STATISTICAL ANALYSIS PLAN (SAP)

Investigational Drug:	**Patiromer for Oral Suspension**
Treatment:	**Heart Failure**
Study Phase:	**Phase 3b**
Study 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)**
Protocol Number:	**PAT-CR-302**
Protocol Version:	**4.0**
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Sponsor:	**Viforpharma, Inc.** **200 Cardinal Way** **Redwood City, CA 94063, USA** [redacted]
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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADaM	Analysis data model
AE	Adverse event
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus disease 2019
CRF	Case report form
CV	Cardiovascular
DSMB	Data Safety Monitoring Board
EAC	Event Adjudication Committee
ECG	Electrocardiogram
EF	Ejection fraction
EGFR	Estimated glomerular filtration rate
EoS	End of study
ESRD	End-stage renal disease
ET	Early termination
FAS	Full analysis set
GCP	Good clinical practice
HF	Heart failure
HFrEF	Heart failure with reduced ejection fraction
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IVRS	Interactive voice response system
IWRS	Interactive web response system
KCCQ	Kansas City Cardiomyopathy Questionnaire
MedDRA	Medical dictionary for regulatory activities
MRA	Mineralocorticoid receptor antagonist
N	Number
NYHA	New York Heart Association
PD	Protocol deviation
PP	Per protocol
PPS	Per protocol set
PT	Preferred term
PV	Protocol violation
RAASi	Renin angiotensin-aldosterone system inhibitor
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard error
SOC	System organ class
SOP	Standard operating procedure
SS	Safety set
TEAE	Treatment emergent adverse event
TFL	Tables, figures and listings
TOC	Table of content
WHO	World health organization

1 STUDY DESCRIPTION

Patiromer is being studied in subjects receiving renin angiotensin-aldosterone system inhibitor (RAASi) medications for the treatment of heart failure with reduced ejection fraction (HFrEF). This study will assess the effects of patiromer on serum potassium (K^+) and use of RAASi / mineralocorticoid receptor antagonist (MRA) medications in heart failure (HF) patients.

1.1 Objectives

Study PAT-CR-302 (DIAMOND Study) has the following primary objective:

- To determine whether patiromer treatment of subjects who developed hyperkalemia while receiving RAASi medications will result in changes in serum potassium levels from baseline at randomization

1.2 Study Design

The DIAMOND study is a prospective Phase 3b multinational, multicenter, double-blind, placebo-controlled, randomized withdrawal, parallel group study that includes screening and an up to 12-week Run-in Phase (all subjects will have patiromer initiated and RAASi medications, including MRA, optimized) and a randomized withdrawal Double-Blinded Treatment Phase. The primary efficacy assessment will be based upon the data collected during the Double-Blinded Treatment Phase.

During the Run-in Phase, which is single blind to the subject, the Investigator will manage RAASi initiation and/or dose escalation as recommended by practice guidelines, using clinical judgment to customize RAASi addition or dose escalation based on subject response. Assessment of serum potassium will occur at each visit. The patiromer dose will be titrated based on the subject's potassium level.

After completing the Run-in Phase and found eligible for the Double-Blinded Treatment Phase of the study, subjects will be randomized. Randomized subjects will begin treatment with patiromer or placebo using the same number of packets established for patiromer at the end of the Run-in Phase and will continue the RAASi regimen being administered at the end of the Run-in Phase

The study will continue until reaching at least the Week 6 visit for each subject. An independent Data Safety and Monitoring Board (DSMB) will act in an advisory capacity to monitor the safety of subjects who participate in this study.

1.3 Method of Assigning Subjects to Treatment Groups

Subjects will be randomized to the treatment arms (1:1 assignment) using permuted block randomization stratified by region. Randomization will take place using a centralized list accessed electronically on the day of randomization after Double-Blinded Treatment Phase eligibility is determined (Day 1).

1.4 Blinding

This is a double-blind study. The sponsor will not have access to unblinded data during the study (with the exception of Viforpharma Drug Safety staff in situations where unblinding is necessary to comply with Regulatory requirements), and there is no expectation that the study data (e.g. adverse events, dosing, or lab results) will unblind the sponsor, investigator or subjects. While study data (e.g. serum potassium changes) may provide some suggestion of the assigned treatment, sufficient variability is expected to prevent true unblinding. The DSMB will have access to unblinded study data as needed.

The sponsor, investigator and subjects will not have access to the unblinded DSMB reports, which will be prepared by an independent statistician and programmers not otherwise involved with the conduct of the study.

