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**Patiromer for the management of hyperkalaemia in patients receiving renin–  
angiotensin–aldosterone system inhibitors for heart failure: design and rationale of  
the DIAMOND trial**

Javed Butler<sup>1</sup>, Stefan D. Anker<sup>2</sup>, Tariq Jamal Siddiqi<sup>3</sup>, Andrew J. S. Coats<sup>4</sup>, Fabio Dorigotti<sup>5</sup>, Gerasimos Filippatos<sup>6</sup>, Tim Friede<sup>7</sup>, Udo-Michael Göhring<sup>5</sup>, Mikhail N. Kosiborod<sup>8</sup>, Lars H. Lund<sup>9</sup>, Marco Metra<sup>10</sup>, Carol Moreno Quinn<sup>5</sup>, Ileana L. Piña<sup>11</sup>, Fausto J. Pinto<sup>12</sup>, Patrick Rossignol<sup>13</sup>, Peter Szecsödy<sup>5</sup>, Peter Van der Meer<sup>14</sup>, Matthew Weir<sup>15</sup>, Bertram Pitt<sup>16</sup>

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## ABSTRACT

**Aims** In patients with current or a history of hyperkalaemia, treatment with renin–angiotensin–aldosterone system inhibitors (RAASi) is often compromised. Patiromer, a novel potassium ( $K^+$ ) binder, may improve serum  $K^+$  levels and adherence to RAASi.

**Methods** The DIAMOND trial will enrol ~820 patients with heart failure with reduced ejection fraction (HFrEF; ejection fraction  $\leq 40\%$ ). Patients meeting the screening criteria will enter a single-blinded run-in phase where they will be started or continued on a mineralocorticoid receptor antagonist (MRA) titrated to 50 mg/day and other RAASi therapy to  $\geq 50\%$  target dose, and patiromer. Patiromer will be titrated up to a maximum three packs/day (8.4 g/pack) to achieve optimal doses of RAASi without hyperkalaemia. The run-in phase will last up to 12 weeks, following which patients will undergo double-blind randomization in a 1:1 ratio to receive either continued patiromer or placebo (patiromer withdrawal). The primary endpoint is the mean difference in serum  $K^+$  from randomization between patiromer and placebo arms. Secondary endpoints will include hyperkalaemia events with  $K^+$  value  $> 5.5$  mEq/L, durable enablement of MRA at target dose, investigator-reported adverse events of hyperkalaemia, hyperkalaemia-related clinical endpoints and an overall RAASi Use Score (using a 0–8-point scale) comprising all-cause

death, occurrence of cardiovascular hospitalization or usage of comprehensive HF medication.

**Conclusion** The DIAMOND trial is designed to determine if patiromer can favourably impact  $K^+$  control in patients with HFrEF with hyperkalaemia or a history of hyperkalaemia leading to RAASi therapy compromise, and in turn improve RAASi use.

**Keywords** heart failure; potassium; hyperkalaemia; patiromer; renin–angiotensin–aldosterone system inhibitors; mineralocorticoid receptor antagonists; adherence; trial design.

## Introduction

Renin–angiotensin–aldosterone system inhibitors (RAASi) are recommended for patients with heart failure with reduced ejection fraction (HFrEF).<sup>1,2</sup> These agents have multiple beneficial effects, but they increase the risk of hyperkalaemia,<sup>3</sup> which is more pronounced in patients with HF, who tend to be older and have chronic kidney disease (CKD) and diabetes mellitus.<sup>4–6</sup> This often contributes to suboptimal prescription of RAASi therapy.<sup>3,7–9</sup> Previous studies have demonstrated that after an episode of hyperkalaemia, RAASi doses are lowered in a large proportion of patients.<sup>10–14</sup> Many patients discontinue therapy permanently and suffer adverse outcomes.<sup>12</sup> Epstein et al. observed that nearly 60% of patients with HF who discontinued RAASi experienced an adverse clinical event.<sup>10</sup> Trevisan et al. showed that stopping mineralocorticoid receptor antagonist (MRA) after a hyperkalaemia episode was associated with a lower risk of recurrent hyperkalaemia but a higher risk of death and cardiovascular (CV) events.<sup>15</sup> Consequently, a gap remains between guideline recommendations and real-world practice, where management of HF with optimal use and dose of RAASi is hindered by hyperkalaemia.

