Visit:

- IWRS entry
- Measure resting heart rate (pulse) after the subject has been sitting quietly for 5 minutes
- Measure blood pressure after the subject has been sitting quietly for 5 minutes (see Section 9.3.2)
- Measure weight
- Collect blood samples for evaluation of:
  - K^+ level (measured locally)
    - Review K^+ results and adjust study medications according to Section 6.7.1.2
  - Serum creatinine, eGFR (measured locally)
- Collect and measure urine ACR (see Section 9.6)
- Assess AEs/special situations
- Record concomitant medications and procedures
- Investigational Pharmacist or qualified designee as assigned by the Principal Investigator performs the following:
  - Perform drug accountability
  - Dispense patiromer/placebo based on kit number(s) assigned by IWRS as needed
- Reimburse MRA (only for subjects who are initiating spironolactone or eplerenone; see Section 6.7.2 and Section 6.8.2) if needed

8.2.5 Week 6 Visit (±14 Days)

If there are changes to ACEi, ARB, ARNi and/or MRA dose or serum K^+ varies outside the intended range, unscheduled weekly or monthly visits should occur until stability (i.e., at 2 consecutive visits) returns.

The following activities will be performed at the Week 6 Visit:

- IWRS entry
- Measure resting heart rate (pulse) after the subject has been sitting quietly for 5 minutes
- Measure blood pressure after the subject has been sitting quietly for 5 minutes (see Section 9.3.2)
- Measure weight
- Collect blood samples for evaluation of:
  - K^+ level (measured locally)
    - Review K^+ results and adjust study medications according to Section 6.7.1.2
  - Serum creatinine, eGFR (measured locally)
- Dispense urine sample containers and provide proper training/instructions on use (Week 10 Visit only; see Section 9.6)
- Assess AEs/special situations
- Record concomitant medications and procedures
- Investigational Pharmacist or qualified designee as assigned by the Principal Investigator performs the following:
  - Perform drug accountability
  - Dispense patiromer/placebo based on kit number(s) assigned by IWRS as needed
- Reimburse MRA (only for subjects who are initiating spironolactone or eplerenone; see Section 6.7.2 and Section 6.8.2) if needed

8.2.6 Week 18 Visit (-30 Days) and Every 3 Months Visit Until Event-Driven EoS (-30 Days)

The following activities will be performed at the Week 18 Visit (i.e., first of the Every 3 Months visits) and at each subsequent visit that will occur every 3 months until the EoS:

- IWRS entry
- Perform KCCQ and EQ-5D-5L questionnaire at 3 (i.e., Week 18), 6, and 12 months and every 12 months thereafter (see Section 9.7)
- Assess NYHA class
- Measure resting heart rate (pulse) after the subject has been sitting quietly for 5 minutes
- Measure blood pressure after the subject has been sitting quietly for 5 minutes (see Section 9.3.2)
- Measure weight
- Collect blood samples for evaluation of (see Table 5):
  - K^+ level (measured locally and by central laboratory)
    - Review K^+ results and adjust study medications according to Section 6.7.1.2
  - Serum chemistry including creatinine, eGFR (central laboratory)
  - Hematology (central laboratory)
  - BNP or NT-proBNP (central laboratory)
  - MRA level at 3 (i.e., Week 18), 6, and 12 months and every 12 months thereafter (see Section 9.2.1)
- Collect and measure urine ACR (see Section 9.6)
- Dispense urine sample containers (see Section 9.6)
- Assess AEs/special situations
- Record concomitant medications and procedures
- Investigational Pharmacist or qualified designee as assigned by the Principal Investigator performs the following:
  - Perform drug accountability
  - Dispense patiromer/placebo based on kit number(s) assigned by IWRS as needed
- Reimburse MRA (only for subjects who are initiating spironolactone or eplerenone; see Section 6.7.2 and Section 6.8.2) if needed.

8.3 Unscheduled Visit Procedures

An unscheduled visit may occur at the discretion of the Investigator.

During the Double-Blinded Treatment Period, anytime there are changes to ACEi, ARB, ARNi and/or MRA dose or interventions for serum K^+ outside the desired range, additional Unscheduled Visits should occur weekly until the ACEi, ARB, ARNi and/or MRA dose or serum K^+ has been stable for at least 2 consecutive visits.

At an unscheduled visit during any phase of the study, the following activities will be performed:

- IWRS entry, in case IMP is to be re-dispensed
- Measure resting heart rate (pulse) after the subject has been sitting quietly for 5 minutes
- Measure blood pressure after the subject has been sitting quietly for 5 minutes (see Section 9.3.2)
- Measure weight
- Collect blood samples for evaluation of:
  - K+ level (measured locally)
  - Serum creatinine, eGFR (measured locally)
- Assess AEs/special situations
- Record concomitant medications and procedures

Any other study assessments (see Section 8.8) may be performed at the discretion of the Investigator during an unscheduled visit.

The following activities are optional during an unscheduled visit:

- Perform physical examination
- Collect blood sample for the evaluation of hematology (central laboratory)
- Investigational Pharmacist or qualified designee as assigned by the Principal Investigator performs the following:
  - Perform drug accountability
  - Dispense patiromer/placebo based on kit number(s) assigned by IWRS

- Reimburse MRA (only for subjects who are initiating spironolactone or eplerenone; see Section 6.7.2 and Section 6.8.2) if needed

8.4 EoS Visit Procedures

The common EoS date will be set by the Sponsor. The common EoS will occur when 820 subjects have completed the Week 6 visit. Recruitment will be stopped, and subjects called in by the sites for the EoS visit when it is projected that a sufficient number of subjects have been enrolled in order for 820 subjects to reach the Week 6 visit. All randomized subjects, including those who prematurely discontinued patiromer/placebo, will complete the EoS Visit within the timeline provided by the Sponsor around the common EoS date. Investigational sites will be notified of the study termination date as soon as possible after the decision is taken and should advise ongoing study subjects of the study termination date thereafter. All randomized subjects with final dose of patiromer/placebo within 1 week of the EoS Visit will complete a Potassium Assessment Visit within 2 weeks or as soon as possible thereafter to assess serum K^+ levels and to collect AE data (see Section 8.6).

The following assessments will be performed at the EoS Visit:

- IWRS entry
- Perform KCCQ and EQ-5D-5L questionnaire (see Section 9.7)
- Assess NYHA class
- Perform physical examination
- Measure resting heart rate (pulse) after the subject has been sitting quietly for 5 minutes
- Measure blood pressure after the subject has been sitting quietly for 5 minutes (see Section 9.3.2)
- Measure weight
- Collect blood samples for evaluation of (see Table 5):
  - K^+ level (measured locally and by central laboratory)
  - Serum chemistry including creatinine, eGFR (central laboratory)
  - Hematology (central laboratory)
  - BNP/NT-proBNP
  - High sensitivity troponin

  - MRA level (see Section 9.2.1)

- Collect urine samples for the evaluation of (see Table 5):
  - Urinalysis
  - Assess urine ACR (see Section 9.6)
  - Urine or serum pregnancy test
- Assess AEs/special situations
- Record concomitant medications and procedures
- Investigational Pharmacist or qualified designee as assigned by the Principal Investigator performs drug accountability and collects all packets or kits dispensed during the Treatment Phase

8.5 Early Termination Procedures

For subjects who prematurely withdraw from the study (before the common EoS date) and who do not allow any further contact (full withdrawal of consent), every effort should be made by the site to ensure that the subject completes the ET Visit, which should be performed on the day of the withdrawal or as soon as possible thereafter. The assessments performed at the ET Visit will be the same as the EoS Visit (see Section 8.4).

8.6 Potassium Assessment Visit Procedures (Up to 2 Weeks After Withdrawal from Patiromer/Placebo Treatment)

All subjects who discontinue patiromer/placebo treatment during the study, including Run-in Failures/Randomization failures, or whose final patiromer/placebo dose is within 1 week of the EoS Visit, will complete a Potassium Assessment Visit within 2 weeks or as soon as possible thereafter to assess serum K^+ and to collect AE data.

The following activities will be performed at the Potassium Assessment Visit:

- Assess NYHA class
- Measure resting heart rate (pulse) after the subject has been sitting quietly for 5 minutes
- Measure blood pressure after the subject has been sitting quietly for 5 minutes (see Section 9.3.2)
- Measure weight
- Collect blood samples for evaluation of (see Table 5):
  - K^+ level (measured locally and by central laboratory)

- Serum chemistry including creatinine, eGFR (central laboratory)
- Hematology (central laboratory)

- Assess AEs/special situations
- Record concomitant medications and procedures

8.7 Follow-up Phone Call (at Least 2 Weeks After EoS/ET Visit and Run-in Failure)

For subjects who performed the Potassium Assessment Visit <2 weeks after ET or EoS a Follow-up Phone Call at least 2 weeks after ET or EoS will be done. Subjects determined as Run-in failed during the Run-in Phase will also have a Follow-up Phone Call after 2 weeks if the Potassium Assessment Visit was performed <2 weeks after Run-in failure.

Assessments performed over the phone call:

- Assess AEs/special situations with an onset date up to 2 weeks after ending study participation
- Concomitant medication assessment for any drugs used to treat an AE with an onset date up to 2 weeks after ending study participation

8.8 Allowed Adaptations in Case of Extraordinary Events, e.g., COVID-19

Extraordinary events may call for specific measures to maintain subject safety and guarantee conduct of clinical investigations according to established general and specific guidelines and regulations to meet agreed regulatory, quality, and scientific expectations.

For this, the following adaptations are considered for specific situations:

- Site visits are not possible within the defined time window, possibly leading to delayed
  - Physical examination: consultation by local physician, follow-up assessment and guidance on drug adaptations via phone, remote visits at subject's home (e.g., home nursing)
  - Laboratory assessments: consultation by local physician, visit at local laboratory for blood analysis, or via home nursing

- Adaptation of IMP: dispense sufficient amount of IMP at previous visit, delivery to subject's home by qualified designee as assigned by the Principal Investigator, or consider handover of IMP to relatives if allowed and in compliance with the applicable ICH Good Clinical Practice (GCP) and other applicable laws and regulations, phone call by treating physician to guide dose adaptation of drugs including RAASi medication, if needed
- On-site monitoring: accept delayed on-site monitoring, conduct remote monitoring
- On-site auditing: accept delayed on-site auditing, conduct remote auditing
- AE/SAE/special situation reporting: frequent phone call visits

- Site visits are not possible within the defined time window, possibly leading to no
  - Physical examination: consultation by local physician, follow-up clinical assessment via phone remote visits at subject's home (e.g., home nursing)
  - Laboratory assessments: consultation by local physician, local laboratory for blood analysis, or via home nursing
  - Adaptation of IMP: dispense sufficient amount of IMP at previous visit, delivery to subject's home by qualified designee as assigned by the Principal Investigator, or consider handover of IMP to relatives if allowed and in compliance with the applicable ICH GCP and other applicable laws and regulations, phone call by treating physician to guide dose adaptation of drugs including RAASi medication, if needed
  - On-site monitoring: accept delayed on-site monitoring, conduct remote monitoring
  - On-site auditing: accept delayed on-site auditing, conduct remote auditing
  - AE/SAE/special situation reporting: frequent phone call visits

9. STUDY ASSESSMENTS

9.1 Potassium

Serum K^+ levels will be assessed locally and/or by central laboratory at all study visits including Unscheduled Visits (Schedule of Events). Detailed instructions on how to draw blood and prepare specimens for analysis are provided in the Laboratory Manual.

The definition of hyperkalemia follows the European Society of Cardiology expert consensus document on the management of hyperkalemia in patients with cardiovascular disease [36]. Hyperkalemia is considered for all serum K^+ values >5.0 mEq/l with the gradings of mild hyperkalemia (serum K^+ >5.0 mEq ≤5.5 mEq/l), moderate hyperkalemia (serum K^+ >5.5 mEq ≤6.0 mEq/l) and severe hyperkalemia (serum K^+ >6.0 mEq).

9.1.1 Preventing, Identifying, and Handling Hemolyzed Samples

Hemolysis of blood specimens may result in spuriously high K^+ levels, potentially leading to inappropriate up-titrating of patiromer/placebo or inappropriate down-titration or discontinuation of ACEi/ARB/ARNi or MRA 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 K^+ 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 K^+ values from 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 K^+ value. If a 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 patiromer/placebo titration and subject management, is hemolyzed (e.g., by visual inspection of the local laboratory serum sample), the site will repeat the K^+ measurement from a separate blood draw within 1 day in order to ensure accurate decision-making regarding management of K^+.

9.1.2 Deviant Serum Potassium Levels During Screening Process

At Screening, serum K^+ is measured twice to assure correct identification of hyperkalemic and normokalemic subjects. Should the 2 serum K^+ levels differ substantially with one value being ≤5.0 and the other >5.0 mEq/L, then a separate blood draw within 1 day, latest the next calendar day will be performed.

9.2 Laboratory Tests

All laboratory assessments will be performed by central laboratory unless specified in the Schedule of Events.