1.5 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) in change in K^+ levels from Baseline. This sample size calculation is based upon the following assumptions: alpha level of 5% (2-sided); difference between group means of 0.116; a SD of 0.5; and 5% loss to follow-up.

2 STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

2.1 Populations Analysed

Four analysis populations will be defined.

2.1.1 Randomized Set

All subjects randomized to study treatment.

2.1.2 Full Analysis Set

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

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

The full analysis set will be the primary population used for the evaluation of efficacy.

2.1.3 Safety Set

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

2.1.4 Run-in Phase Set

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

At the beginning of the Covid-19 pandemic, in order to ensure subject safety, all subjects who were in the Run-in Phase were discontinued. These subjects were given the opportunity to be re-screened once Covid-19 restrictions were eased in their respective locations. Those who were still eligible were entered into the Run-in Phase again.

Details for handling the adverse event, laboratory and concomitant medication data for subjects with two separate periods of Run-in Phase are provided in the appropriate sections below.

2.2 General Considerations

Efficacy analyses will be performed by planned treatment (i.e. as randomized), and safety analyses by actual treatment received.

For continuous variables, descriptive statistics will include the number of subjects, mean, standard deviation (SD), standard error (SE), median, 25th and 75th percentiles, minimum and maximum.

For categorical variables, descriptive statistics will include frequencies and percentages in each category.

For time-to-event variables, the descriptive statistics will include the median, 95% CI, 25th and 75th percentiles, minimum and maximum. Counts (percentages) of subjects with events and of subjects censored will also be provided.

When mean change from baseline is summarized, subjects will only be included in the analysis if they have both a baseline value and a post-baseline value at the time point of interest.

Detailed statistical analyses are specified in sections below.

On June 24, 2021, sites were informed that the study would be closing and that subjects should be brought in for their End of Study (EoS) visit as soon as possible. After this date, many sites incorrectly began to titrate and/or discontinue blinded study drug medication prior to the EoS visit. Because this practice was wide-spread, data after June 24, 2021 will be censored for purposes of efficacy analyses. Sensitivity analyses, including data after June 24, 2021, will be conducted for the primary and key secondary endpoints. Safety and exposure analyses will primarily be conducted using all data. Some sensitivity analyses may be conducted using data only through June 24, 2021, as appropriate.

2.3 Subject Disposition

The number and percentage of subjects randomized, subjects who receive randomized study treatment, and subjects who complete study (or are terminated early) will be summarized by treatment group and overall. The number and percentage of randomized subjects terminating from the study early will be presented by reason. In addition, a summary of subject disposition as of June 24, 2021 will be provided.

The Randomized Set, FAS, and SS will be summarized by treatment group and overall.

The number and percentage of subjects who signed informed consent, screen failures and screen failure reasons will be summarized. The number and percentage of subjects in the Run-in phase, subjects who receive patiromer during the Run-in phase, and the reasons for the subjects not randomized at the end of the Run-in Phase will be summarized. Listings of subject disposition will be provided.

2.4 Protocol Deviations

Protocol deviations will be summarized for the Randomized Set. The number and percentage of subjects with protocol deviations will be summarized by category of deviation, separately for the Run-in Phase and the Blinded Treatment Phase, for each treatment group and overall. A listing of protocol deviations will be provided.

2.5 Demographics and Baseline Characteristics

Demographics will be summarized for the Randomization Set, the Full Analysis Set, and the Run-in Set. Baseline and screening characteristics will be summarized for the Randomized Set and the Full Analysis Set. Screening characteristics will be summarized for the Run-in Phase Set.

The summary of demographic information will include age, sex, race and ethnicity. The summary of patient characteristics at baseline will include, but is not limited to weight, height, body mass index, hyperkalemia status, prespecified medical history (for example, diabetes types, heart failure including New York Heart Association (NYHA) class, ejection fraction (EF), myocardial infarction, stroke, other arrhythmias, serum potassium, estimated glomerular filtration rate (eGFR)).

Listings of demographics and baseline characteristics will be provided.

2.6 General Medical History

General medical and surgery history will be coded in accordance with MedDRA 23.0 or an updated version and summarized for the Randomized Set, the FAS, and the Run-in Phase Set by body system (or procedure) for each treatment group and overall.

A listing of general medical history will be provided.