Patiromer is a sodium-free, novel potassium ( $K^+$ ) binder that is well tolerated and efficacious in maintaining normokalaemia. The DIAMOND (Patiromer for the Management of Hyperkalemia in Subjects Receiving RAASi Medications for the Treatment of Heart Failure; NCT03888066) trial was initially designed to evaluate whether patiromer-enabled RAASi therapy can improve clinical outcomes in patients with HFrEF with either hyperkalaemia or history of hyperkalaemia-related compromise of RAASi therapy. However, related to the impact of ongoing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic on clinical trials, the trial's primary endpoint was changed to serum  $K^+$  control prior to closeout and database lock or unblinding of treatment assignment.

## Study design

### Trial structure and oversight

The DIAMOND trial is a prospective phase 3b multinational, multicentre, double-blind, randomized withdrawal, parallel-group, placebo-controlled trial that is designed to evaluate whether patiromer treatment in patients who developed hyperkalaemia while receiving RAASi medications will result in improvements in  $K^+$  concentration and in turn lead to optimization of RAASi use consistent with guidelines. The trial is conducted in accordance with the principles of the Declaration of Helsinki and the International Council on Harmonization guidelines for Good Clinical Practice. An independent ethics committee approved the clinical protocol at every participating centre. All subjects provide written informed consent. The sponsor is Vifor Pharma, Inc.

The trial was designed by the Executive Committee, whose members included academic investigators and representatives of Vifor Pharma, Inc. The Executive Committee was responsible for developing the trial protocol, supervising the development of case report forms, and the statistical plan, overseeing the enrolment, and the quality of follow-up. National leaders from different countries ensured that investigators remain committed to their responsibilities and encourage recruitment. A blinded Endpoint Adjudication Committee assessed all potential clinical events to evaluate whether they adhere to prespecified criteria for a clinical or a safety endpoint. An independent Data Monitoring Committee was responsible for assuring safety and making recommendations regarding the continuity or cessation of the trial. The members of these Committees are listed in the *Appendix*.

### Study participants

Men and women aged  $\geq 18$  years who have chronic HFrEF, New York Heart Association functional class II–IV symptoms with a left ventricular ejection fraction of  $\leq 40\%$  as measured by any echocardiographic, radionuclide, magnetic resonance imaging, angiographic, or computerized tomography within 12 months from randomization are eligible for enrolment (*Table 1*). Subjects are required to have hyperkalaemia at screening (defined by two  $K^+$

values of  $>5.0$  mEq/L) while receiving an angiotensin-converting enzyme inhibitor (ACEi)/angiotensin II receptor blocker (ARB)/angiotensin receptor-neprilysin inhibitor (ARNi), and/or an MRA. Alternatively, subjects are also eligible if they are normokalaemic at screening but have a prior history of RAASi discontinuation due to hyperkalaemia. *Table 2* displays the brain natriuretic peptide and N-terminal pro B-type brain natriuretic peptide thresholds that had to be met for inclusion, according to history of atrial fibrillation and previous HF hospitalizations. Subjects with an estimated glomerular filtration rate (eGFR)  $<30$  mL/min/1.73 m<sup>2</sup> per the Chronic Kidney Disease Epidemiology Collaboration equation, acute decompensated HF within 4 weeks before screening, symptomatic hypotension or systolic blood pressure  $<90$  mmHg, or any significant comorbidity which may impact the patient's clinical course, independent of HF, were excluded from the trial. A complete list of exclusion criteria is provided in *Table 3*.