See Table 5 for the list of central laboratory assays.

Table 5 List of Central Laboratory Assays

Serum Chemistry Panel	Hematology
Alanine aminotransferase	WBC count
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	Spot urine for albumin and creatinine (for ACR)
Potassium	**Other**
Sodium	BNP/NT-proBNP
Total cholesterol	High sensitivity troponin
Total protein	MRA level (see Section 9.2.1)
Uric acid	Pregnancy test (urine)[(1)]

1 If needed, serum pregnancy test will be locally measured.

Notes: ACR=Albumin-to-creatinine ratio; BNP=Brain natriuretic peptide; eGFR=Estimated glomerular filtration rate; MRA=Mineralocorticoid receptor antagonist; NT-proBNP=N-terminal pro b-type brain natriuretic peptide; WBC=White blood cell.

To qualify for the study, subject must have eGFR ≥20 mL/min/1.73 m^2 at Screening from a single local laboratory analysis of serum creatinine and calculation using the CKD-EPI creatinine equation. If the local laboratory does not provide an eGFR value using the CKD-EPI creatinine equation, the National Kidney Foundation online eGFR calculator (https://www.kidney.org/professionals/kdoqi/gfr_calculator) may be used.

For subjects who develop anuria during the study, urine assessments will not be required.

9.2.1 MRA Level

Blood samples from subjects receiving an MRA will be analyzed for MRA levels. Please refer to the Laboratory Manual for additional information. MRA must be taken in the morning before blood withdrawal for analysis of MRA levels.

9.3 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.

9.3.1 Heart Rate

Heart rate is to be measured for a full 60 seconds or as provided using the oscillometric blood pressure device.

9.3.2 Blood Pressure

Blood pressure will be performed using an oscillometric device after resting for 5 minutes. Blood pressure data for each visit should be recorded in the respective eCRF.

9.4 Physical Examination

Physical examination will be performed as indicated in the Schedule of Events. 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.

9.5 ECG Assessment

If the Investigator is concerned regarding any K^+ value, a retest of K^+ 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 K^+-related ECG change is observed, the Investigator should apply the appropriate standard of care to stabilize the myocardium, which may include any or all of the following

depending on the subject's clinical situation: intravenous calcium gluconate, intravenous insulin and glucose, inhaled beta2-agonists. In such cases, the ECG should be repeated within 2 to 3 minutes following any of the above interventions, and the subject should be assessed for referral to an emergency care facility.

9.6 Urine Collection for ACR

Urine samples will be collected as indicated in the Schedule of Events. The urine sample containers will be dispensed at the visit prior to the study visit where urine ACR is assessed and subjects will be provided with training and instructions on proper use of the urine containers. For the Run-in Phase Week 1 Visit assessment of urine ACR, the urine sample containers will be dispensed at the Screening Visit. For the Blinded Treatment Phase, at the Day 3 Visit, the urine sample container will be dispensed at the Day 1/Baseline Visit (see Section 8). Note: Urine ACR is collected and measured at the Run-in Phase Week 1 Visit only and not assessed at other Run-in Phase Visits.

The subject will be collecting the urine samples at home. Two urine samples will be collected: (1) the first morning void the day prior to, and (2) the first morning void the day of the study visit where urine samples will be collected from the subject. 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.

For subjects who develop anuria during the study, urine assessments will not be required.

9.7 Patient-Reported Outcomes

Patient-reported outcomes KCCQ and 5Q-5L questionnaires will be completed by the subjects before study staff performs any clinic or study assessments to avoid biasing the subjects' responses. The study coordinators will review the subject's responses immediately after completion of the questionnaires by subject to ensure that all questions are answered. The site will use the KCCQ and 5Q-5L questionnaires to complete the corresponding modules in the electronic data capture (EDC) system. The original questionnaires must be retained as source documentation.

KCCQ

The KCCQ is a self-administered instrument that is composed of 23 items, which quantifies the frequency, severity, and recent change in physical function and symptoms. Subjects will complete the KCCQ as indicated in the Schedule of Events.

EQ-5D-5L Questionnaire

The EQ-5D-5L questionnaire is composed of 5 questions each with 5 levels (e.g., no problems, slight problems, moderate problems, severe problems, and extreme problems) representing 5 health domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-5D-5L questionnaire also includes a visual analog scale 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 as indicated in the Schedule of Events.

9.8 Contraception in Women of Child-Bearing Potential

For females of child-bearing potential, urine or serum pregnancy test is performed at Screening, Day 1/Baseline Visit, and EoS/ET Visit.

Methods of birth control in sexually active subjects approved for use during this study include:

- Hormonal birth control (oral, skin patch, or injection for at least 28 days prior to the first Screening Visit)
- Removal of the uterus or tubal ligation (already performed at least 6 months before screening)
- Intrauterine device (already performed at least 6 months before screening)
- Male partner who has had a vasectomy
- Condom with spermicidal foam/gel/film/cream/suppository

Females of non-child-bearing potential must be postmenopausal with amenorrhea for 12 consecutive months before the Screening Visit or serum follicle stimulating hormone levels consistent with postmenopausal status as per the Investigator's judgment.

9.9 Assessment of Left Ventricular Ejection Fraction

The date for the left ventricular ejection fraction measurement used to determine eligibility must be <12 months before the Screening date. The left ventricular ejection fraction may have been measured by echocardiographic, radionucleotide, MRI, angiographic, or computerized tomography methods. If the assessment results in a range of values, then the average value is to be used.

9.10 HEOR Assessments

The objective is to select and include HEOR parameters as exploratory endpoints in the study protocol with the aim of analyzing both health-related quality of life and healthcare resource utilization. The choice of HEOR endpoints will be agreed and validated by payers and evaluators of Health Technology Assessment bodies from the US and Europe. The former will allow us to design a cost-effectiveness model, fed with clinical and HEOR data from DIAMOND, which will be potentially adaptable to the payers requirements in the US and those from five key European countries. The HEOR analysis will be described in a separate SAP.

10. EVALUATION, RECORDING, AND REPORTING OF ADVERSE EVENTS

10.1 Definition of Adverse Events

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 [36]. 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 10.3), including signs or symptoms associated with an underlying condition that were not present prior to the AE reporting period; (2) a pre-existing condition that has worsened in severity or frequency or changed in character after the subject signs the ICF 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.

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 (see Section 10.8)

- Pregnancy (see Section 10.8.3.2 for reporting obligations)

10.2 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 2 weeks after the EoS. For screen-failed subjects the AE reporting period ends at the time of screen failure. All AEs persisting at the time of study completion will be followed by the Investigator through contact with the subject until resolution or stabilization, or the subject is lost to follow-up and cannot be contacted. The outcome must be documented in the subject's source documents. The Investigator must report any SAEs that occur after the protocol specified reporting period if according to the

Investigator's assessment there was a reasonable possibility that the SAE was related to patiromer/placebo or any study procedures.

10.3 Eliciting Adverse Events

If the subject reports an AE, it is the Investigator's responsibility to acquire sufficient information in order to assess causality. This may require additional laboratory testing, physical examinations, telephone contacts, etc.

In order to avoid bias in eliciting AEs, subjects should be asked a non-leading question, such as "How are you feeling?" It is also important to question the subject in a non-leading way about changes in their health or concomitant medication usage since their last visit. This information should be collected prior to completion of assessments at all study visits. In addition, any symptoms/conditions reported during assessments and deemed to be clinically significant by the Investigator will be assessed as AEs.

10.4 Assessing Adverse Events

10.4.1 Intensity/Severity

The medical assessment of intensity will be determined by using the following definitions:

- Mild: The AE is easily tolerated and does not interfere with usual activity
- Moderate: The AE interferes with daily activity, but the subject is still able to function
- Severe: The AE is incapacitating, and the subject is unable to work or complete usual activity

A new event will be documented each time the intensity of an event has changed.

It is important to note the distinctions between severe AEs and serious AEs (SAEs). Severity is a classification of intensity of a specific event (as in mild, moderate, or severe); however, the event itself may be of relatively minor medical significance (such as severe headache). An SAE, however, is an AE that meets any of the regulatory specified criteria required for designation as seriousness described in Section 10.7.1 (i.e., a headache may be severe (interferes significantly with subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs).

10.4.2 Causality and Reporting

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 will each assess relatedness of the AE to the investigational drugs, patiromer/placebo, 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 drug 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.

10.4.3 Outcome Categorization

Outcome is classified as: recovered/resolved (i.e., without sequelae); recovered/resolved with sequelae; not recovered/not resolved; fatal; or unknown (if follow-up is not possible).

If the outcome of an SAE is reported as recovered/resolved with sequelae, the Investigator specifies the kind of sequelae on the SAE form. If the outcome of an SAE is reported as unknown, the Investigator specifies (on the SAE form) the rationale why unknown was selected.

"Fatal" is to be recorded as an outcome when the AE results in death. 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. If more than one AE is possibly related to the subject's death, the outcome of death will be indicated for the AE that, in the opinion of the Investigator, is the most plausible cause of death. All other ongoing AE/SAEs will be recorded as not recovered/not resolved at the time of death.

10.5 Recording and Reporting

10.5.1 Persistent or Recurrent Adverse Events

AEs that extend continuously, without resolution, between trial assessments will only be recorded once in the eCRF. A new event will be documented each time the intensity of an event has changed.

AEs that resolve and subsequently recur will have each recurrence recorded separately in the eCRF.

10.5.2 Diagnosis Versus Signs and Symptoms

Where possible, the Investigator reports a diagnosis rather than individual signs and symptoms or abnormal laboratory values. However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded in the eCRF. If a diagnosis is subsequently established, all previously reported AEs based on signs and symptoms should be nullified and replaced by 1 AE report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

The Investigator should use standard medical terminology/concepts; avoid colloquialisms and abbreviations. Only 1 AE term should be recorded in each event field in the eCRF.

10.5.3 Pre-existing Medical Conditions

A pre-existing medical condition is one that is present at the Screening Visit for this study. Such conditions should be recorded on the medical history eCRF. A pre-existing medical condition should be recorded as an AE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the AE eCRF, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

10.5.4 Clinical Laboratory Evaluations

Not every out-of-range laboratory result qualifies as an AE. A laboratory investigation result must be reported as an AE if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation). For the purpose of this study, AEs should be reported if K^+ <4.0 mEq/L or >5.0 mEq/L
- Results in a medical intervention (e.g., K^+ supplementation for hypokalemia) or a change in concomitant therapy

- Presents shift of a parameter from a normal value to a pathological value or a further worsening of an already pathological value

- Is clinically significant in the Investigator's judgment

It is the Investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing treatment or after the end of treatment with the investigational product, and the range of variation of the respective parameter within its reference range, must be taken into consideration.

The Investigator has the responsibility to determine the clinical significance of each abnormality.

If, at the end of the Treatment Phase, there are pathological laboratory values which were not present at Baseline, further clinical or laboratory investigations should be performed until the values return to within reference range or until a plausible explanation (e.g., concomitant disease) is found for the pathological laboratory values.

The Investigator should decide, based on the above criteria and the clinical condition of a subject, whether a change in a laboratory parameter is clinically significant and therefore represents an AE. If the Investigator considers such an AE as serious (e.g., medically significant event fulfilling criteria per Section 10.7.1), it must be reported as an SAE.

If a laboratory abnormality meeting the above criteria is a sign of a disease or syndrome only the diagnosis should be recorded in the eCRF.

If a laboratory abnormality meeting the above criteria is not a sign of a disease or syndrome, the abnormality itself should be recorded in the eCRF, along with a descriptor indicating if the test result is above or below the normal range (e.g., "elevated K^+," as opposed to "abnormal K^+").

If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the AE, for example, hypercalcemia or hypoglycemia. Observations of the same laboratory abnormality from visit to visit should not be repeatedly recorded in the eCRF unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

All pathological laboratory findings/values diagnosed throughout the treatment period should be reviewed by the Investigator to provide a final clinical assessment in view of the dynamic of laboratory changes/abnormalities.

10.5.5 Abnormal Vital Signs and Other Abnormalities

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/placebo
- Required treatment or subject referral for further testing outside the protocol (repeat testing or titration are within protocol procedures)

It is the Investigator's responsibility to review all vital sign, ECG, and other safety findings. Medical and scientific judgment should be exercised in deciding whether an isolated abnormality should be classified as an AE.

If a clinically significant abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded in the eCRF.

Observations of the same clinically significant abnormality from visit to visit should not be repeatedly recorded in the eCRF unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

10.6 Adverse Drug Reaction and Reference Safety Information

10.6.1 Adverse Drug Reaction

An adverse drug reaction (ADR) is an untoward and unintended response to an IMP related to any dose administered. This definition implies a reasonable possibility of a causal relationship between the event and the IMP. This means that there are facts (evidence) or arguments to suggest a causal relationship.

All AEs judged as having a reasonable causal relationship to a medicinal (investigational) product will be designated as ADRs.