2.7 Study Drug Dosing and Compliance

The following summaries of exposure to blinded study drug (patiromer or placebo) will be provided for the SS, by treatment group:

- Duration: calculated as [last dose date]-[first dose date]+1.
- Total dose: calculated for each subject as the total dosage received
- Mean daily dose: calculated for each subject as the total dose divided by the duration of study drug exposure
- Number and type of titrations (up or down)
- Number of non-zero dose days

Treatment compliance will be calculated for each subject and summarized by treatment group. Dosing compliance will be derived from the total dose of study drug taken by a subject divided by the prescribed total dose over the treatment period, multiplied by 100. Descriptive statistics will be provided for dose compliance. The summary of study drug dosing and compliance will be presented separately for the Run-in and Double-Blinded Treatment Phases.

The primary exposure analyses will be conducted using all data. Sensitivity analyses may be conducted, using only the data through June 24, 2021.

A listing of all study drug dosing and compliance data will be provided.

2.8 Prior/Concomitant Medications and Procedures

All prior and concomitant medications including heart failure and RAASi drugs will be coded using the current version of the World Health Organization Drug dictionary (WHO Drug Global B3 March 2019). Prior and concomitant medications, including heart failure and RAASi drugs, will be separately summarized in the SS. Counts and percentages of subjects using each medication will be computed and summarized by treatment group.

Prior medications are medications with start date before the date of first dose of patiromer in the Run-in phase.

Summaries of concomitant medications will be provided separately for the Run-in and Double-Blinded Treatment Phases.

Concomitant medications during the Run-in Phase are medications with a start date on or before the end of the Run-in Phase and a stop date on or after the first patiromer dose date in the Run-in Phase, or no stop date at all. For subjects who were in the Run-in Phase twice, data from the second Run-in will be summarized. Data from the first Run-in will be included in listings only.

Concomitant medications in the Double-Blinded Treatment Phase are medications with a stop date on or after the first date of treatment in the Randomized Treatment Phase, or no stop date at all. Additional summaries may be provided for concomitant medications of interest.

Summaries of the percent of subjects at 100% and 50% of the target dose for ACEi, ARB, ARNi, MRA and beta blockers will be provided at Baseline, Day 3, and Weeks 1, 2, 6, and 18 for the Safety Set, by treatment group.

Listings of all prior and concomitant medications will be provided.

Listings of concomitant procedures will be presented.

2.9 **Study Endpoints**

Study PAT-CR-302 (DIAMOND Study) has the following primary endpoint:

- Changes in serum potassium levels from baseline

Hierarchical Key Secondary Endpoints:

1. Hyperkalemia events with a serum K^+ value >5.5 mEq/L
2. Durable enablement to stay on the MRA target dose (50 mg daily spironolactone or eplerenone), as assessed by the between-treatment-group difference of the cumulative frequency of subjects not staying on that target dose
   Note: Discontinuation of the target dose for at least 14 days (or less if at the end of study) is required to confirm this endpoint.
3. Investigator reported events of hyperkalemia (first and recurrent)
4. Hyperkalemia related hard outcomes 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^+ >5.0-6.0 mEq/L
5. RAASi Use Score (Win Ratio)

Other Secondary Endpoints:

- Durable enablement to stay on the target dose of ACE/ARB/ARNI, as assessed by the between-treatment-group difference of the cumulative frequency of subjects not staying on that target dose
  Note: Discontinuation of the target dose for at least 14 days (or less if at the end of study) 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^+ >5.0-6.0 mEq/L
- KCCQ questionnaire, OSS, CSS and TSS during the treatment phase
- Investigator reported events of hyperkalemia (first event)
- 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
- Time to first occurrence of CV death or CV hospitalization
- Time to MRA discontinuation
  Note: Discontinuation of MRA, and no re-introduction after the event..
- Time to first occurrence of MRA discontinuation or death
- Time to ACEi/ARB/ARNi discontinuation
  Note: Discontinuation of ACEi/ARB/ARNi, and no re-introduction after the event..
- Time to first occurrence of ACEi/ARB/ARNi discontinuation or death

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 Day 3 of the Blinded Treatment Phase
- Change in NT-proBNP from screening
- Change in high sensitivity troponin from baseline at randomization
- Functional status by NYHA class
- 30-day HF re-hospitalization rate after a prior HF hospitalization
- Changes in serum K^+ from Baseline to individual visits
- Slope of eGFR change during the study

Safety Endpoints:

- Adverse events
- All-cause mortality
- 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

2.10 Statistical Assessment of Efficacy Endpoints

2.10.1 Primary Analyses

The primary analysis will be based upon the mean change in serum K^+ levels from Baseline and is analysed by means of a mixed model for repeated measures (MMRM) approach. The model will include data through the last scheduled visit for which at least 10% of subjects have assessments.