### **Study visits and follow-up**

Following screening, eligible subjects are enrolled into a single-blinded run-in phase with weekly visits. The purpose of the run-in phase is to control K<sup>+</sup> levels with patiomer while simultaneously optimizing the use and doses of RAASi medications, including MRA (titrated to 50 mg/day). Patiomer is titrated up to a maximum of three packs/day (8.4 g/pack). After the run-in phase that can last for up to 12 weeks, subjects undergo double-blind randomization in a 1:1 ratio, to receive either continued patiomer or placebo (patiomer withdrawal) (*Figure 1*). Randomization is performed by using permuted block design and is stratified by geographic region. Randomized subjects continue the same number of packets of patiomer as established at the end of the run-in phase and are instructed to continue the ACEi/ARB/ARNi and MRA regimen that was administered at the end of the run-in phase.

Prior to initiation of assigned patiomer/placebo, and as part of the randomization criteria, K<sup>+</sup> concentration is measured at baseline. Thereafter, samples for the measurement are collected at every visit, starting from Day 3, and then at Weeks 1, 2, 6, 18 and every 3 months thereafter until the end of study (EoS). The original EoS date would have been set



by the sponsor when sufficient number of subjects would have been enrolled to reach the expected number of events. However, the study endpoint was changed to control of  $K^+$  levels, and the total number of patients enrolled was adjusted. Patient-reported outcomes are evaluated using the Kansas City Cardiomyopathy Questionnaire and EuroQol five-dimension, five-level (EQ-5D-5L) questionnaire. Subjects are monitored for changes in renal function, especially during medication adjustments and when there is a change in clinical status. All randomized subjects are followed for the occurrence of prespecified outcome events during the course of the trial. Subjects who prematurely discontinue patiromer/placebo should remain in the study for the collection of events data up to and including the common EoS and receive usual care during the study phase.

### **Primary and secondary endpoints**

The original primary endpoint of the trial was to assess the efficacy of patiromer-enabled optimization of RAASi therapy on time to CV death or first CV hospitalization. However, due to the impact of the SARS-CoV-2 pandemic, and resulting coronavirus disease 2019 (COVID-19), slowing of the enrolment rate, and the shift in hospitalization patterns and the adaptations of the treatment practices for HF, there was a profoundly lower-than-expected enrolment rate as well as event rate.<sup>16</sup> Additionally, considering the risk to the patients as well as the logistics concern related to the impact on COVID-19 pandemic on the operations of the trial, the objective of the study was adjusted by the academic oversight team and the sponsor while the study remained blinded.

The primary endpoint was changed to mean change in  $K^+$  levels from baseline to all available post-baseline  $K^+$  values (with sufficient numbers of patients at follow-up visits) to be analysed by a mixed model for repeated measures approach. A Gaussian linear model for repeated measures will be used to evaluate the primary endpoint with treatment, geographic region, sex, baseline type 2 diabetes mellitus status and treatment by visit interaction serving as factors, and baseline  $K^+$  level and eGFR as covariates. All analyses will be restricted to serum  $K^+$  levels and not substituted by plasma values, as plasma values

are systematically lower.<sup>17</sup>  $K^+$  values, either central or local laboratory measured, will be assessed at all visits, and if both values are present at a given visit, then central values will be used. Least squares mean changes from baseline will be reported for both treatment groups with 95% confidence intervals (CI) 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.

Secondary efficacy endpoints will be analysed in a hierarchical manner and summarized descriptively through the calculation of point estimates by treatment group along with 95% CIs for the treatment differences. First, the time to the first event of hyperkalaemia ( $K^+ >5.5$  mEq/L) will be analysed. Second, the time to event of reduction of the MRA dose below target (50 mg of spironolactone or eplerenone) will be assessed using a Cox proportional hazards regression model. Discontinuation of target dose would be required for at least 14 days, or less if at the end of the study. Third, investigator-reported adverse events of hyperkalaemia (time-to-first and recurrent) will be analysed 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) hyperkalaemia events and time to death as terminating event will be performed. Hyperkalaemia-related specific outcomes will be analysed using the unmatched win-ratio approach, with the following hierarchical components, all assessed during comparable follow-up times: time to CV death; total number of CV hospitalizations; and the total number of hyperkalaemia events with  $K^+ >6.5$  mEq/L,  $>6.0$ – $6.5$  mEq/L and  $>5.0$ – $6.0$  mEq/L. In addition, 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 for that pair of patients. Hierarchical components of the RAASi use score are illustrated in *Figure 2*.<sup>18</sup> This score, ranging from 0 to 8 points, will be analysed at the respective time points for each patient in each comparison, and consists of all-cause death, total number of CV hospitalizations, and HF medication use. A list of other secondary endpoints, other endpoints and safety evaluations are provided in *Table 4*.