10.6.2 Reference Safety Information

The Reference Safety Information (RSI) presents the basis for expectedness assessment of an ADR for expedited reporting and annual safety reporting, as well as surveillance of subject's safety in a clinical trial by regulatory (and ethic) bodies.

In the context of this study, the RSI for patiromer is integrated in Table 19 of the patiromer IB.

10.7 Serious Adverse Event

10.7.1 Definition of Serious Adverse Event

An SAE is defined as any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (the term life-threatening in the definition of serious refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe)
- Requires inpatient hospitalization or prolongation of existing hospitalization. Hospitalization for elective surgery, i.e., a planned, non-emergency medical procedure, social hospitalizations and hospitalizations lasting less than 24 hours are not considered SAEs
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event (i.e., medically significant)

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These events should also be considered as serious.

Any worsening of a pre-existing medical condition or any new medical condition that meets the above SAE criteria should be considered as an SAE.

The Investigator is encouraged to discuss with the CRO or Sponsor any AEs for which the issue of seriousness is unclear or questionable.

10.7.1.1 Situations That Are Not Considered SAEs

The following situations are not considered as SAEs:

- Elective or pre-planned surgery for a pre-existing condition that has not worsened
- Routine health assessments requiring admission not associated with any deterioration in condition
- Social admission (lack of housing, family circumstances, etc.)

10.7.2 Serious Adverse Event Reporting

The SAE reporting period begins at the time the ICF is signed by the subject. The SAE reporting period ends 2 weeks following the EoS or until 2 weeks after last study drug administration, whichever is longer. If the final Follow-up Visit is conducted as a telephone call rather than a formal visit, the Investigator must report any SAEs that occur during this period.

The occurrence of an SAE must be immediately reported to the Sponsor (or its delegate, e.g., CRO) within 24 hours of awareness by facsimile, email, or telephone/via EDC system. This includes all SAEs (independent of relationship to study treatment).

A death occurring during the study or which comes to the attention of the Investigator within 2 weeks after the EoS or until 2 weeks after the last study drug administration, whichever is longer, whether considered treatment-related or not, must be reported to the CRO/Sponsor.

Any SAE considered to have a causal relationship (i.e., related) to the investigational product and discovered by the Investigator at any time after the study should be reported. A rationale for the assessment of a causal relationship must be provided by the Investigator. Any safety information that is obtained after database lock of the clinical database will be documented in the safety database and implications for handling the data in the clinical database assessed on an individual case basis.

The onset date of the SAE is defined as the date the signs and symptoms/diagnosis became serious (i.e., met at least one of the criteria for seriousness; see Section 10.7.1). If the subject experiences an AE and it progresses into an SAE, a new SAE should be recorded. The original AE stop date should be the same as the start date of the SAE. However, when the SAE resolves and the pre-existing AE is still ongoing, this should be recorded as a new AE. The resolution date of an SAE is defined as when the symptoms resolve, or the event is considered chronic (e.g., sequelae) or stable, and/or if the seriousness criteria are no longer applicable.

The Investigator must complete the SAE report form and verify the accuracy of the information recorded on the SAE pages with the source documents. The Sponsor SAE report form will be completed in capital letters, in medical terms, in English and to the best extent possible given the time constraints. Any supporting documentation (e.g., hospital discharge summary, autopsy report/death certificate, etc.) should be sent/transmitted along with the (follow-up) SAE report form. The supporting information provided should not reveal a subject's identity beyond the agreed study identifier. The Investigator should ensure that the information reported is accurate and consistent.

At a minimum, the following should be provided at the time of the initial SAE report:

- Study name and/or number

- Subject number, age, and gender/sex
- Event description/verbatim (including onset date of the SAE, outcome, and reason for it being considered serious)
- Relationship to patiromer/placebo (i.e., causality)
- Patiromer/placebo dose (number of packets) and administration dates
- Action taken with patiromer/placebo
- Severity of the event
- Investigator name and address
- Name of the reporter (including site name or number and country), and,
- Dated signature of the Investigator or Sub-/Co-Investigator

When using electronic methods of reporting SAEs, some of the information in the above list may be generated by the electronic system.

Since SAEs are also AEs, the information for the AE eCRF and SAE form should be consistent.

Follow-up information must be handled in the same way and reported within the same time frame as the initial SAE report. A safety contact sheet will be provided by the Sponsor to the Investigator (prior to first subject providing informed consent) detailing all applicable contact information for safety reporting. This contact sheet will be kept up to date with any changes being provided to the Investigator immediately.

Where possible, the Investigator should report a diagnosis rather than signs and symptoms.

Death should be considered an outcome and not a distinct event. In case of a fatal outcome, the Investigator should provide a working diagnosis (event which caused outcome, e.g., death due to fatal myocardial infarction) instead of reporting only death; and an autopsy report should be provided where possible. If the cause of death later becomes available (e.g., after autopsy), this working diagnosis should be replaced by the established cause of death.

All recorded SAEs, regardless of relationship to investigational product, will be followed up until resolution, stabilization, or the subject is lost to follow-up and cannot be contacted. After the completion of the 2 weeks follow-up after the EoS, updates should be submitted to the Sponsor (or its delegate, CRO) using the Sponsor SAE report form. In circumstances where the Investigator is unable to make contact with the subject (or his/her relatives), the Investigator must provide a written statement (recorded in the subject's source documents) to the Sponsor (or its delegate, CRO), confirming that the subject is lost to follow-up.

SAE information that is obtained after the EoS should be reported to:

Sponsor-Vifor Pharma:

Email address: [redacted]

FAX: [redacted] or [redacted]

Please reference further guidance provided along with the EDC system entry.

10.7.2.1 Study Endpoints

All events potentially related to the endpoint of CV death or CV hospitalizations or urgent HF visits will be collected starting from the date of randomization. For the purposes of this protocol, the following events are considered SAEs and must be reported as described in Section 10.7.2.

- Death from any cause
- Any CV event leading to hospitalization (e.g., HF, myocardial infarction, stroke, unstable angina, arrhythmia)

The following CV hospitalization events will be counted towards the endpoint:

- HF hospitalization or equivalent urgent HF visit (e.g., emergency room or outpatient visit for worsening HF during which the subject received intravenous medications for the treatment of HF)
- Type I acute myocardial infarction (including both ST segment elevation myocardial infarction and non-ST segment elevation myocardial infarction) leading to hospitalization
- All types of arrhythmia including atrial fibrillation requiring leading to hospitalization
- Hypertension emergency; systolic blood pressure ≥180 mmHg leading to hospitalization
- Stroke leading to hospitalization

Based on the specific study design and the advanced underlying disease state of the recruited subject population, events suggestive of the study outcomes would automatically qualify to meet the criteria of seriousness in this study. These events include known consequences of the underlying disease and are anticipated to occur in the study population independent of drug exposure (see above bullet points). These events would be reported, collected and monitored during the course of the study like all other SAEs, but would not be reported individually in an expedited manner, unless the Investigator and/or Sponsor has

deemed it to have reasonable possibility that the study drug caused the event and would follow the reporting process of a SUSAR.

The DSMB will monitor the identified events during the conduct of the study and alert if there is evidence of causal relationship between patiromer/placebo and the event following their analysis.

10.7.3 SUSARs

The definition of a SUSAR is any ADR (see Section 10.6.1) that is both serious (see Section 10.7.1) and unexpected (per the RSI; see Section 10.6.2) that is felt to have a reasonable suspected causal relationship to a medicinal product.

10.7.3.1 SUSAR Reporting

The Investigator is responsible for notifying the IRB in accordance with local regulations of all SUSARs that occur. The Investigator must review and file the associated safety report with the IB.

10.8 Special Situations

10.8.1 Definition of Special Situations

The following are defined as special situations:

- Use of an IMP during pregnancy or breastfeeding
- Medication abuse: the persistent or sporadic, intentional excessive use of study medication by the subject (not for therapeutic purpose)
- Medication error: any unintentional error in the prescribing, dispensing or administration of an IMP during the study. (Medication errors are any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional or subject)
- Medication misuse: an intentional and inappropriate use of an IMP by the subject for a therapeutic purpose not in accordance with the protocol dose, route of administration, and/or the indication(s) (e.g.: Subject deliberately took the medication twice daily instead of once daily)
- Medication overdose: the administration of a quantity of study medication given per administration or per day which is 3 times above the protocol maximum permitted dose
- Drug interaction involving study medication
- Unexpected therapeutic or clinical benefit from study medication use

Suspected AEs associated with medication errors of the IMP or use outside that foreseen in the protocol (e.g., overdose) are also considered as ADRs. Any special situation occurring with/without ADR/AE shall be recorded in the study-specific documentation by the Investigator.

10.8.2 Special Situation Recording and Reporting

All special situations have to be documented in the subject's eCRF and source documents.

If any special situation leads to an SAE (see Section 10.7.1), then the event has to be immediately reported to the Sponsor (or its delegate; e.g., CRO) within 24 hours of awareness by facsimile, email or telephone/via EDC system.

Medication error due to product dose omission (subject forgetting to take a dose), does not need to be documented in the eCRF if the product dose omission did not occur consecutively, and compliance is not <80%.

10.8.3 Pregnancy Exposure and Birth Events

10.8.3.1 Definition of Pregnancy Exposure and Birth Events

When a female subject becomes pregnant during the study and study treatment has been administered to the subject, the outcome of the pregnancy needs to be monitored and the safety of the mother and unborn child need to be safeguarded (as per protocol, pregnancy is an exclusion criteria). Therefore, the outcome of all such pregnancies (including normal births) must be followed up and documented, even if the subject was withdrawn from the study or the study has been completed.

Women of child-bearing potential, defined as a premenopausal female capable of becoming pregnant, should have a negative pregnancy test prior to randomization. Study medication must not be initiated by the Investigator until a report of a negative pregnancy test has been obtained.

Effective birth control must be used (in female subjects) before beginning study medication, during study dosing, and for 4 weeks following discontinuation of study medication; see Section 9.8.

A female subject must immediately inform the Investigator if she becomes pregnant during the study, and she will be instructed by the Investigator to stop taking study medication. The Medical Monitor must be contacted immediately. The Investigator should counsel the subject and discuss the risks of continuing with the pregnancy and the possible effects on the fetus.

The Investigator is responsible for monitoring the subject and pregnancy outcome and reporting this information to the Sponsor. Every effort should be made to gather information regarding the pregnancy outcome until 90 days postpartum (or otherwise as appropriate).

10.8.3.2 Pregnancy Exposure and Birth Events Recording and Reporting

If a female subject becomes pregnant or is suspected of being pregnant while participating in this study, the investigational product will be permanently discontinued, and the event must be reported to Drug Safety upon receipt of information by the study staff. Pregnancies must be reported throughout the conduct of the study including 4 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 Drug Safety within 24 hours of becoming aware on the Sponsor Report on Exposure to Medicines During Pregnancy 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 an 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).

11. STUDY COMMITTEES

11.1 DSMB

The independent DSMB will act in an advisory capacity to the Sponsor to monitor the safety of subjects who participate in this study. The DSMB is governed by a charter which explains the working procedures and responsibilities of the DSMB [38].

11.2 Event Adjudication Committee

The independent Event Adjudication Committee (EAC) will adjudicate all events relating to the study endpoints based on prospectively defined criteria detailed in the EAC charter. EAC members must not be employees of the study Sponsor and consists of, at minimum, 3 qualified members (at least one cardiologist specializing in HF); see EAC charter for further details [39]. The EAC will be blinded to study treatment allocations while adjudicating the events. Endpoint adjudication will occur on an ongoing basis throughout the Blinded Treatment Phase of the study.

11.3 Steering Committee

The independent Steering Committee will advise the Sponsor scientifically as well as monitor trial progress and conduct. The specific areas of focus for the Steering Committee are protocol design, execution, analysis, interpretation, and publication of the DIAMOND study, and any proposed sub-studies.

12. STATISTICAL ANALYSIS

12.1 Statistical Methods

Detailed methodology for summary and statistical analyses of the data collected in this trial will be documented in an SAP. A general description of the planned methods is provided below. Any deviation from the SAP will be noted and explained in the final study report.

12.2 Sample Size and Power Calculations

The sample size of 410 subjects per treatment arm (total of 820 subjects) has been calculated to provide 90% power to detect a difference between the control group (placebo) and the active group (patiromer) on the mean change in K^+ levels from Baseline. This sample size calculation was based upon the following assumptions: alpha level of 5% (2-sided), a difference between group means of 0.116, an SD of 0.5, and a 5% annual rate of loss to follow-up.

12.3 Randomization

Subjects will be randomized to the treatment arms (1:1 assignment) using permuted block randomization stratified by geographic region. Randomization will take place using a centralized list accessed electronically via IWRS on the day of randomization, after randomization eligibility is determined.

12.4 Analysis Sets

12.4.1 Randomized Set

All subjects randomized to study treatment.