The primary analysis will include only local laboratory serum potassium data from assessments on or before June 24, 2021. A sensitivity analysis will be performed that also includes data after June 24, 2021.

All analyses will be restricted to serum K^+ assessments and not substituted by plasma values as they are known to be systematically lower. A Gaussian linear model for repeated measures will be used, 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.

Changes in treatment effect over follow-up time will be explored 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 [1, 2].

The following additional sensitivity analyses will be conducted by re-running the primary MMRM as follows:

- Using local serum potassium data without a cutoff at June 24, 2021
- Using both local and central serum potassium data on or before June 24, 2021 (if both values are present at a visit, the centrally assessed serum potassium will be used)
- Using only central serum potassium data on or before June 24, 2021:

2.10.2 Secondary Endpoint Analyses

Key secondary efficacy endpoints will be tested sequentially in the order listed below (i.e. fixed-sequence method to preserve the familywise type I error rate) using the full analysis set, and will be summarized descriptively through the calculation of point estimates by treatment group along with 95% confidence intervals (CI) for the treatment differences.

For each key secondary endpoint, the primary analysis will use only data through June 24, 2021. A sensitivity analysis that includes all data will also be performed for each key secondary endpoint.

The following lists the secondary endpoints and the analysis methods 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 analysed using a Cox proportional hazards regression model. The treatment difference will be reported as hazard ratio (HR) with 95% CI and p-value from a Wald-type test considering the null hypothesis that the HR is equal to 1. 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 (50 mg spironolactone or eplerenone): The time to the first event of reduction of the MRA dose below target is analysed using a Cox proportional hazards regression model. The treatment difference will be reported as hazard ratio (HR) with 95% CI and p-value from a Wald-type test considering the null hypothesis that the HR is equal to 1. 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 analysed using a negative binomial regression with the logarithm of the individual follow-up time as offset. The treatment difference will be reported as rate ratio (RR) with 95% CI and p-value from a Wald-type test considering the null hypothesis that the RR is equal to 1. A joint frailty model of the total (first and recurrent) hyperkalemia events and time to death as terminating event may be implemented. 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.

- Hyperkalemia-related hard outcomes are analysed using the un-matched 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 events with serum K+ >6.0-6.5 mEq/L
  5. Total number of hyperkalemia events with serum K+ >5.0-6.0 mEq/L

  A death with cause classified as “undetermined” by the event adjudication committee will be considered as a CV death.

- RAASi Use Score will be analysed 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, based on 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 comparator subject) 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

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
- 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.

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

For analyses based upon the negative binomial distribution, the subject level count data will be modelled as a function of treatment with the natural log of the subject level follow-up time taken into account in the estimation of the event rate.

2.10.3 Other Secondary Endpoint Analyses

The additional endpoints listed below (Other Secondary Endpoints) will be summarized by treatment arm. When treatment comparisons are made, 95% CI and unadjusted p-values will be presented in the FAS set.

For each of these additional secondary endpoints, the analysis will be conducted using only data through June 24, 2021. Endpoints originally planned to be assessed at the EoS visit will instead be assessed using the last available data on or before June 24, 2021.

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

  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) [redacted]
- Hyperkalemia toxicity events with serum K^+ >6.5 mEq/L [redacted]
- Hyperkalemia events with serum K^+ >6.0-6.5 mEq/L [redacted]

- Emergency treatment for hyperkalemia (hospitalization or emergency room) [redacted]
- Total number of hyperkalemia events with serum K^+ >5.0-6.0 mEq/L [redacted]
- Investigator reported events of hyperkalemia (time to first event) [redacted].
- Proportion of subjects on ≥50% of target dose of ACEi, ARB, or ARNi and ≥50% of target dose of MRA at the EoS Visit [redacted]
- Time to first occurrence of CV death or CV hospitalization [redacted]
- Time to MRA discontinuation, [redacted]
- Time to first occurrence of MRA discontinuation or death, [redacted]
- Time to ACEi/ARB/ARNi discontinuation, [redacted]
- Time to first occurrence of ACEi/ARB/ARNi discontinuation or death, [redacted]

2.10.4 Other Analyses

The analyses listed below will be conducted using only data through June 24, 2021, except for the analysis of high sensitivity troponin. [redacted]

Endpoints originally planned to be assessed at the EoS visit will instead be assessed using the last available data on or before June 24, 2021.