### Sample size and power calculation

The sample size of 410 subjects per treatment arm for a total of 820 subjects will provide 90% power to detect a difference between the placebo and the patiomer group on the mean change in  $K^+$  levels from baseline. This sample size calculation was based upon the following assumptions: 2-sided alpha level of 5%, a difference between group means of 0.116, a standard deviation of 0.5, and a 5% loss to follow-up.<sup>19</sup>

### Discussion

The DIAMOND trial will evaluate whether the use of patiomer, a novel  $K^+$  binder, allows better serum  $K^+$  control in patients with HFrEF who are hyperkalaemic or have a history of hyperkalaemia and are being optimized on RAASi therapy. Previous studies have consistently demonstrated an association between elevated  $K^+$  levels with lower use of RAASi, which has poor prognostic implications in HFrEF.<sup>4,5</sup> High  $K^+$  levels often leads to dose reduction or discontinuation of these proven therapies.<sup>4-6</sup> Patiomer is a non-absorbable polymer that binds to free  $K^+$  in the gastrointestinal tract, thereby reducing the amount of  $K^+$  being absorbed in the blood.<sup>20</sup> This ensures maintenance of normokalaemia without incurring adverse events due to the suboptimal dosing of guideline-recommended HF therapies.

The safety and efficacy of patiomer in patients with HF and/or CKD receiving RAASi therapy were initially established in several key clinical studies. In the 4-week PEARL-HF trial (Evaluation of Patiomer in Heart Failure Patients), patients treated with patiomer were significantly more likely to increase their dose of spironolactone from 25 to 50 mg/day compared with those receiving placebo without experiencing hyperkalemia.<sup>19</sup> Similarly, in the 12-week OPAL-HK study (A Two-Part, Single-Blind, Phase 3 Study Evaluating the Efficacy and Safety of Patiomer for the Treatment of Hyperkalemia in patients with chronic kidney disease and hyperkalemia), 6% and 56% of patients in the patiomer and placebo groups, respectively, had to discontinue RAASi therapy due to recurrence of hyperkalaemia.<sup>21</sup> However, the reliability of these findings is limited by small sample size, short follow-up

period and restricted analysis of HF subgroups that were not well phenotyped. Similar to patiromer, sodium zirconium cyclosilicate (SZC) is also a Food and Drug Administration-approved treatment for chronic hyperkalaemia.<sup>22,23</sup> The PRIORITIZE HF study (Potassium Reduction Initiative to Optimize RAAS Inhibition Therapy With Sodium Zirconium Cyclosilicate in Heart Failure) trial was also evaluating the efficacy and safety of using SZC to initiate and intensify RAASi therapy in HFrEF. However, the trial was prematurely terminated due to the COVID-19 pandemic, which resulted in a reduced sample size and inconclusive results.<sup>24</sup> The REALIZE-K (Study to Assess Efficacy and Safety of SZC for the Management of High Potassium in Patients With Symptomatic HFrEF Receiving Spironolactone) trial is currently ongoing to determine if SZC can allow safe optimization of RAASi in patients with HFrEF while maintaining normokalaemia.<sup>25</sup>