12.4.2 Full Analysis Set

The full analysis set consist of all subjects who satisfy the following criteria:

- Randomized to treatment
- Received at least 1 dose of randomized treatment

This set will be used for the evaluation of efficacy.

12.4.3 Safety Set

The safety set (SS) consists of all subjects who have taken at least 1 dose of randomized study medication. The subjects in this group will be analyzed based on the treatment they received with data summarized separately for the Run-in and Blinded Treatment Phases of the study.

12.4.4 Run-in Phase Set

The Run-in Phase Set will consist of subjects that signed informed consent, entered the Run-in Phase, and received patiromer, but were not randomized. This set will be used to summarize safety related events that may be related to patiromer treatment.

12.5 Background and Demographic Characteristics

Demographic and Baseline characteristics will be summarized for the Randomized Set and the Run-in Phase Set.

Summaries of continuous variables will include the mean, SD, 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.

12.6 Study Medication

The total amount of drug given will be calculated for each subject and will be compared to the amount expected to be given for each subject. Treatment compliance will be calculated for each subject and summarized by treatment group.

12.7 Concomitant Therapy

Concomitant medications (as defined in Section 6.8.4) will be categorized according to a standard dictionary (World Health Organization Drug Dictionary). Counts and percentages of subject use for each medication will be computed and summarized by treatment group. Summaries will be provided for the periods before and after randomized treatment was received.

12.8 Efficacy Evaluations

12.8.1 Primary

The primary analysis will be based upon the mean change in serum K^+ levels from Baseline and is analyzed by means of an MMRM approach including all available post Baseline data. All analyses will be restricted to serum K^+ assessments and not substituted by plasma values as they are known to be systematically lower. Central laboratory values and/or local laboratory will be used at all visits, and if both values are present at one visit, then central laboratory values will be used. A Gaussian linear model for repeated measures with treatment, geographic region, sex, baseline T2DM status, and visit as factors, and baseline K^+ level, baseline eGFR as covariates. The error terms are assumed to follow a multivariate normal distribution with unstructured covariance. Least squares mean changes from Baseline will be reported for both treatment groups with 95% CIs as well as the difference between the least squares group means with 95% CI and p-value testing the null hypothesis of no treatment effect.

Sensitivity analyses for the primary endpoint will be based upon the use of all CV deaths and hospitalizations (i.e., recurrent event analysis) recorded during follow-up using the following methods: will explore changes in treatment effect over follow-up time by including treatment by visit interactions in the above-mentioned model. In addition, sensitivity analyses for the primary endpoint will explore changes in treatment effect over follow-up time by including treatment by visit interactions in the above-mentioned model. In addition, sensitivity analyses accounting for potentially informative missingness will be based upon a Win Ratio approach [4,40].

12.8.2 Key Secondary Endpoints (Hierarchically Ordered)

Secondary efficacy endpoints will be tested sequentially in the order listed below (i.e., fixed-sequence method to preserve the family-wise error rate) and summarized descriptively through the calculation of point estimates by treatment group along with 95% CIs for the treatment differences. The following lists the secondary endpoints and the analysis method to be used:

- Hyperkalemia events: The time to the first event of hyperkalemia with a serum K+ value >5.5 mEq/L as per the measured values from the central or local laboratories is analyzed using a Cox proportional hazards regression model. The event probabilities will be estimated using the Aalen-Johansen estimator of the cumulative incidence function accounting for competing events such as death.

- Durable enablement to stay on the MRA target dose (of 50 mg spironolactone or eplerenone): The time to the event of reduction of the MRA dose below target is analyzed using a Cox proportional hazards regression model. The event probabilities will be estimated using Aalen-Johansen estimator of the cumulative incidence function accounting for competing events such as death.

  Note: Discontinuation of the target dose for at least 14 days (or less if at the EoS) is required to confirm this endpoint.

- Investigator reported AEs of hyperkalemia (first and recurrent) are analyzed using a negative binomial regression with the logarithm of the individual follow-up time as offset. A joint frailty model of the total (first and recurrent) hyperkalemia events and time to death as terminating event. If all-cause mortality is substantial in number and differential between the treatment groups, then the joint frailty model would become the main analysis approach. Note: For analyses based upon the negative binomial distribution, the subject level count data will be modeled as function of treatment with the natural log of the subject level follow-up time taken into account in the estimation of the event rate.

- Hyperkalemia-related hard outcomes are analyzed using the Win Ratio approach with the following hierarchical components (all assessed during comparable follow-up times):

  1. Time to CV death
  2. Total number of CV hospitalizations
  3. Total number of hyperkalemia toxicity events with serum K+ >6.5 mEq/L
  4. Total number of hyperkalemia toxicity events with serum K+ >6.0-6.5 mEq/L
  5. Total number of hyperkalemia toxicity events with serum K+ >5.0-6.0 mEq/L

- RAASi Use Score which will be analyzed using the Win Ratio approach for each pair of patients at the end of the comparable follow-up period that is appropriate for that pair of patients with the following additive components. Points are accumulated from two components at the respective time for each patient in each comparison:

  <u>Component A:</u>

  – If during the follow-up (to the respective end of follow-up in the comparison) there was a death, the subject is assigned 0 points

  – If during the follow-up (to the respective end of follow-up in the comparison) there was a CV hospitalization, but the subject is alive at the end of that follow-up, the subject is assigned 1 point

  – If during the follow-up (to the respective end of follow-up in the comparison) there was no CV hospitalization and the subject is alive at the end of that follow-up, the subject is assigned 2 points

  <u>Component B:</u>

  Further points are collected for the treatment status at the respective end of follow-up in the comparison:

  – For ACEi/ARB/ARNi use: >50% of the target dose = 2 points

  – For ACEi/ARB/ARNi use: >0 and up to 50% of the target dose = 1 point

  – For MRA use: >50% of the target dose = 2 points

  – For MRA use: >0 and up to 50% of the target dose = 1 point

  – For beta-blocker use: >50% of the target dose = 2 points

– For beta-blocker use: >0 and up to 50% of the target dose = 1 point

In summary, each subject in each comparison can have 0-8 points (sum of Components A and B) and all subjects are compared using this score at the respective appropriate follow-up time point.

The regression analyses will be adjusted for geographic region as the stratification factor of the randomization and relevant baseline characteristics of the subjects.

12.8.3 Other Secondary Endpoints

The additional endpoints listed below (Other Secondary Endpoints), will also be summarized descriptively by treatment arm in the full analysis set:

- Durable enablement to stay on the target dose of ACE/ARB/ARNi

  Note: Discontinuation of the target dose for at least 14 days (or less if at the EoS) is required to confirm this endpoint

- Durable hyperkalemia-free enablement to stay on the MRA target dose (days on 50 mg MRA without presence of hyperkalemia)
- Hyperkalemia toxicity events with serum K^+ >6.5 mEq/L
- Hyperkalemia toxicity events with serum K^+ >6.0-6.5 mEq/L
- Emergency treatment for hyperkalemia (hospitalization or emergency room)
- Total number of hyperkalemia toxicity events with serum K^+ >5.0-6.0 mEq/L
- KCCQ questionnaire - OSS, CSS and TSS
- Investigator reported events of hyperkalemia (recurrent events)
- Proportion of subjects on ≥50% of target dose of ACEi, ARB, or ARNi and ≥50% of target dose of MRA at the EoS Visit
- Time to first occurrence of CV death or CV hospitalization

12.8.4 Other Endpoints

- CV death
- First and recurrent CV hospitalizations
- First and recurrent HF hospitalizations (or equivalent in outpatient clinic)
- Patient-reported outcome: EQ-5D-5L questionnaire

- Proportion of subjects on any dose of MRA at the EoS Visit
- Proportion of subjects on any dose of ACEi, ARB, or ARNi at the EoS Visit
- Change in proteinuria from Screening
- Change in NT-proBNP from Screening
- Change in high sensitivity troponin from Baseline
- Functional status by NYHA class
- 30-day HF re-hospitalization after a prior HF hospitalization
- HEOR analyses
- Changes in serum K^+ from Baseline to individual visits

12.8.5 Subgroups of Interest

Descriptive analyses (including the presentation of 95% CIs) will be produced for the subgroups specified below. These descriptive analyses will be summarized graphically through the use of forest plots.

Subgroups to be analyzed include:

- At Screening, hyperkalemic versus normokalemic with a history of hyperkalemia
- Screening use of ARNi (Yes or No)
- Screening use of eplerenone or spironolactone (Yes or No)
- Screening comorbidity:
  - Diabetes mellitus (Yes or No)
  - CKD stage (Stage 3b versus Stages 1–3a, Stage ≤3a versus Stage ≥3b, Stage 4 versus Stage <4)
  - NYHA Class (II versus III–IV)
- Region (US versus Non-US)

  Note: Depending on actual subject recruitment, additional comparisons between other regions, e.g., Latin America, Western Europe, Eastern Europe, will be defined in the SAP
- Gender (male or female)

- Age (age group categories will be defined prior to unblinding)
- Race/ethnicity (limited to racial/ethnic subgroups that comprise 20% or more of the study population)
- Median NT-proBNP at Screening

12.9 Safety Evaluations

The following safety variables will be summarized using the safety set:

- AEs and SAEs (coded using Medical Dictionary for Regulatory Activities (MedDRA); see Study Manual for MedDRA version), including all-cause mortality
- Slope of eGFR change during the study will be estimated and compared between treatment groups using a repeated measures analysis with time treated as a continuous variable
- Decline in eGFR >50% or ESRD, renal death, or need for dialysis
- Laboratory parameters other than those defined as efficacy endpoints

AE summaries will be provided separately for: (1) AEs with start date on or after first dose date during the Run-in Phase and on or before the date of randomization; and (2) AEs with start date on the day after randomization. Summaries will consist of counts (%) by system organ class (SOC), preferred term (PT) and severity in the Run-in Phase, and by SOC, PT, severity, and treatment in the blinded withdrawal phase. The following types of AEs will be summarized:

- All treatment-emergent adverse events (TEAEs)
- TEAEs related to study medication (patiromer/placebo) and to RAASi
- TEAEs leading to study medication discontinuation (patiromer/placebo) and to RAASi discontinuation
- SAEs

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

12.10 Interim Analyses

No interim analysis is planned.

13. STUDY ETHICAL CONSIDERATIONS

13.1 Ethical Conduct of the Study

The study will be conducted according to the principles of the World Medical Association's Declaration of Helsinki [41], and the International Council for Harmonisation (ICH) guidelines for GCP [42] as amended. The Sponsor will ensure that the study complies with all local, federal, or country regulatory requirements.

The Investigator must ensure the anonymity of all subjects participating in the study. Each subject will be assigned a unique subject number, and this should be used on all forms associated with the subject's documents or samples that will be supplied to the Sponsor or any party completing testing on behalf of the Sponsor (e.g., blood for central laboratory assessments).

All anonymous data remains the property of the Sponsor.

13.2 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 unique subject numbers, instead of names. If results of this study are reported in medical journals or at meetings or may be submitted to competent regulatory authorities in connection with regulatory procedures such as applications to authorize the marketing of pharmaceutical products, 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, if applicable, 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 US, each ICF may also include authorization allowing the institution, Investigator, and the Sponsor 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. All Independent Ethics Committee (IEC)/IRB-approved ICF versions must be provided to the Sponsor for regulatory purposes.

13.3 IRB or EC/IEC

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 IB, 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 the Sponsor 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 the Sponsor. The Investigator must also inform the IRB/IEC of any protocol changes or amendments, changes to the IB, 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.

14. 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.

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

The Investigator will also permit the Sponsor 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, eCRFs, and drug accountability records. If the FDA or other regulatory agency should schedule an inspection, the Investigator should notify the Sponsor and/or designee immediately.

The following steps will be taken to ensure that the trial is conducted by the investigational site in compliance with the study protocol, 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

14.1 Quality Management: Critical Processes and Data

The following processes and data have been identified during the risk management activities for this trial as critical to ensure human subject protection and the reliability of trial results.

14.1.1 Critical Processes

Throughout the study, the clinical study team will work to ensure that the trial is operationally feasible and focuses on study activities essential to human subject protection and the reliability of trial results, including, but not limited to:

- Study protocol design and implementation

- Tools and procedures supporting data collection and processing
- Tools and procedures safeguarding the rights and protection of human subjects
- Activities essential to trial decision-making and compliance

15. REPORTING AND RECORDING OF DATA

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/placebo.

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.

15.1 Source Documentation

The Investigator must maintain adequate and accurate source documents upon which case reports for each subject are based. They are to be separate and distinct from eCRFs. These records should include detailed notes on:

- The medical history prior to participation in the study
- The basic identifying information, such as demographics, that link the subject's source documents with the eCRFs
- The results of all diagnostic tests performed, diagnoses made, therapy provided, and any other data on the condition of the subject
- The subject's exposure to study treatment
- All AEs and pregnancies
- All special situations as defined in Section 10.8
- The subject's exposure to any concomitant therapy
- All relevant observations and data on the condition of the subject throughout the study
- The oral and written communication with the subject regarding the study treatment (including the risks and benefits of the study); the date of informed consent must be recorded in the source documentation

All data for the study must be available in source documentation.