- CV death [redacted]
- First and recurrent CV hospitalizations [redacted]
- First and recurrent HF hospitalizations (or equivalent in outpatient clinic) [redacted]
- KCCQ questionnaire - OSS, CSS and TSS [redacted]
- Mean change in EQ-5D-5L total score based on a visual analog scale from randomization to each time point measured post-randomization [redacted]

- Proportion of subjects on any dose of MRA at the EoS Visit, [redacted]
- Proportion of subjects on any dose of ACEi, ARB or ARNi at the EoS Visit, [redacted]
- Mean Change in proteinuria from Day 3 of the Blinded Treatment Phase to the EoS Visit, [redacted]
- Mean Change in NT-proBNP from screening to each time point measured post-randomization for which at least 10% of subjects have an assessment, [redacted]
- Mean Change in high sensitivity troponin from randomization at the EoS Visit, [redacted]
- Change in Functional status by NYHA class [redacted]t
- 30-day HF re-hospitalization rate after a prior HF hospitalization, [redacted]
- Mean changes in serum K+ from Baseline to individual visits
- Slope of eGFR change during the study, [redacted]

[redacted]

[redacted]

[redacted].

2.11 **Analyses of Data in the Run-in Period**

The analyses described in this section will use a modified Run-in Set. Subjects in the Run-in Set who were discontinued prematurely from Run-in during Spring 2020 due to Covid-19 or were discontinued prematurely after study closure was announced on June 24, 2021, will be excluded.

Screening Characteristics

Differences between the modified Run-in and Randomized Sets will be summarized for selected characteristics at Screening.

Predictors of Selected Outcomes During Run-in

Summary statistics will be provided for the following outcomes in Run-in, separately for the Randomized Set and the modified Run-in Phase Set:

- Inability to achieve MRA target dose (stable for at least one week) during Run-in
- Inability to achieve ACEi/ARB/ARNi target dose (stable for at least 1 week) during Run-in

- Inability to achieve at least 50% of the ACEi/ARB/ARNi target dose (stable for at least 1 week) during Run-in
- Hyperkalemia event during Run-in ($K^+ > 5.5$)
- Hypokalemia event during Run-in

For the above outcomes, selected screening characteristics will be assessed as potential predictors. Characteristics to be assessed may include, but are not limited to:

- eGFR < 60;
- NT-proBNP
- Systolic BP
- Ischemic cause of heart failure (Y/N)
- Diabetes Mellitus (Y/N)
- Sex (M/F)
- NYHA (I, II vs. III vs. IV)
- BMI
- Hyperkalemia (Y/N) – as a predictor of inability to reach target dose

RAASi Medication Use

Use and dose level of RAASi heart failure medications will be summarized at the end of the Run-in Period, separately for the modified Run-in Set and the Randomized Set.

KCCQ

Summary statistics will be provided for the FAS for the KCCQ Overall Summary Score at Screening, at Baseline, and for the Change from Screening to Baseline.

2.12 Baseline and Screening Definitions

2.12.1 Baseline

Unless otherwise specified, Baseline is defined as the value of a variable at the Day 1/Baseline Visit. If there is a missing value at the Day 1/Baseline Visit, Baseline is defined as the last available non-missing value on or before and ≤ 10 days prior to the first dose of blinded study medication.

For randomized but not treated subjects, Baseline is defined as the value at the Day 1/Baseline Visit; if missing, it is defined as the last available non-missing value on or before and ≤ 10 days prior to the date of randomization

Some laboratory tests are assessed by both the central laboratory and a local laboratory. In these cases, the following baseline values are defined:

- Local Baseline (Bsl_L) is defined as above using only local values
- Central Baseline (Bsl_C) is defined as above using only central values

- Central/Local Baseline (Bsl_CL) is defined as the Central Baseline (Bsl_C) if available, and as the Local Baseline (Bsl_L) if the Central Baseline is missing
- Local/Central Baseline (Bsl_LC) is defined as the Local Baseline (Bsl_L) if available, and as the Central Baseline (Bsl_C) if the Central Baseline is missing

In general, if an analysis includes only local laboratory test results for a specific laboratory test value, Bsl_L is used to calculate change from Baseline and is used as the baseline covariate in models; if the analysis includes only central laboratory test results, Bsl_C is used; if the analysis includes both central and local test results, Bsl_CL or Bsl_LC is used.

Tables and figures will specify what baseline is being used for the table or figure.

