



## Clinical trial results:

### 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)

#### Summary

|                          |                               |
|--------------------------|-------------------------------|
| EudraCT number           | 2018-005030-38                |
| Trial protocol           | PL CZ NL ES HU DE BG GB BE IT |
| Global end of trial date | 02 September 2021             |

#### Results information

|                                |                   |
|--------------------------------|-------------------|
| Result version number          | v1 (current)      |
| This version publication date  | 10 September 2022 |
| First version publication date | 10 September 2022 |

#### Trial information

##### Trial identification

|                       |            |
|-----------------------|------------|
| Sponsor protocol code | PAT-CR-302 |
|-----------------------|------------|

##### Additional study identifiers

|                                    |                     |
|------------------------------------|---------------------|
| ISRCTN number                      | -                   |
| ClinicalTrials.gov id (NCT number) | NCT03888066         |
| WHO universal trial number (UTN)   | -                   |
| Other trial identifiers            | IND number : 075615 |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Vifor Pharma, Inc.   |
| Sponsor organisation address | 200 Cardinal Way, Redwood City, United States, CA 94063  |
| Public contact               | DIAMOND Clinical Study Team, Vifor Pharma, Inc., 001 8447359772, Diamond_Information@viforpharma.com |
| Scientific contact           | DIAMOND Clinical Study Team, Vifor Pharma, Inc., 001 8447359772, Diamond_Information@viforpharma.com |

Notes:

#### Paediatric regulatory details

|  |    |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

|  |                   |
|--|-------------------|
| Analysis stage                                       | Final             |
| Date of interim/final analysis                       | 02 September 2021 |
| Is this the analysis of the primary completion data? | Yes               |
| Primary completion date                              | 02 September 2021 |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 02 September 2021 |
| Was the trial ended prematurely?                     | No                |

Notes:

## General information about the trial

Main objective of the trial:

To assess the effects of patiromer on serum potassium (K+) in heart failure (HF) participants compared with placebo.

Protection of trial subjects:

The study was conducted in accordance with the principles of the Declaration of Helsinki including amendments in force up to and including the time the study was conducted.

The study was conducted in compliance with the International Council for Harmonisation (ICH) E6 Guideline for Good Clinical Practice (GCP), Committee for Proprietary Medicinal Products Guideline (CPMP/ICH/135/95), compliant with the EU Clinical Trial Directive (Directive 2001/20/EC) and/or the Code of Federal Regulations (CFR) for informed consent and protection of subject rights (21 CFR, Parts 50 and 56), and in accordance with United States Food and Drug Administration (FDA) regulations.

Prior to initiation of the study, the protocol, the subject information sheet, and the informed consent form (ICF) were reviewed and approved by Independent Ethics Committees (IECs) or Institutional Review Boards (IRBs), operating in accord with current regulations.

Background therapy:

Subjects receiving angiotensin-aldosterone system inhibitor (RAASi) medications for the treatment of heart failure with reduced ejection fraction (HFrEF).

During the Treatment Phase, subjects randomized to either patiromer or placebo continued the doses of RAASi medications optimized at the end of the Run-in Phase.

Evidence for comparator: -

|   |               |
|---|---------------|
| Actual start date of recruitment                          | 24 April 2019 |
| Long term follow-up planned                               | No            |
| Independent data monitoring committee (IDMC) involvement? | No            |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                |
|--------------------------------------|----------------|
| Country: Number of subjects enrolled | Netherlands: 4 |
| Country: Number of subjects enrolled | Poland: 80     |
| Country: Number of subjects enrolled | Spain: 25      |
| Country: Number of subjects enrolled | Belgium: 2     |
| Country: Number of subjects enrolled | Bulgaria: 91   |
| Country: Number of subjects enrolled | Czechia: 9     |
| Country: Number of subjects enrolled | France: 2      |
| Country: Number of subjects enrolled | Germany: 6     |
| Country: Number of subjects enrolled | Hungary: 19    |
| Country: Number of subjects enrolled | Italy: 7       |
| Country: Number of subjects enrolled | Argentina: 32  |

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Brazil: 16             |
| Country: Number of subjects enrolled | Canada: 1              |
| Country: Number of subjects enrolled | Georgia: 257           |
| Country: Number of subjects enrolled | Israel: 12             |
| Country: Number of subjects enrolled | Mexico: 10             |
| Country: Number of subjects enrolled | Russian Federation: 79 |
| Country: Number of subjects enrolled | Serbia: 8              |
| Country: Number of subjects enrolled | Ukraine: 156           |
| Country: Number of subjects enrolled | United States: 62      |
| Worldwide total number of subjects   | 878                    |
| EEA total number of subjects         | 245                    |

Notes:

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### Subjects enrolled per age group

|   |     |
|---|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 0   |
| Adolescents (12-17 years)                 | 0   |
| Adults (18-64 years)                      | 350 |
| From 65 to 84 years                       | 505 |
| 85 years and over                         | 23  |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

From a total of 1642 subjects screened, 1195 of these subjects entered Run-in Phase. A total of 1168 subjects received patiomer during Run-in Phase, and 878 of these subjects were randomized to receive patiomer or placebo during the Treatment Phase.