15.2 Case Report Forms/Electronic Data Record

An eCRF is designed to record all of the protocol required information to be reported to the Sponsor 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. 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.

eCRFs should be completed in a timely manner to the respective visit (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 the Sponsor 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., MedDRA and World Health Organization Drug Dictionary).

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

15.3 Records 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 the Sponsor, and other pertinent data.

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

15.4 Site Documentation

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified.

16. PROCEDURE FOR MODIFICATION OF PROTOCOL OR PREMATURE TERMINATION OF THE STUDY

16.1 Protocol Deviations

The Investigator will not deviate from the protocol without prior written approval from the Sponsor, 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 (see Section 16.2). The criteria describing protocol deviation(s) and how they will be handled will be documented in the Study Manual.

16.2 Protocol Amendments

Protocol amendments, except where necessary to eliminate an immediate hazard to subjects, must be made only with the prior approval of the Sponsor. Each applicable Regulatory Authority/IRB/EC/IEC will review and approve amendments prior to their implementation. Regulatory Authority/IRB/EC/IEC approval need not be obtained prior to removal of an immediate hazard to subjects.

16.3 Study Termination

The Sponsor reserves the right to terminate the study in its entirety or at a site at any time. Reasons for termination may include (but are not limited to) unsatisfactory subject enrollment with respect to quality and/or quantity, site is unable to comply with the requirements of the protocol or GCP, or data recording is inaccurate and/or incomplete.

In terminating the study, the Sponsor and the Investigator will assure that adequate consideration is given to the protection of the subject's interests. Both parties will arrange the procedures on an individual basis after review and consultation and in accordance with the study contract.

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

The study may be terminated or suspended upon request of regulatory authorities.

17. POLICY FOR PUBLICATION AND PRESENTATION OF DATA

The Clinical Trial Agreement describes the Sponsor's publication terms.

In accordance with applicable laws and regulations, the Sponsor will publicly register and provide all mandatory information regarding this trial including, to the extent and within the timelines required, a summary of the trial data and results.

18. REFERENCES

1. PAT-CR-302 Study Manual. A multicenter, double-blind, placebo-controlled, randomized withdrawal, parallel group study of patiromer for the management of hyperkalemia in subjects receiving renin-angiotensin-aldosterone system inhibitor (RAASi) medications for the treatment of heart failure (DIAMOND). Version 5.0 PAT-CR-302 Study Manual for Protocol Amendment v4.0. Redwood City (CA): Vifor Pharma Inc.; 2021 June 23.
2. Lin DY, Wei LJ, Yang I, Ying Z. Semiparametric regression for the mean and rate functions of recurrent events. J R Statist Soc B. 2000;62(Part4):711-30.
3. Ariti CA, Cleland JGF, Pocock SJ, Pfeffer MA, Swedberg K, Granger CB, et al. Days alive and out of hospital and the patient journey in patients with heart failure: Insights from the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) program. Am Heart J. 2011 Nov;162(5):900-6.
4. Finkelstein DM, Schoenfeld DA. Combining mortality and longitudinal measures in clinical trials. Statist Med. 1999;18:1341-54.
5. Ponikowski P, Anker SD, AlHabib KF, Cowie MR, Force TL, Hu S, et al. Heart failure: preventing disease and death worldwide. ESC Heart Failure. 2014;1:4-25. Epub 2014 Aug 29.
6. Dev S, Hoffman TK, Kavalieratos D, Heidenreich P, Wu W-C, Schwenke DC, et al. Barriers to adoption of mineralocorticoid receptor antagonists in patients with heart failure: a mixed-methods study. J Am Heart Assoc. 2016;5:e002493. p. 1-11.
7. Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, et al. Heart disease and stroke statistics—2017 update: a report from the American Heart Association. Circulation. 2017 Mar 7;135(10):e146-603.
8. Collins AJ, Pitt B, Reaven N, Funk S, McGaughey K, Wilson D, et al. Association of serum potassium with all-cause mortality in patients with and without heart failure, chronic kidney disease, and/or diabetes. Am J Nephrol. 2017;46:213-21. Epub 2017 Sep 2.
9. Damman K, Tang WH, Felker GM, Lassus J, Zannad F, Krum H, McMurray JJ. Current evidence on treatment of patients with chronic systolic heart failure and renal insufficiency: practical considerations from published data. J Am Coll Cardiol 2014; 63:853–71.
10. Rossignol P, Agarwal R, Canaud B, Charney A, Chatellier G, Craig JC, et al. Cardiovascular outcome trials in patients with chronic kidney disease: challenges associated with selection of patients and endpoints. Eur Heart J. 2017;1-8.
11. Allen LA, Fonarow GC, Liang L, Schulte PJ, Masoudi FA, Rumsfeld JS, et al. Medication initiation burden required to comply with heart failure guideline recommendations and hospital quality measures. Circulation. 2015 Oct 6;132:1347-53.

12. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey Jr DE, Colvin MM, et al. 2016 ACC/AHA/HFSA Focused update on new pharmacological therapy for heart failure: an update of the 2013 ACCF/AHA guideline for the management of heart failure. J Am Coll Cardiol. 2016 Sep 27;68(13):1476-88.

13. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Eur Heart J. 2016;37:2129-200m.

14. Maggioni AP, Anker SD, Dahlström U, Filippatos G, Ponikowski P, Zannad F, et al. Are hospitalized or ambulatory patients with heart failure treated in accordance with European Society of Cardiology guidelines? Evidence from 12,440 patients of the ESC Heart Failure Long-Term Registry. Eur J Heart Fail. 2013;15:1173-84. Epub 2013 Aug 26.

15. Desai AS, Swedberg K, McMurray JJV, Granger CB, Yusuf S, Young JB, et al. Incidence and predictors of hyperkalemia in patients with heart failure: an analysis of the CHARM Program. J Am Coll Cardiol. 2007 Nov 13;50(20):1959-66.

16. Rossignol P, Pitt B, Thompson A, Zannad F. Roadmap for cardiovascular prevention trials in chronic kidney disease. Lancet. 2016 Oct 22;388:1964-6.

17. Edner M, Benson L, Dahlström U, Lund LH. Association between renin-angiotensin system antagonist use and mortality in heart failure with severe renal insufficiency: a prospective propensity score-matched cohort study. Eur Heart J. 2015;36:2318-26. Epub 2015 Jun 11.

18. Zannad F, Rossignol P, Stough WG, Epstein M, Alonso Garcia MdlA, Bakris GL, et al. New approaches to hyperkalemia in patients with indications for renin angiotensin aldosterone inhibitors: considerations for trial design and regulatory approval. Int J Cardiol. 2016;216:46-51. Epub 2016 Apr 19.

19. Ferreira JP, Butler J, Rossignol P, Pitt B, Anker SD, Kosiborod M, et al. Abnormalities of potassium in heart failure: JACC State-of-the-Art review. J Am Coll Cardiol. 2020 Jun 9;75(22):2836–50.

20. Epstein M, Reaven NL, Funk SE, McGaughey KJ, Oestreicher N, Knispel J. Evaluation of the treatment gap between clinical guidelines and the utilization of renin-angiotensin-aldosterone system inhibitors. Am J Manag Care. 2015 Sep;21(11):S212-20.

21. Ouwerkerk W, Voors AA, Anker SD, Cleland JG, Dickstein K, Filippatos G, et al. Determinants and clinical outcome of uptitration of ACE-inhibitors and beta-blockers in patients with heart failure: a prospective European study. Eur Heart J. 2017;38:1883-90. Epub 2017 Mar 11.

22. Bandak G, Sang Y, Gasaparini A, Chang AR, Ballew SH, Evans M, et al. Hyperkalemia after initiating renin-angiotensin system blockade: The Stockholm Creatinine Measurements (SCREAM) Project. J Am Heart Assoc. 2017;6:e005428. 13 p.

23. Trevisan M, de Deco P, Xu H, Evans M, Lindholm B, Belloco R, et al. Incidence, predictors and clinical management of hyperkalaemia in new users of mineralocorticoid receptor antagonists. Eur J Heart Fail. 2018;20(8):1217-26. Epub 2018 Apr 18.

24. Veltassa (patiromer) for oral suspension Prescribing Information. Version 5. Redwood City, CA, Relypsa, Inc. 2018 May.

25. Pitt B, Bakris GL, Bushinsky DA, Garza D, Mayo MR, Stasiv Y, et al. Effect of patiromer on reducing serum potassium and preventing recurrent hyperkalaemia in patients with heart failure and chronic kidney disease on RAAS inhibitors. Eur J Heart Fail. 2015;17:1057-65. Epub 2015 Oct 12.

26. Bakris GL, Pitt B, Weir MR, Freeman MW, Mayo MR, Garza D, et al. Effect of patiromer on serum potassium level in patients with hyperkalemia and diabetic kidney disease. The AMETHYST-DN randomized clinical trial. JAMA. 2015 Jul 14;314(2):151-61.

27. Rossignol P, Dobre D, McMurray JJV, Swedberg K, Krum H, van Veldhuisen DJ, et al. Incidence, determinants, and prognostic significance of hyperkalemia and worsening renal function in patients with heart failure receiving the mineralocorticoid receptor antagonist eplerenone or placebo in addition to optimal medical therapy: results from the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF). Circ Heart Fail. 2014 Jan;7:51-8.

28. Aldahl M, Jensen A-SC, Davidsen L, Eriksen MA, Hansen SM, Nielsen BJ, et al. Associations of serum potassium levels with mortality in chronic heart failure patients. Eur Heart J. 2017;38:2890-6. Epub 2017 Aug 14.

29. Krogager ML, Torp-Pedersen C, Mortensen RN, Køber L, Gislason G, Søgaard P, et al. Short-term mortality risk of serum potassium levels in hypertension: a retrospective analysis of nationwide registry data. Eur Heart J. 2017;38:104-12. Epub 2016 Apr 20.

30. Investigator's Brochure Patiromer for Oral Suspension. (Veltassa®). Version 13.0. Final report. Redwood City (CA): Relypsa, Inc.; 2020 Jul 13.

31. Bianchi S, Batini V, Bigazzi R. The renal effects of mineralocorticoid receptor antagonists. Int J Cardiol. 2015;200:20-4. Epub 2015 May 22.

32. KDIGO. KDIGO Clinical practice guideline for the management of blood pressure in chronic kidney disease. Kidney Int Suppl. 2012 Dec;2(5):337-414.

33. National Kidney Foundation. KDOQI Clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. Guideline 11: Use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in CKD. Am J Kidney Dis. 2004 May;43(5 Suppl 1):S183-205. [Accessed on 2016 Jun 29]. Available from: https://kidneyfoundation.cachefly.net/professionals/KDOQI/guidelines_bp/guide_11.htm.

34. Aldactone® spironolactone tablets, USP Prescribing Information. New York, G.D. Searle LLC Division of Pfizer Inc. 2014 Oct.

35. Bushinsky DA, Spiegel DM, Gross C, Benton WW, Fogli J, Gallant KMH, et al. Effect of patiromer on urinary ion excretion in healthy adults. Clin J Am Soc Nephrol. 2016 Oct;11:1769-76.

36. Rosano GMC, Tamargo J, Kjeldsen KP, Lainscak M, Agewall S, Anker SD, et al. Expert consensus document on the management of hyperkalaemia in patients with cardiovascular disease treated with renin angiotensin aldosterone system inhibitors: coordinated by the Working Group on Cardiovascular Pharmacotherapy of the European Society of Cardiology. Eur Heart J Cardiovasc Pharmacother. 2018;4:180-8. Epub 2018 May 3.

37. European Medicines Agency. ICH Topic E2A: Note for guidance on clinical safety data management: definitions and standards for expedited reporting. CPMP/ICH/377/95. 1995 Jun.

38. Chebotareva J. A multicenter, double-blind, placebo-controlled, randomized withdrawal, parallel group study of patiromer for the management of hyperkalemia in subjects receiving renin-angiotensin-aldosterone system inhibitor (RAASi) medications for the treatment of heart failure (DIAMOND). Data and Safety Monitoring Board. Final report. Redwood City (CA): Relypsa Inc.; 2019 Apr 18. Protocol No.: PAT-CR-302. Syneos Health Project Code: 7000009A.

39. Catapane EK. A multicenter, double-blind, placebo-controlled, randomized withdrawal, parallel group study of patiromer for the management of hyperkalemia in subjects receiving renin-angiotensin-aldosterone system inhibitor (RAASi) medications for the treatment of heart failure (DIAMOND). Version 1.0. DIAMOND Endpoint Adjudication Committee Charter. Final report. Redwood City (CA): Relypsa Inc.; 2019 Dec 11.

40. Pocock SJ, Ariti CA, Collier TJ, Wang D. The win ratio: a new approach to the analysis of composite endpoints in clinical trials based on clinical priorities. Eur Heart J. 2012;33:176-82. Epub 2011 Sep 6.