The following are specific exceptions to these rules:

- For eGFR, Bsl_CL is defined differently than for other laboratory parameters. The definition is: the value of the Central Baseline (Bsl_C); if missing, the value of the Local Baseline (Bsl_L); if missing, the value at Day 3, with preference for the central value
- Urine ACR is assessed only by the central laboratory, and is collected only during Run-in, at Day 3, Week 2, Week 18, and at each 3-month visit during the Double-blinded Treatment Phase. For analyses of proteinuria, Baseline is defined as the central value of urine ACR at the Day 3 Visit.

2.12.2 Screening

Unless otherwise specified, the screening value of a variable is defined as the value of the variable at the Screening Visit. If there is a missing value at the Screening Visit, the screening value is defined as the earliest available non-missing value on or before the first dose of patiromer in the Run-in Phase and on or after the first date in the Screening period. If a subject was screened more than once, only the last screening that was associated with entry into Run-in will be considered. If the subject never entered Run-in, only the last screening period for the subject will be considered.

For laboratory tests that are assessed by both a local and a central laboratory at Screening, the following Screening values are defined:

- The Local Screening value (Scr_L) is defined as above using only local values
- The Central Screening value (Scr_C) is defined as above using only central values
- The Central/Local Screening value (Scr_CL) is defined as the Central Screening value (Scr_C) if available, and as the Local Screening value (Scr_L) if the Central Screening value is missing

If an analysis includes only local laboratory test results, Scr_L is used to calculate change from Screening; if the analysis includes only central laboratory test results, Scr_C is used; if the analysis includes both central and local test results, Scr_CL is used.

NT-proBNP is assessed by the local and central laboratories at Screening, but after Screening is assessed only by the central laboratory, at Week 18 and at each 3-month visit during the Double-blinded Treatment Phase. For analyses of change from Screening, the Scr_CL value will be used.

Two sets of subgroups are defined by laboratory screening values. These are the CKD and NT-proBNP subgroups. In both cases, Scr_CL will be used to determine subgroup assignments.

2.13 Study Day and Visit Windows

The first date of dosing with the study medication (patiromer/placebo) will be used as the Reference Date for Study Day calculation.

The Study Day for date of first dosing is Day 1. The Study Day for all other study events is defined as follows:

- If a date is prior to the Reference Date, Study Day is defined as [date] - [Reference Date], so the Study Day for the day before date of first dose is defined as Day -1.
- If a date is on or after the Reference Date, Study Day is defined as [date] - [date of blinded study drug] +1; hence, the Study Day for the day after first dose is defined as Day 2.

Unless otherwise specified, summaries by visit will use the visit weeks/months reported in the database and include the results collected at scheduled visits.

The analyses which are not limited to scheduled visits (e.g. adverse events, incidence of laboratory test values within a given range, and time to event analyses), will include all available values of the variable of interest, irrespective of whether it was collected at a scheduled or unscheduled visit. For central laboratory data, the visit information from the central laboratory will be used to determine whether a visit is scheduled or unscheduled.

2.14 Handling of Missing Data

Missing data will be reflected primarily through the use of censoring for incomplete follow-up. The approach will depend on the particular analysis.

2.14.1 Missing Information for Adverse Events

For subjects with the missing information for adverse events, the following imputation rules will be applied:

- An adverse event with onset date equivalent to the first dosing date will be considered to be treatment-emergent unless there is evidence to conclude that it is not.
- An adverse event with missing severity will be assigned to the highest severity observed for the subject, among all events with the same preferred term; if there are no other adverse events (AEs) with same preferred term and non-missing severity, the adverse event will be counted as severe.
- An adverse event with missing relationship to study drug (patiromer/placebo) will be assigned to possible relationship (i.e. related).

2.14.2 Missing Dates or Partially Missing Dates

Missing or partially missing dates will be imputed conservatively for prior and concomitant medications/procedures, medical history, and adverse events. Specific rules for handling missing or partially missing dates are provided in “Appendix A: Imputation of Dates”. Appendix A: Imputation of Dates

No imputations for any other missing safety data will be undertaken.

2.15 **Subgroup Analyses**

Descriptive analyses (including the presentation of 95% confidence intervals) will be produced for the subgroups specified below for the primary and key secondary endpoints. These descriptive analyses will be summarized graphically through the use of forest plots.