In circumstances where discontinuation of RAASi therapy is deemed necessary in HFrEF due to hyperkalaemia, guidelines suggest that the drug discontinuation period is kept to a minimum with the reintroduction of RAASi therapy when possible.<sup>1,2,26</sup> However, evidence suggests that a significant proportion of these patients are unable to benefit from these recommendations due to prescriber inertia or persistent risk or fear of hyperkalaemia.<sup>5,6</sup> Indeed, MRAs are often discontinued but rarely restarted after an episode of hyperkalaemia.<sup>12</sup> The DIAMOND study included high-risk subjects (e.g. those with CKD, diabetes mellitus, older age, elevated natriuretic peptides) who pose the greatest therapeutic dilemma to clinicians, because they have the highest risk of developing hyperkalaemia but stand to benefit most from RAASi therapies. The DIAMOND trial will also assess clinical endpoints, such as time to CV death and CV hospitalization, but will not be powered for them. It will also evaluate quality-of-life measures. In addition, the trial will assess a novel composite endpoint including a RAASi use score using the win ratio.<sup>18</sup>

The COVID-19 pandemic continues to evolve and has affected all aspects of clinical research, including enrolment, conduct of study procedures, and the natural history trajectory of the disease process, which has had an impact on outcomes. The DIAMOND trial is the first, and so far only, trial that was designed to assess clinical outcomes with the

use of an enablement strategy for RAASi therapy. Unfortunately, for the foreseeable future, this question will remain unanswered with the change in the plans for the DIAMOND trial described herein. These dynamics will continue to affect other trials and hinder development of novel therapies for various diseases, underscoring the need for adapting to alternate research strategies to achieve these goals.

The DIAMOND trial will be the largest trial ever performed to assess the impact of patiromer on  $K^+$  control in patients with HFrEF with hyperkalaemia or a history of hyperkalaemia on a background of guideline-directed RAASi medication. Given the contraindication of hyperkalaemia with the usage of RAASis, this trial will add significantly to our knowledge about controlling  $K^+$  levels and the possible benefits of enabling RAASis in patients with HFrEF with the use of patiromer.

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### **Conflict of Interest**

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**FIGURE LEGENDS**

**Figure 1** Design of the DIAMOND trial. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; EoS, end of study; 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; R, randomization; RAASi, renin–angiotensin–aldosterone system inhibitor;  $sK^+$ , serum potassium.

**Figure 2** Hierarchical components of the renin–angiotensin–aldosterone system inhibitors use score. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; BB, beta blockers; CV, cardiovascular; MRA, mineralocorticoid receptor antagonist.



**Table 1 Inclusion criteria for the DIAMOND trial**

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1. Subject provides written informed consent prior to study participation
  2. Age 18 years or greater
  3. Current New York Heart Association class II–IV
  4. Left ventricular ejection fraction  $\leq 40\%$ , measured by any echocardiographic, radionuclide, magnetic resonance imaging, 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. Estimated glomerular filtration rate  $\geq 30$  mL/min/1.73 m<sup>2</sup> at screening (based on a single local laboratory analysis of serum creatinine and calculation using the CKD-EPI equation)
  7. Hyperkalaemia at screening (defined by two local K<sup>+</sup> 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 ACEi/ARB/ARNi, and/or MRA  
OR  
Normokalaemia at screening (defined by two local K<sup>+</sup>  $\geq 4.0$ – $\leq 5.0$  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 hyperkalaemia documented by usual care K<sup>+</sup> 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 childbearing potential must be non-lactating, must have a negative pregnancy test at screening, and must agree to continue using contraception 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
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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<sup>a</sup> level must be greater than 150 pg/mL (18 pmol/L) or NT-proBNP must be greater than 600 pg/mL (71 pmol/L)
- b) With atrial fibrillation at screening, BNP<sup>a</sup> level must be greater than 300 pg/mL (35 pmol/L) or NT-proBNP must be greater than 1200 pg/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<sup>a</sup> level must be greater than 300 pg/mL (35 pmol/L) or NT-proBNP must be greater than 1200 pg/mL (142 pmol/L)
- b) With atrial fibrillation at screening, BNP<sup>a</sup> level must be greater than 600 pg/mL (71 pmol/L) or NT-proBNP must be greater than 2400 pg/mL (284 pmol/L)

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ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; BNP, brain natriuretic peptide; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; HF, heart failure; K<sup>+</sup>, serum potassium; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro B-type brain natriuretic peptide; RAASi, renin-angiotensin-aldosterone system inhibitor.

<sup>a</sup>For subjects treated with ARNi (sacubitril/valsartan) in the previous 4 weeks before screening, only NT-proBNP values are to be considered.