41. World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human subjects. 2013 Oct. p. 1-8.

42. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). ICH Harmonised Guideline E6(R2): Integrated addendum to ICH E6(R1): guideline for good clinical practice. 2016 Nov 9.

19. SUMMARY OF CHANGES: PROTOCOL AMENDMENT VERSION 3.0 TO 4.0

Note: New text is in bold font, deleted text is presented with strikethrough, and other modified (moved) text is in italic.

No	Section Number	Descriptive Statement/ Rationale Regarding Revision	Previous Text (If Applicable)	Revised and/or New Text
1	Title Page	Updated to reflect amendment	9 April 2021	**23 June 2021**
2	Synopsis			
3	Synopsis Section 3		~~To determine if patiromer treatment of subjects who developed hyperkalemia while receiving RAASi medications will result in continued use of RAASi medications in accordance with heart failure (HF) treatment guidelines and thereby decrease the occurrence of the combined endpoint of cardiovascular (CV) death and CV hospitalization events compared with placebo treatment.~~	**To assess the effects of patiromer compared with placebo serum K^+ in HF patients.**
4	Synopsis		Study Population: Subjects with HF with reduced ejection fraction (HFrEF) who are hyperkalemic (serum K^+ >5.0 mEq/L) while receiving treatment with RAASi medications or who are normokalemic (serum K^+ ≥4.0–≤5.0 mEq/L) but have a history of hyperkalemia ~~in the 12 months~~ prior to Screening with subsequent reduction or discontinuation of a RAASi medication.	Study Population: Subjects with HF with reduced ejection fraction (HFrEF) who are hyperkalemic (serum K^+ >5.0 mEq/L) while receiving treatment with RAASi medications or who are normokalemic (serum K^+ ≥4.0–≤5.0 mEq/L) but have a history of hyperkalemia prior to Screening with subsequent reduction or discontinuation of a RAASi medication.
5	Synopsis Section 4.2		Duration: Each subject's participation includes a Run-in Phase (single-blinded, up to 12 weeks) followed by the Treatment Phase (double-blinded, ~~anticipated to be at least 6 *months* per subject~~). ~~The study will continue until the required number of composite endpoint events have occurred.~~ Study duration for	Duration: Each subject's participation includes a Run-in Phase (single-blinded, up to 12 weeks) followed by the Treatment Phase (double-blinded, anticipated to **be reaching** at least 6 **weeks** per subject). Study duration for individual subjects will vary, depending

No	Section Number	Descriptive Statement/ Rationale Regarding Revision	Previous Text (If Applicable)	Revised and/or New Text
			individual subjects will vary, depending on the ~~rate of occurrence of composite endpoint events. Given the assumptions underlying the study design, accumulation of the requisite number of composite endpoint events is expected to occur over approximately 2.5 years~~. Subjects who prematurely discontinue patiromer/placebo will remain in the study for the collection of ~~composite endpoint~~ event data up to and including the common end of study (EoS) and will receive usual care during the study phase.	on their **individual enrollment date**. Subjects who prematurely discontinue patiromer/placebo will remain in the study for the collection of **clinical events** data up to and including the common end of study (EoS) and will receive usual care during the study phase.
6	Synopsis Section 5.2		7. Hyperkalemia at Screening (defined by 2 local serum K^+ values of >5.0 mEq/L, each obtained from a separate venipuncture, e.g., one in each arm or 2 separate venipunctures in the same arm) • While receiving ACEi/ARB/ARNi, and/or MRA OR Normokalemia at Screening (defined by 2 local serum K^+ ≥4.0-≤5.0 mEq/L, each obtained from a separate venipuncture, e.g., one in each arm or 2 separate venipunctures in the same arm) • With a history of hyperkalemia documented by a usual care serum K^+ measurement >5.0 mEq/L • While on ~~MRA~~ • ~~Leading to a subsequent and permanent discontinuation of the MRA medication~~	7. Hyperkalemia at Screening (defined by 2 local serum K^+ values of >5.0 mEq/L, each obtained from a separate venipuncture, e.g., one in each arm or 2 separate venipunctures in the same arm) while receiving ACEi/ARB/ARNi, and/or MRA OR Normokalemia at Screening (defined by 2 local serum K^+ ≥4.0–≤5.0 mEq/L each obtained from a separate venipuncture, e.g., one in each arm or two separate venipunctures in the same arm) with a history of hyperkalemia documented by a usual care serum K^+ measurement >5.0 mEq/L, while on **RAASi treatment in the 12 months prior to Screening** leading to a subsequent and permanent dose decrease or discontinuation of one or more **RAASi medications**

No	Section Number	Descriptive Statement/ Rationale Regarding Revision	Previous Text (If Applicable)	Revised and/or New Text
			~~• MRA discontinuation occurred >2 weeks prior to Screening~~ ~~OR~~ ~~For MRA naive subjects with normokalemia at Screening (defined by 2 local serum K^+ values ≥4.0 ≤5.0 mEq/L, each obtained from a separate venipuncture, e.g., one in each arm or 2 separate venipunctures in the same arm)~~ ~~• With a history of hyperkalemia documented by a usual care serum K^+ measurement >5.0 mEq/L~~ ~~• While on an ACEi/ARB/ARNi~~ • ~~Leading to a subsequent, permanent~~ dose decrease or discontinuation of one ~~of the ACEi/ARB/ARNi~~ medication ~~• ACEi/ARB/ARNi dose decrease or discontinuation occurred >2 weeks prior to Screening~~	
7	Synopsis Section 5.3		~~20. Planned or scheduled dialysis within 3 months from Screening~~	
8	Synopsis Section 5.4		1. Current MRA dose is at least ~~50% of~~ the target dose* (e.g., spironolactone 25 mg/day, eplerenone 25 mg/day) and has been stable for at least 1 week	1. Current MRA dose is at least the target dose* (e.g., spironolactone **50** mg/day, eplerenone **50** mg/day) and has been stable for at least 1 week
9	Synopsis Section 3		Primary Endpoint: ~~• Time to first occurrence of CV death or CV hospitalization~~	Primary Endpoint: • **Changes in serum K^+ levels from Baseline.**

No	Section Number	Descriptive Statement/ Rationale Regarding Revision	Previous Text (If Applicable)	Revised and/or New Text
				Note: All analyses will be restricted to serum K^+ levels and not substituted by plasma values as they are known to be systematically lower. Both central laboratory and local laboratory values will be used at all visits; however, if both values are available at one visit, then central laboratory values will be used.
10	Synopsis Section 3		Secondary Endpoints: • ~~Proportion of subjects on ≥50% of target dose of ACEi, ARB, or ARNi and ≥50% of target dose of MRA at the EoS Visit~~ • ~~Total HF hospitalizations (or equivalent in outpatient clinic)~~ • ~~Change from randomization in the clinical summary score of Kansas City Cardiomyopathy Questionnaire (KCCQ) at 8 months~~	**Key** Secondary Endpoints (**Hierarchically Ordered)** **1. Hyperkalemia events with a serum K^+ value >5.5 mEq/L.** **2. Durable enablement to stay on the MRA target dose (of 50 mg daily spironolactone or eplerenone), as assessed by the between treatment groups difference of the cumulative frequency of patients not staying on the target dose.** ***Note: Discontinuation of the target dose for at least 14 days (or less if at the EoS) is required to confirm this endpoint.*** **3. Investigator reported events of hyperkalemia (first and recurrent events).** **4. Hyperkalemia-related hard outcomes endpoints (Win Ratio)** **a. Time to CV death** **b. Total number of CV hospitalizations** **c. Total number of hyperkalemia toxicity events with serum K^+ >6.5 mEq/L** **d. Total number of hyperkalemia events with serum K^+ >6.0-6.5 mEq/L**

No	Section Number	Descriptive Statement/ Rationale Regarding Revision	Previous Text (If Applicable)	Revised and/or New Text
				e. Total number of hyperkalemia events with serum K^+ >5.0 mEq/L **5. RAASi Use Score (Win Ratio).** ***Note: This score (of 0–8 points) will be analyzed at the respective time points for each patient in each comparison, and it consists of the following components:*** **a. All-cause death** **b. Occurrence of a CV hospitalization** **b. HF medication use and dose for i) an ACEi/ARB/ARNi, ii) an MRA, and iii) a beta-blocker**
11	Synopsis Section 3		-	**Other Secondary Endpoints** **• Durable enablement to stay on the target dose of ACE/ARB/ARNi.** ***Note: Discontinuation of the target dose for at least 14 days (or less if at the EoS) is required to confirm this endpoint*** **• Durable hyperkalemia-free enablement to stay on the MRA target dose (days on 50mg MRA without presence of hyperkalemia)** **• Total number of hyperkalemia toxicity events with serum K^+ >6.5 mEq/L** **• Total number of hyperkalemia events with serum K^+ >6.0-6.5 mEq/L** **• Emergency treatment for hyperkalemia (hospitalization or emergency room)** **• Total number of hyperkalemia events with serum K^+ >5.0 mEq/L**

No	Section Number	Descriptive Statement/ Rationale Regarding Revision	Previous Text (If Applicable)	Revised and/or New Text
				• **KCCQ questionnaire, changes in OSS, CSS and TSS** • **Investigator reported events of hyperkalemia (first events)** • Proportion of subjects on ≥50% of target dose of ACEi, ARB, or ARNi and ≥50% of target dose of MRA at the EoS Visit • **Time to first occurrence of CV death or CV hospitalization**
12	Synopsis Section 3		Other Endpoints: • ~~Emergency treatment for hyperkalemia (hospitalization or emergency room)~~ • Patient-reported outcome: EQ-5D-5L questionnaire • ~~Proportion of subjects with change in the patient-reported outcome, KCCQ, greater than 5 points at 8 months after randomization~~ • ~~Time to first occurrence of HF hospitalization (or equivalent in outpatient clinic)~~ • ~~Total CV hospitalizations~~ • Proportion of subjects on any dose of MRA at the EoS Visit • Proportion of subjects on any dose of ACEi, ARB, or ARNi at the EoS Visit • Change in proteinuria from Screening • Change in NT-proBNP from Screening • Change in high sensitivity troponin from Baseline • Functional status by NYHA class	Other Endpoints: • **CV death** • **First and recurrent CV hospitalizations** • **First and recurrent** HF hospitalizations (or equivalent in outpatient clinic) • Patient-reported outcome: EQ-5D-5L questionnaire • Proportion of subjects on any dose of MRA at the EoS Visit • Proportion of subjects on any dose of ACEi, ARB, or ARNi at the EoS Visit • Change in proteinuria from Screening • Change in NT-proBNP from Screening • Change in high sensitivity troponin from Baseline

No	Section Number	Descriptive Statement/ Rationale Regarding Revision	Previous Text (If Applicable)	Revised and/or New Text
			• 30-day HF re-hospitalization after a prior HF hospitalization • Health Economics and Outcomes Research (HEOR) analyses	• Functional status by NYHA class • 30-day HF re-hospitalization after a prior HF hospitalization • Health Economics and Outcomes Research (HEOR) analyses • **Changes in serum K^+ from Baseline to individual visits**
13	Synopsis Section 3		Safety Evaluations: • -	Safety Evaluations: • **All-cause mortality**
14	Synopsis Section 3		Safety Evaluations: • Laboratory parameters *including serum K^+*	Safety Evaluations: • Laboratory parameters **other than those defined as efficacy endpoints**
15	Synopsis		EoS Visit (~~Event-Driven~~)	EoS Visit
16	Synopsis		~~This design will also accelerate the collection of endpoints required for the objective of the study.~~	
17	Synopsis Section 12.2		Sample Size: The sample size of *1,194* subjects per treatment arm (total of *2,388* subjects) has been calculated to provide 90% power to detect a difference between the control group (placebo) and the active group (patiromer) on ~~the time until the first occurrence of CV death or CV hospitalization (total of 844 events)~~. This sample size calculation was based upon the following assumptions: alpha level of 5% (2 sided), ~~24 months to accrue the subjects (uniform accrual), a minimum of 6 months of follow-up, a 30% annual rate for the control arm, a treatment effect associated with a hazard ratio (control/active) of 0.8,~~ a	Sample Size: The sample size of **410** subjects per treatment arm (total of **820** subjects) has been calculated to provide 90% power to detect a difference between the control group (placebo) and the active group (patiromer) on the **mean change in K^+ levels from Baseline**. This sample size calculation was based upon the following assumptions: alpha level of 5% (2 sided), **a difference between group means of 0.116 a standard deviation (SD) of 0.5 and** a 5% rate of loss to follow-up.