The key subgroups to be analysed are:

- At screening, hyperkalemic vs normokalemic with a history of hyperkalemia
- BMI
- Ejection fraction (< versus ≥ median observed value)
- AF ongoing at screening (Yes versus No)
- Ischemic vs non-ischemic
- Screening use of ARNi (Yes versus No)
- Screening use of MRA (Yes versus No)
- Screening comorbidity:
    - Diabetes mellitus (Yes versus No)
- Baseline comorbidity:
    - CKD stage
        - eGFR ≥ 60 versus < 60
        - eGFR ≥ 45 versus < 45
    - NYHA class (II vs III-IV)
- Region (D vs A, B, C)
- Sex (Male or Female)
- Age (< versus ≥ median observed value)
- NT-proBNP at screening (≤ versus > median observed value)

The following subgroups will also be analysed:

- History of AF (Yes versus No)
- Region
    - US vs Non-US
    - Georgia + Ukraine vs all other countries

  Note: depending on actual patient recruitment, additional comparisons between other regions, e.g., Latin America, Western Europe, Eastern Europe, Japan may be conducted
- Age < 65 versus ≥ 65
- Age < 75 versus ≥ 75
- Age < 80 vs ≥ 80

2.16 Pooling Strategy for Strata

The number of subjects randomized is quite large relative to the number of strata. As such, no pooling of strata is planned for data analysis.

2.17 Safety Analyses

Statistical analyses will be descriptive in nature and will not be routinely tested for statistical significance. Safety analyses will be based upon the clinical database only. Events recorded in the safety database will be reconciled with the clinical database prior to database lock.

The primary safety analyses will be conducted using all data. Some sensitivity analyses using the data cutoff as June 24, 2021 may be undertaken, as appropriate.

For subjects who were in the Run-in Phase twice, data from the second Run-in will be summarized. Data from the first Run-in will be included in listings only.

2.17.1 Adverse Events

Adverse events (AEs) and serious adverse events (SAEs) coded using MedDRA (MedDRA version 23.0 or an updated version), including all-cause mortality, will be summarized descriptively.

AE summaries will be provided separately for the Run-in Phase and the Blinded Treatment Phase in the SS.

AE summaries will consist of counts (%) by MedDRA SOC and PT in the Run-in Phase, and by MedDRA SOC, PT and treatment arm in the Treatment Phase. The following types of AEs will be summarized:

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

AE summaries will also be presented in the Run-in Phase Set.

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

2.17.2 Laboratory and Vital Sign Parameter Analyses

Laboratory parameters (central) and vital signs will be summarized descriptively using the SS by treatment arm for each scheduled visit where the parameter is measured. Both the observed value and the change from baseline will be summarized. The summary of laboratory parameters will be provided for the Blinded Treatment Phase in the SS. The incidence of central laboratory test results in ranges of interest will be summarized by treatment group in the SS. These summaries will include but are not limited to the following:

- Serum potassium < 3.0, < 3.5, < 3.8, > 5.0, and ≥ 5.5 mEq/L
- Serum magnesium < 1.4, < 1.2, and < 1.0 mg/dL

- Serum calcium > 10.2 mg/dL

Central laboratory shift tables from Baseline to End of Study in the SS will be provided for selected laboratory results.

Decline in eGFR > 50%, or end-stage renal disease (ESRD), or renal death, or need for dialysis at any time after randomization will be summarized by count (%). If the number of subjects experiencing this composite endpoint is sufficient, Kaplan-Meir curves for each treatment arm in the SS will also be provided.

Listings will include results from local and central labs, at both scheduled and unscheduled visits.

Listings will be provided for all serum chemistry parameters, hematology, urinalysis, urine ACR, NT-proBNP, and high sensitivity troponin. Listings of all blood pressure, heart rate, weight, and height data will be provided.

2.17.3 Death

A listing of all deaths will be provided. The listing will include date of death, primary cause of death and any associated AEs.

2.17.4 Physical Examination

Abnormalities found in physical examinations will be summarized in the SS by treatment group at Screening and at EoS/ET visit.

A listing for all physical examination data will be provided.

2.17.5 12-lead Electrocardiogram (ECG)

Number and percentage of subjects with normal/abnormal and clinically significant abnormal ECG findings at screening will be summarized in the SS.

A listing for all 12-lead ECG data will be provided.

2.17.6 Special Situation

A listing will be provided for all reported special situations.

2.17.7 Pregnancy Reports

A listing for all pregnancy tests will be provided.

A listing for all reports on exposure to medicine during pregnancy will be provided.

2.18 Interim Analysis and Data Monitoring

An independent Data and Safety Monitoring Board (DSMB) will meet periodically to monitor the study.

As part of these reviews, the DSMB will receive summaries of study conduct measures as well as unblinded safety data. No interim analysis for efficacy will be conducted.