**Table 2 Brain natriuretic peptide and N-terminal pro B-type brain natriuretic peptide threshold levels (based on local laboratory), comorbidities, and previous hospitalizations**

	Subjects with hospitalization for HF or equivalent <sup>a</sup> within last 12 months	Subjects with no hospitalization for HF or equivalent <sup>a</sup> within last 12 months
Subjects presenting without atrial fibrillation when the blood sample was collected	BNP <sup>b</sup> >150 pg/mL (18 pmol/L) or NT-proBNP >600 pg/mL (71 pmol/L)	BNP <sup>b</sup> >300 pg/mL (35 pmol/L) or NT-proBNP >1200 pg/mL (142 pmol/L)
Subjects presenting with atrial fibrillation when the blood sample was collected	BNP <sup>b</sup> >300 pg/mL (35 pmol/L) or NT-proBNP >1200 pg/mL (142 pmol/L)	BNP <sup>b</sup> >600 pg/mL (71 pmol/L) or NT-proBNP >2400 pg/mL (284 pmol/L)

BNP, brain natriuretic peptide; HF, heart failure; NT-proBNP, N-terminal pro B-type brain natriuretic peptide.

<sup>a</sup>E.g. urgent emergency room or outpatient visit for worsening HF during which the subject received intravenous medications for the treatment of HF.

<sup>b</sup>For subjects treated with angiotensin receptor-neprilysin inhibitor (sacubitril/valsartan) in the previous 4 weeks before screening, only NT-proBNP values are to be considered.

**Table 3 Exclusion criteria for the DIAMOND trial**

- 
1. Current acute decompensated heart failure within 4 weeks before screening. Subjects with a discharge from a hospitalization for acute decompensation of heart failure 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 within 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 surgery (e.g. bariatric surgery or large bowel resection)
  10. A major cardiovascular event within 4 weeks prior to screening, including acute myocardial infarction, stroke (or transient ischaemic attack), a life-threatening atrial or ventricular arrhythmia, or resuscitated cardiac arrest
  11. Liver enzymes (alanine aminotransferase, aspartate aminotransferase) >5 times upper limit of normal at screening based on the local laboratory
  12. 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
  13. Presence of any condition (e.g. drug/alcohol abuse; acute illness) that, in the opinion of the investigator, places the subject at undue risk, or prevents complete participation in the trial procedures, or potentially jeopardizes the quality of the study data
-

- 
14. 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
  15. Known hypersensitivity to patiromer (RLY5016) or its components
  16. 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
  17. An employee, spouse, or family member of the Sponsor (Vifor Pharma), investigational site or the Contract Research Organization
  18. Planned or scheduled dialysis within 3 months from screening
-

**Table 4 List of secondary endpoints, other endpoints and safety evaluations****Key Secondary Endpoints (Hierarchically Ordered)**

1. Hyperkalaemia events with a serum K<sup>+</sup> 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 hyperkalaemia (first and recurrent events)
4. Hyperkalaemia-related hard outcomes endpoints (win ratio)
  - a. Time to CV death
  - b. Total number of CV hospitalizations
  - c. Total number of hyperkalaemia toxicity events with serum K<sup>+</sup> >6.5 mEq/L
  - d. Total number of hyperkalaemia events with serum K<sup>+</sup> >6.0–6.5 mEq/L
  - e. Total number of hyperkalaemia events with serum K<sup>+</sup> >5.0 mEq/L

5. RAASi use score (win ratio)

*Note: This score (of 0–8 points) will be analysed 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 (iii) a beta blocker

**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 EoS) is required to confirm this endpoint.*

- Durable hyperkalaemia-free enablement to stay on the MRA target dose (days on 50 mg MRA without hyperkalaemia)
- Total number of hyperkalaemia toxicity events with K<sup>+</sup> >6.5 mEq/L