No	Section Number	Descriptive Statement/ Rationale Regarding Revision	Previous Text (If Applicable)	Revised and/or New Text
			5% ~~annual~~ rate of loss to follow-up ~~due to non-CV deaths and the time to event follows an exponential distribution. The power will be approximately 80% if a gamma frailty is assumed with a variance of 4.0.~~	
18	Synopsis		Study Sites: ~~460~~	Study Sites: **375**
19	Synopsis Section 12.8.1		Statistical Methods: ~~The primary analysis will be based upon the time to the first occurrence of the primary endpoint consisting of a CV death or CV hospitalization (or equivalent in outpatient clinic). The test of significance will be based upon a stratified (randomization strata) log-rank test. The treatment effect will be summarized using the hazard ratio (HR) and 95% confidence interval (CI) calculated using a stratified (randomization strata) Cox regression model with treatment as the model parameter. In these analyses, subjects will be censored as of their last assessment for the primary endpoint as well as for deaths for non-CV causes. Sensitivity analyses for the primary endpoint will be based upon the use of all CV deaths and hospitalizations (i.e., recurrent event analysis) recorded during follow-up using the following methods:~~ ~~• Extended Cox model [2]~~ ~~• Days alive outside of the hospital [3]~~ ~~• Rank based analysis [4]~~ ~~Additional descriptive statistics will be calculated to better understand the recurrent events pattern. In particular, the HR will be estimated within event count using a conditional model (gap-time method) that allows both the underlying hazard and HR to vary (Prentice, Williams and Peterson, 1981) with a robust variance estimator. In this approach, subjects~~	Statistical Methods: **The mean change in serum K^+ levels from Baseline is analyzed by means of a mixed model for repeated measures (MMRM) approach including all available follow-up data. A Gaussian linear model for repeated measures with treatment, geographic region, sex, baseline Type 2 diabetes mellitus (T2DM) status and visit as factors, and baseline K^+ level, baseline eGFR as covariates. The error terms are assumed to follow a multivariate normal distribution with unstructured covariance.** **Sensitivity analyses for the primary endpoint will explore changes in treatment effect over follow-up time by including treatment by visit interactions in the above-mentioned model. In addition, sensitivity analyses accounting for potentially informative missingness will be based upon a Win Ratio approach.** Secondary efficacy endpoints will be tested in the order listed (i.e., fixed-sequence method to preserve the family-wise error rate) and summarized descriptively through the calculation of point estimates by treatment group along with 95% CIs for the treatment differences. Other endpoints will be

No	Section Number	Descriptive Statement/ Rationale Regarding Revision	Previous Text (If Applicable)	Revised and/or New Text
			~~experiencing a death are removed from the risk sets for subsequent events. Additional estimates will be calculated treating CV death as a competing risk for the occurrence of CV hospitalizations.~~ Secondary efficacy endpoints will be tested in the order listed (i.e., fixed-sequence method to preserve the family-wise error rate) and summarized descriptively through the calculation of point estimates by treatment group along with 95% CIs for the treatment differences. Other endpoints will be summarized using descriptive methods. Safety evaluations include AEs and serious adverse events (SAEs) (including all-cause mortality); slope of eGFR change during the study; decline in eGFR >50% or ESRD, renal death, or need for dialysis; and serum K+ level. Safety variables will be summarized using the safety set. ~~An~~ interim analysis is planned ~~when 50% of the planned primary endpoint events are recorded~~.	summarized **using the calculation of point estimates by treatment group along with 95% CIs for the treatment differences and** descriptive **methods as appropriate.** Safety evaluations include AEs and serious adverse events (SAEs) (including all-cause mortality); slope of eGFR change during the study; decline in eGFR >50% or ESRD, renal death, or need for dialysis; and serum K^+ level. Safety variables will be summarized using the safety set. **No** interim analysis is planned.
20	Study Schema		− EoS Visit ~~Event driven~~	− EoS Visit
21	Section 2		-	**Patients with HF and CKD are among those at the highest risk of severe outcomes of COVID-19 infection. Treatment practices for this patient population have been adapted to reduce risks of exposure to infection during hospital visits, disrupting clinical care and impacting the conduct of randomized clinical trials such as the DIAMOND study. The first priority has been to protect the safety of the patients in the trial and to respect the need of the healthcare system to prioritize efforts to contain the pandemic. This has**

No	Section Number	Descriptive Statement/ Rationale Regarding Revision	Previous Text (If Applicable)	Revised and/or New Text
				led to a fewer patients enrolled in the trial than anticipated. **Due to the changing treatment landscape in HFrEF, the lower-than-expected recruitment rate due to the COVID-19 pandemic and the lower-than-expected event rates, the Sponsor with recommendations from the Executive Steering Committee of the study decided to change the study objectives and the primary and secondary endpoints. The decision was made to maximize the scientific value of the data already collected in DIAMOND, while at the same time ensuring the safety and wellbeing of patients. It will also take into account the way the unprecedented demands of the COVID-19 pandemic altered clinical care during this period.** **It is therefore hypothesized that patiromer can be used to treat hyperkalemia that develops in high risk HFrEF patients while receiving treatment with RAASi. This is expected to result in improved adherence to guideline RAASi treatment, and less hyperkalemic events compared with the current standard of care in these patients, which includes RAASi dose reduction or discontinuation.**
22	Section 2		Therefore, the present multinational, multicenter, double-blind, placebo-controlled, randomized withdrawal, parallel group study of subjects with HFrEF who have developed hyperkalemia (serum K+ >5.0 mEq/L) while being treated with RAASi medications is designed to determine if patiromer	Therefore, the present multinational, multicenter, double-blind, placebo-controlled, randomized withdrawal, parallel group study of subjects with HFrEF who have developed hyperkalemia (serum K+ >5.0 mEq/L) while being treated with RAASi

No	Section Number	Descriptive Statement/ Rationale Regarding Revision	Previous Text (If Applicable)	Revised and/or New Text
			treatment will result ~~in greater adherence to HF treatment guidelines and thereby decrease the occurrence of CV hospitalization and CV death~~ compared with placebo treatment.	medications is **re-**designed to determine if patiromer treatment will result in **better K^+ control** compared with placebo treatment.
23	Section 4.2		Each eligible subject's participation includes a Screening Phase (within a maximum of 10 calendar days), Run-in Phase (single-blinded, up to 12 weeks) followed by the Treatment Phase (double-blinded, ~~anticipated to be at least 6 months per subject). The study will continue until the required number of composite endpoint events, i.e., time to first occurrence of CV death or CV hospitalization have occurred.~~ Study duration for individual subjects will vary, depending on the ~~rate of occurrence of composite endpoint events.~~ Given the assumptions underlying the study design, accumulation of the requisite number of composite endpoint events is expected to occur over approximately 2.5 years. The common EoS ~~date~~ *will be determined using the accrual rate of composite safety endpoint events to project the date when there should be sufficient data to provide adequate power for the composite primary endpoint analysis*.	Each eligible subject's participation includes a Screening Phase (within a maximum of 10 calendar days), Run-in Phase (single-blinded, up to 12 weeks) followed by the Treatment Phase (double-blinded, **variable per subject**). Study duration for individual subjects will vary, **depending on their individual enrollment date.** The common EoS will **occur when 820 subjects have completed the Week 6 visit. Recruitment will be stopped** when **it is projected that a** sufficient number of subjects have been enrolled **in order for 820 subjects to reach the Week 6 visit**.
24	Section 5.2		6. eGFR ≥*20* mL/min/1.73 m^2 at Screening (based on a single local laboratory analysis of serum creatinine and calculation using the CKD-EPI equation; see Section 9.2)	6 eGFR ≥**30** mL/min/1.73 m^2 at Screening (based on a single local laboratory analysis of serum creatinine and calculation using the CKD-EPI equation; see Section 9.2)

No	Section Number	Descriptive Statement/ Rationale Regarding Revision	Previous Text (If Applicable)	Revised and/or New Text
25	Section 5.2		7. Hyperkalemia at Screening (defined by 2 local serum K^+ values of >5.0 mEq/L, each obtained from a separate venipuncture, e.g., one in each arm or 2 separate venipunctures in the same arm) • While receiving an ACEi/ARB/ARNi, and/or an MRA OR Normokalemia at Screening (defined by 2 local serum K^+ ≥4.0–≤5.0 mEq/L, each obtained from a separate venipuncture, e.g., one in each arm or 2 separate venipunctures in the same arm) • With a history of hyperkalemia documented by a usual care serum K^+ measurement >5.0 mEq/L • While on an ~~MRA~~ • ~~Leading to a subsequent and permanent discontinuation of the MRA medication~~ • ~~MRA discontinuation occurred >2 weeks prior to Screening~~ ~~OR~~	7. Hyperkalemia at Screening (defined by 2 local serum K^+ values of >5.0 mEq/L, each obtained from a separate venipuncture, e.g., one in each arm or two separate venipunctures in the same arm) while receiving an ACEi/ARB/ARNi, and/or an MRA OR Normokalemia at Screening (defined by 2 local serum K^+ ≥4.0–≤5.0 mEq/L, each obtained from a separate venipuncture, e.g., one in each arm or two separate venipunctures in the same arm) with a history of hyperkalemia documented by a usual care serum K^+ measurement >5.0 mEq/L while on **RAASi treatment in the 12 months prior to Screening leading to a subsequent and permanent dose decrease or discontinuation of one or more RAASi medications**

No	Section Number	Descriptive Statement/ Rationale Regarding Revision	Previous Text (If Applicable)	Revised and/or New Text
			For MRA naive subjects and normokalemia at ~~Screening (defined by 2 local serum K^+ values ≥4.0 ≤5.0 mEq/L) each obtained from a separate venipuncture, e.g., one in each arm or 2 separate venipunctures in the same arm)~~ • ~~With a history of hyperkalemia documented by a usual care serum K^+ measurement >5.0 mEq/L~~ • ~~While on an ACEi/ARB/ARNi~~ • ~~Leading to a subsequent, permanent dose decrease or discontinuation of one of the ACEi/ARB/ARNi medication~~ • ~~ACEi/ARB/ARNi dose decrease or discontinuation occurred >2 weeks prior to Screening~~	
26	Section 5.3		~~20. Planned or scheduled dialysis within 3 months from Screening~~	20. -
27	Section 6.7.2		~~Note: The aim for all subjects for the MRA dose should be 50 mg/day, but randomization can occur at 25 mg/day.~~	-
28	Section 6.7.3		~~Note: The aim for all subjects for the MRA dose should be 50 mg/day. However, the MRA dose must be at least 25 mg/day for at least 1 week for subjects to meet the randomization criteria.~~	For subjects who are on <50 mg/day of MRA, double their current dose up to 50 mg/day. Assess tolerance to the 50 mg target dose. MRA dose is at least **50** mg/day and has been stable for at least 1 week

No	Section Number	Descriptive Statement/ Rationale Regarding Revision	Previous Text (If Applicable)	Revised and/or New Text
			• MRA dose is at least *25* mg/day and has been stable for at least 1 week	
29	Section 8.2		If a subject cannot be randomized on the same day the randomization criteria were met, then the subject *must* be randomized within 1 week and all assessments described in Section 8.2.1 will be performed.	If a subject cannot be randomized on the same day the randomization criteria were met, then the subject **should** be randomized within 1 week and all assessments described in Section 8.2.1 will be **repeated on the day of randomization**.
30	Section 8.4		~~Event-Driven~~ EoS Visit Procedures The common end of the study date will be set by the Sponsor ~~based on when the study is projected to accrue the required number of events of CV mortality or CV hospitalization~~. Investigational sites will be notified of the study termination date ~~approximately 3 months prior to study closure~~ and should advise ongoing study subjects of the study termination date thereafter	EoS Visit Procedures The common end of the study date will be set by the Sponsor. **The common EoS will occur when 820 subjects have completed the Week 6 visit. Recruitment will be stopped, and subjects called in by the sites for the EoS visit when** it is projected that a sufficient number of **subjects have been enrolled in order for 820 subjects to reach the Week 6 visit.** All randomized subjects, including those who prematurely discontinued patiromer/placebo, will complete the EoS Visit within the timeline provided by the Sponsor around the common EoS date. Investigational sites will be notified of the study termination date **as soon as possible after the decision is taken** and should advise ongoing study subjects of the study termination date thereafter
31	Section 9.1		-	The definition of hyperkalemia follows the European Society of Cardiology expert consensus document on the management of hyperkalemia in patients with cardiovascular disease [37]. Hyperkalemia is