3 CHANGES FROM THE PROTOCOL

The protocol specifies that blood samples be taken during the study in order to analyse subject MRA levels.

The complete, validated MRA concentration data will not be available at the time of database lock, and analyses of that data will not be included for the CSR. The complete and validated data will be delivered later and analysed separately.

Slope of eGFR change during the study was proposed as a safety endpoint in the protocol. In the SAP it has been changed to an efficacy endpoint, and will be analysed using an mmrm model similar to those used for other efficacy endpoints.

Analyses during Run-in have been added to the SAP.

4 REFERENCES

1. Finkelstein DM, Schoenfeld DA. Combining mortality and longitudinal measures in clinical trials. Statist Med. 1999;18:1341-54.
2. 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.
3. Lachin JM. Worst-rank score analysis with informatively missing observations in clinical trials. Controlled Clinical Trials. 1999; 20: 408-422.

APPENDIX A: IMPUTATION OF DATES

1 Imputation of Missing/Partially Missing Adverse Event Dates

1.1 Incomplete Start Date:

Partially missing AE start/stop dates will be imputed in the analysis dataset model (ADaM) dataset for AEs, according to the rules below. However, listings of AE data will present the date as is, with missing date components left blank.

If the AE end date is complete with no missing year, month, or day, and a partially missing start date imputed by the rules below is after the AE end date, then the imputed start date will be equal to the end date.

Missing day and month

- If the year is the **same** as the year of the first dosing date, then the day and month of the first doing date will be assigned to the missing fields.
- If the year is **prior to** the year of first dosing date, then December 31 will be assigned to the missing fields.
- If the year is **after** the year of first dosing, then January 1 will be assigned to the missing fields.

Missing day only

- If the month and year are the **same** as the year and month of first dosing date, then the first dosing date will be assigned to the missing day.
- If either the year of the partial date is **before** the year of the first dosing date or the years of the partial date and the first dosing date are the same but the month of partial date is **before** the month of the first dosing date, then the last day of the month will be assigned to the missing day.
- If either the year of the partial date is **after** the year of the first dosing date or the years of the partial date and the first dose date are the same but the month of partial date is **after** the month of the first dosing date, then the first day of the month will be assigned to the missing day.

Missing day, month, and year

- No imputation is needed. The corresponding AE will be included as a TEAE.

1.2 Incomplete Stop Date:

If the imputed stop date is before the start date, then the imputed stop date will be equal to the start date.

Missing day and month

- If the year of the incomplete stop date is the **same** as the year of the last dosing date, then the day and month of the last dosing date will be assigned to the missing fields.
- If the year of the incomplete stop date is **prior to** the year of the last dosing date or prior to the year of the first dosing date, then December 31 will be assigned to the missing fields.
- If the year of the incomplete stop date is **prior to** the year of the last dosing date but is the same as the year of the first dosing date, then the first dosing date will be assigned to the missing date.
- If the year of the incomplete stop date is **after** the year of the last dosing date, then January 1 will be assigned to the missing fields.

Missing day only

- If the month and year of the incomplete stop date are the **same** as the month and year of the last dosing date, then the day of the last dosing date will be assigned to the missing day.

- If either the year of the partial date is **not equal to** the year of the last dosing date or the years of the partial date and the last dosing date are the same but the month of partial date is **not equal to** the month of the last dosing date, then the last day of the month will be assigned to the missing day.

2 Imputation of Dates for Prior/Concomitant Medications/Procedures

Partially missing start/stop dates for prior/concomitant medications and partially missing start dates for prior/concomitant procedures will be imputed in the ADaM dataset for prior/concomitant medications/procedures. However, listings of prior/concomitant medications/procedures data will present the date as is, with missing date components left blank.

For prior/concomitant medications, if the stop date is complete with no missing year, month, or day, and the partially missing start date imputed by the rule below is after the stop date, then the start date will be imputed by the stop date.

Partially missing prior/concomitant medication/procedure start dates will be imputed by the earliest possible date given the non-missing field(s) of the date.

Partially missing prior/concomitant medication stop dates will be imputed by the latest possible date given the non-missing field(s) of the date.

3. Imputation of Dates for Pre-specified Medical History

Partially missing start dates for pre-specified medical history will be imputed in the ADaM dataset for pre-specified medical history. However, listings of pre-specified medical history data will present the date as is, with missing date components left blank.

A partially missing pre-specified medical history start date will be imputed by the earliest possible date given the non-missing field(s) of the date and will be on or prior to the screening visit date.