- 
- Total number of hyperkalaemia toxicity events with  $K^+$  >6.0–6.5 mEq/L
  - Emergency treatment for hyperkalaemia (hospitalization or emergency room)
  - Total number of hyperkalaemia toxicity events with  $K^+$  >5.0–6.0 mEq/L
  - KCCQ, OSS, CSS and TSS during the treatment phase
  - Investigator-reported events of hyperkalaemia (recurrent events)
  - Proportion of subjects on  $\geq 50\%$  of target dose of ACEi, ARB, or ARNi and of MRA at the EoS visit
  - Time to first occurrence of CV death or CV hospitalization

**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 rehospitalization after a prior HF hospitalization
- Health economics and outcomes research analyses
- Mean difference in  $K^+$  change from baseline between active and placebo arms at other time points

**Safety evaluations:**

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

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; BNP, brain natriuretic peptide; CSS, clinical summary score; CV, cardiovascular; eGFR, glomerular filtration rate; EoS, end of study; HF, heart failure; K<sup>+</sup>, serum potassium; KCCQ, Kansas City Cardiomyopathy Questionnaire; MRA, mineralocorticoid receptor antagonists; NT-proBNP, N-terminal pro B-type brain natriuretic peptide; NYHA, New York Heart Association; OSS, overall summary score; RAASi, renin–angiotensin–aldosterone system inhibitor; TSS, total symptom score.