No	Section Number	Descriptive Statement/ Rationale Regarding Revision	Previous Text (If Applicable)	Revised and/or New Text
				considered for all serum K^+ values >5.0 mEq/l with the gradings of mild hyperkalemia (serum K^+ >5.0 mEq ≤5.5 mEq/l), moderate hyperkalemia (serum K^+ >5.5 mEq ≤6.0 mEq/l) and severe hyperkalemia (serum K+ >6.0 mEq).
32	Section 10.7.2.1		Composite Study Endpoints: All events potentially related to the ~~composite primary~~ endpoint of CV death or CV hospitalizations or urgent HF visits will be collected starting from the date of randomization. For the purposes of this protocol, the following events are considered SAEs and must be reported as described in Section 10.7.2.	Study Endpoints: All events potentially related to the endpoint of CV death or CV hospitalizations or urgent HF visits will be collected starting from the date of randomization. For the purposes of this protocol, the following events are considered SAEs and must be reported as described in Section 10.7.2.
33	Section 10.7.2.1		The following CV hospitalization events will be counted towards the ~~primary~~ endpoint:	The following CV hospitalization events will be counted towards the endpoint:
34	Section 12.2		~~Following Claggett (2018), simulations were conducted to investigate the effect of heterogeneity of the subject level exponential risk on the power of the proposed sample size for the primary analysis (log-rank test for the time to first occurrence of CV death or CV hospitalization) [39]. Based upon an assumed heterogeneity factor of 4.0 (i.e., gamma frailty with variance of 4.0), the proposed sample will have approximately 80% power. A recurrent event analysis (LWYY test) would have approximately 78% power assuming 30% of events result in death and 20% treatment effect attenuation after each event.~~	-

No	Section Number	Descriptive Statement/ Rationale Regarding Revision	Previous Text (If Applicable)	Revised and/or New Text
35	Section 12.8.1		The primary analysis will be based upon the ~~time to the first occurrence of the primary endpoint consisting of a CV death or CV hospitalization (or equivalent in outpatient clinic). The test of significance will be based upon a stratified (randomization strata) log-rank test. The treatment effect will be summarized using the HR and 95% CI calculated using a stratified (randomization strata) Cox regression model with treatment as the only model parameter. In these analyses, subjects will be censored as of their last assessment for the primary endpoint as well as for deaths for non-CV causes.~~ Sensitivity analyses for the primary endpoint ~~will be based upon the use of all CV deaths and hospitalizations (i.e., recurrent event analysis) recorded during follow-up using the following methods:~~ ~~• Extended Cox model [2]~~ ~~• Days alive outside of the hospital [3]~~ ~~• Rank based analysis [4]~~ ~~Additional descriptive statistics will be calculated to better understand the recurrent events pattern. In particular, the HR will be estimated within event count using a conditional model (gap-time method) that allows both the underlying hazard and HR to vary [40] with a robust variance estimator. In this approach, subjects experiencing a death are removed from the risk sets for subsequent events. Additional estimates will be calculated treating CV death as a competing risk for the occurrence of CV hospitalizations~~	The primary analysis will be based upon **the mean change in serum potassium levels from Baseline and is analyzed by means of an MMRM approach including all available post baseline data. All analyses will be restricted to serum K^+ assessments and not substituted by plasma values as they are known to be systematically lower. Central laboratory values and/or local laboratory will be used at all visits, and if both values are present at one visit, then central laboratory values will be used. A Gaussian linear model for repeated measures with treatment, geographic region, sex, baseline T2DM status and visit as factors, and baseline potassium level, baseline eGFR as covariates. The error terms are assumed to follow a multivariate normal distribution with unstructured covariance. Least squares mean changes from Baseline will be reported for both treatment groups with 95% CIs as well as the difference between the least squares group means with 95% CI and p-value testing the null hypothesis of no treatment effect.** **Sensitivity analyses for the primary endpoint will be based upon the use of all CV deaths and hospitalizations (i.e., recurrent event analysis) recorded during follow-up using the following methods: will explore changes in treatment effect over follow-up time by including treatment by visit interactions in the above-mentioned model.**

No	Section Number	Descriptive Statement/ Rationale Regarding Revision	Previous Text (If Applicable)	Revised and/or New Text
				In addition, sensitivity analyses for the primary endpoint will explore changes in treatment effect over follow-up time by including treatment by visit interactions in the above-mentioned model. In addition, sensitivity analyses accounting for potentially informative missingness will be based upon a Win Ratio approach [4,31].
36	Section12.8.2		-	**Key Secondary Endpoints (Hierarchically Ordered)** **• Hyperkalemia events: The time to the first event of hyperkalemia with a serum K^+ value >5.5 mEq/L as per the measured values from the central or local laboratories is analyzed using a Cox proportional hazards regression model. The event probabilities will be estimated using the Aalen-Johansen estimator of the cumulative incidence function accounting for competing events such as death.** **• Durable enablement to stay on the MRA target dose (of 50 mg spironolactone or eplerenone): The time to reduction of the MRA dose below target is analyzed using a Cox proportional hazards regression model. The event probabilities will be estimated using Aalen-Johansen estimator of the cumulative incidence function accounting for competing events such as death.**

No	Section Number	Descriptive Statement/ Rationale Regarding Revision	Previous Text (If Applicable)	Revised and/or New Text
				Note: Discontinuation of the target dose for at least 14 days (or less if at the EoS) is required to confirm this endpoint. **• Investigator reported AEs of hyperkalemia (first and recurrent) are analyzed using a negative binomial regression with the logarithm of the individual follow-up time as offset.** **A joint frailty model of the total (first and recurrent) hyperkalemia events and time to death as terminating event. If all-cause mortality is substantial in number and differential between the treatment groups, then the joint frailty model would become the main analysis approach.** **Note: For analyses based upon the negative binomial distribution, the subject level count data will be modeled as function of treatment with the natural log of the subject level follow-up time taken into account in the estimation of the event rate.** **• Hyperkalemia-related hard outcomes are analyzed using the Win Ratio approach with the following hierarchical components (all assessed during comparable follow-up times)** **1. Time to CV death** **2 Total number of CV hospitalizations** **3 Total number of hyperkalemia toxicity events with serum K+ >6.5 mEq/L** **4 Total number of hyperkalemia toxicity events with serum K+ >6.0-6.5 mEq/L**

No	Section Number	Descriptive Statement/ Rationale Regarding Revision	Previous Text (If Applicable)	Revised and/or New Text
				5 Total number of hyperkalemia toxicity events with serum K+ >5.0-6.0 mEq/L **• RAASi Use Score which will be analyzed using the Win Ratio approach for each pair of patients at the end of the comparable follow-up period that is appropriate for that pair of patients with the following hierarchical components. Points are accumulated from two components at the respective time for each patient in each comparison:** **<u>Component A:</u>** **• If during the follow-up (to the respective end of follow-up in the comparison) there was a death, the subject is assigned 0 points** **• If during the follow-up (to the respective end of follow-up in the comparison) there was a CV hospitalization, but the subject is alive at the end of that follow-up, the subject assigned 1 point** **• If during the follow-up (to the respective end of follow-up in the comparison) there was no CV hospitalization and the subject is alive at the end of that follow-up, the subject is assigned 2 points** **Component B:** **Further points are collected for the treatment status at the respective end of follow-up in the comparison** **• For ACEi/ARB/ARNi use: >50% of the target dose = 2 points**

No	Section Number	Descriptive Statement/ Rationale Regarding Revision	Previous Text (If Applicable)	Revised and/or New Text
				• **For ACEi/ARB/ARNi use: >0 and up to 50% of the target dose = 1 point** • **For MRA use: >50% of the target dose = 2 points** • **For MRA use: >0 and up to 50% of the target dose = 1 point** • **For beta-blocker use: >50% of the target dose = 2 points** • **For beta-blocker use: >0 and up to 50% of the target dose = 1 point** **In summary, each subject in each comparison can have 0-8 points (sum of Components A and B) and all subjects are compared using this score at the respective appropriate follow-up time point.** **The regression analyses will be adjusted for geographic region as the stratification factor of the randomization and relevant baseline characteristics of the subjects.**
37	Section 12. 8. 3		*Secondary* • Proportion of subjects on ≥50% of target dose of ACEi, ARB, or ARNi and ≥50% of target dose of MRA at the EoS Visit ~~with analysis using Fisher's Exact Test~~ • ~~Total HF hospitalizations (or equivalent in outpatient clinic) analyzed using the negative binomial distribution~~ • ~~Change from randomization in the clinical summary score of KCCQ at 8 months~~ ~~For analyses based upon the negative binomial distribution, the subject level count data will be modeled as function of~~	**Other** Secondary **Endpoints** The additional endpoints listed below (Other **Secondary** Endpoints), will also be summarized descriptively by treatment arm in the full analysis set: • **Durable enablement to stay on the target dose of ACE/ARB/ARNi** ***Note: Discontinuation of the target dose for at least 14 days (or less if at the EoS) is required to confirm this endpoint***

No	Section Number	Descriptive Statement/ Rationale Regarding Revision	Previous Text (If Applicable)	Revised and/or New Text
			~~treatment with the natural log of the subject level follow-up time taken into account in the estimation of the event rate.~~ The additional endpoints listed below (Other Endpoints), will also be summarized descriptively by treatment arm in the full analysis set: • Emergency treatment for hyperkalemia (hospitalization or emergency room) ~~• Patient-reported outcome: EQ-5D-5L questionnaire~~ ~~• Proportion of subjects with change in the patient-reported outcome, KCCQ, greater than 5 points at 8 months after randomization~~ ~~• Time to first occurrence of HF hospitalization (or equivalent in outpatient clinic)~~ ~~• Total CV hospitalizations (or equivalent in outpatient clinic)~~ ~~• Proportion of subjects on any dose of MRA at the EoS Visit~~ • Proportion of subjects on ~~any dose~~ of ACEi, ARB, or ARNi at the EoS Visit ~~• Change in proteinuria from Screening~~ ~~• Change in NT-proBNP from Screening~~ ~~• Change in high sensitivity troponin from Baseline~~ ~~• Functional status by NYHA class~~ ~~• 30-day HF re-hospitalization after a prior HF hospitalization~~ ~~• HEOR analyses~~	• **Durable hyperkalemia-free enablement to stay on the MRA target dose (days on 50mg MRA without presence of hyperkalemia)** • **Hyperkalemia toxicity events with serum K+ >6.5 mEq/L** • **Hyperkalemia toxicity events with serum K+ >6.0-6.5 mEq/L** • Emergency treatment for hyperkalemia (hospitalization or emergency room) • **Total number of hyperkalemia toxicity events with serum K+ >5.0-6.0 mEq/L** • **KCCQ questionnaire - OSS, CSS and TSS** • **Investigator reported events of hyperkalemia (recurrent events)** • Proportion of subjects on **≥50% of target dose of ACEi, ARB, or ARNi and ≥50% of target** dose of MRA at the EoS Visit • **Time to first occurrence of CV death or CV hospitalization**
38	Section12.8.4		-	• **CV Death**

No	Section Number	Descriptive Statement/ Rationale Regarding Revision	Previous Text (If Applicable)	Revised and/or New Text
				• **First and recurrent CV hospitalizations** • **First and recurrent HF hospitalizations (or equivalent in outpatient clinic)** • **Patient-reported outcome: EQ-5D-5L questionnaire** • **Proportion of subjects on any dose of MRA at the EoS Visit** • **Proportion of subjects on any dose of ACEi, ARB, or ARNi at the EoS Visit** • **Change in proteinuria from Screening** • **Change in NT-proBNP from Screening** • **Change in high sensitivity troponin from Baseline** • **Functional status by NYHA class** • **30-day HF re-hospitalization after a prior HF hospitalization** • **HEOR analyses** • **Changes in serum K^+ from Baseline to individual visits**
39	Section 12.9		Safety Evaluations ~~• Serum K^+~~	Safety Evaluations • **Laboratory parameters other than those defined as efficacy endpoints**
40	Section 12.10		~~The blinded monitoring of event rates is planned throughout the study to check the assumptions used for the sample size calculations to predict the timing of interim and final analyses. In addition, an independent DSMB will meet periodically to monitor the study. As part of these reviews, the DSMB will~~	**No interim analysis is planned.**

No	Section Number	Descriptive Statement/ Rationale Regarding Revision	Previous Text (If Applicable)	Revised and/or New Text
			~~receive summaries of study conduct measures as well as unblinded safety and efficacy data.~~ ~~To protect the study from prematurely being closed for a finding of efficacy, the DSMB will be requested to use the O'Brien-Fleming (Lan-DeMets implementation) for evaluating the primary efficacy endpoint in a formal interim analysis of efficacy. A single such evaluation is planned when 50% of the planned primary endpoint events are positively adjudicated.~~ ~~The final analysis will take into account the interim analysis. As such, the significance level at the final analysis will be adjusted, following Lan-DeMets, to take into account the exact timing of the interim analysis.~~	
41	Section 18		-	**40. Pocock SJ, Ariti CA, Collier TJ, and Wang T. The win ratio: a new approach to the analysis of composite endpoints in clinical trials based on clinical priorities, European Heart Journal, Volume 33, Issue 2, January 2012, Pages 176–182, https://doi.org/10.1093/eurheartj/ehr352 7.**
42	Section 18		-	**36. Rosano GMC, Tamargo J, Kjeldsen KP, Lainscak M, Agewall S, Anker SD, et al. Expert consensus document on the management of hyperkalaemia in patients with cardiovascular disease treated with renin angiotensin aldosterone system inhibitors: coordinated by the Working Group on Cardiovascular Pharmacotherapy of the European Society of Cardiology. Eur Heart J Cardiovasc Pharmacother. 2018;4(3):180–8.**