Figure 1

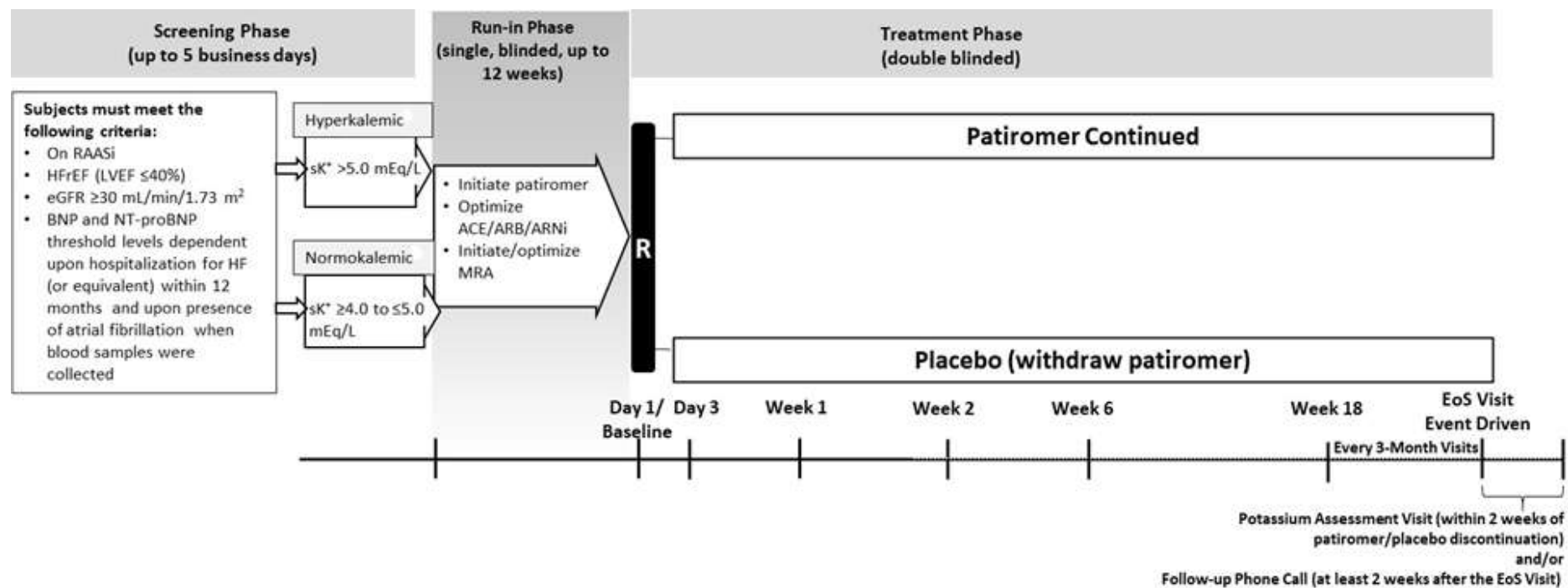
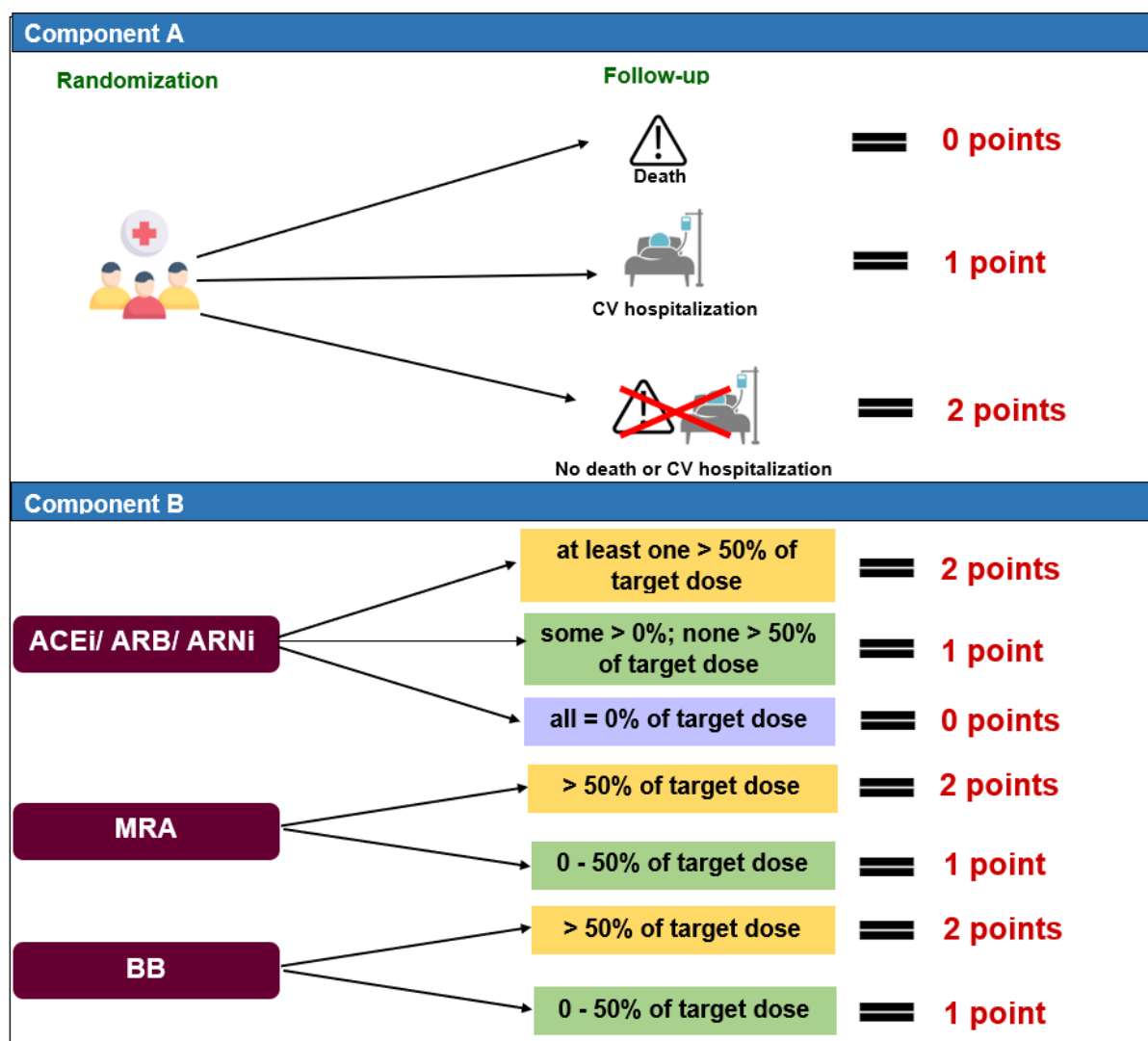


Figure 2



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