### Period 1

|                              |                                  |
|------------------------------|----------------------------------|
| Period 1 title               | Treatment Phase (overall period) |
| Is this the baseline period? | Yes                              |
| Allocation method            | Randomised - controlled          |
| Blinding used                | Double blind                     |
| Roles blinded                | Subject, Investigator            |

Blinding implementation details:

The Run-in Phase was single blinded for the subject. The Treatment Phase was double-blind.

### Arms

|                              |          |
|------------------------------|----------|
| Are arms mutually exclusive? | Yes      |
| <b>Arm title</b>             | Patiomer |

Arm description:

Randomized subjects who received continued treatment with patiomer during the Treatment Phase.

|  |                            |
|--|----------------------------|
| Arm type                               | Experimental               |
| Investigational medicinal product name | Patiomer                   |
| Investigational medicinal product code |                            |
| Other name                             | Veltassa®                  |
| Pharmaceutical forms                   | Powder for oral suspension |
| Routes of administration               | Oral use                   |

Dosage and administration details:

The same number of packets as established for patiomer at the end of the Run-in Phase but were to be up- or down-titrated depending on local serum K<sup>+</sup> levels.

During the Run-in Phase, patiomer was to be taken at a starting oral dose of 1 packet/day (8.4 g/day) either with or without food. Based upon the K<sup>+</sup> management algorithms, patiomer was to be increased by 1 packet per day in intervals of at least 1 week ( $\pm 3$  days). If hypokalemia developed during the Treatment Phase, then the study drug was to be down-titrated (lowest acceptable dose was 0 packets/day) until local serum K<sup>+</sup>  $\geq 4.0$  mEq/l. Doses of patiomer were 0 packets/day, 1 packet/day, 2 packets/day, and 3 packets/day (maximum dose).

|                  |         |
|------------------|---------|
| <b>Arm title</b> | Placebo |
|------------------|---------|

Arm description:

Randomized subjects who discontinued treatment with patiomer of the Run-in-Phase and received placebo during the Treatment Phase.

|  |                            |
|--|----------------------------|
| Arm type                               | Placebo                    |
| Investigational medicinal product name | Placebo                    |
| Investigational medicinal product code |                            |
| Other name                             | microcrystalline cellulose |
| Pharmaceutical forms                   | Powder for oral suspension |
| Routes of administration               | Oral use                   |

Dosage and administration details:

The same number of packets as established for patiomer at the end of the Run-in Phase but were to be

up- or down-titrated depending on local serum K<sup>+</sup> levels.

During the Run-in Phase, patiromer was to be taken at a starting oral dose of 1 packet/day (8.4 g/day) either with or without food. Based upon the K<sup>+</sup> management algorithms, placebo was to be increased by 1 packet per day in intervals of at least 1 week ( $\pm 3$  days). If hypokalemia developed during the Treatment Phase, then the study drug was to be down-titrated (lowest acceptable dose was 0 packets/day) until local serum K<sup>+</sup>  $\geq 4.0$  mEq/l. Doses of placebo were 0 packets/day, 1 packet/day, 2 packets/day, and 3 packets/day (maximum dose).

| <b>Number of subjects in period 1</b>     | Patiromer | Placebo |
|---|-----------|---------|
| Started                                   | 439       | 439     |
| Completed                                 | 360       | 367     |
| Not completed                             | 79        | 72      |
| Sponsor's decision                        | 1         | -       |
| Physician decision                        | 20        | 13      |
| Consent withdrawn by subject              | 21        | 25      |
| Treatment discontinuation                 | 2         | 2       |
| Adverse event, non-fatal                  | 27        | 21      |
| Early study termination                   | -         | 1       |
| End of study visit not completed/delayed  | 1         | 3       |
| Lost to follow-up                         | 1         | -       |
| Delayed visit and insufficient study drug | 6         | 6       |
| Protocol deviation                        | -         | 1       |

## Baseline characteristics

### Reporting groups

|  |           |
|--|-----------|
| Reporting group title  | Patiromer |
| Reporting group description:<br>Randomized subjects who received continued treatment with patiromer during the Treatment Phase.                                    |           |
| Reporting group title  | Placebo   |
| Reporting group description:<br>Randomized subjects who discontinued treatment with patiromer of the Run-in-Phase and received placebo during the Treatment Phase. |           |

| Reporting group values                | Patiromer | Placebo | Total |
|---------------------------------------|-----------|---------|-------|
| Number of subjects                    | 439       | 439     | 878   |
| Age categorical<br>Units: Subjects    |           |         |       |
| <65 years                             | 181       | 169     | 350   |
| ≥65 years                             | 258       | 270     | 528   |
| Age continuous<br>Units: years        |           |         |       |
| arithmetic mean                       | 66.6      | 67.1    |       |
| standard deviation                    | ± 10.0    | ± 9.9   | -     |
| Gender categorical<br>Units: Subjects |           |         |       |
| Female                                | 112       | 126     | 238   |
| Male                                  | 327       | 313     | 640   |

## End points

### End points reporting groups

|  |                                       |
|--|---------------------------------------|
| Reporting group title  | Patiromer                             |
| Reporting group description:<br>Randomized subjects who received continued treatment with patiromer during the Treatment Phase.  |                                       |
| Reporting group title  | Placebo                               |
| Reporting group description:<br>Randomized subjects who discontinued treatment with patiromer of the Run-in-Phase and received placebo during the Treatment Phase.   |                                       |
| Subject analysis set title   | All subjects                          |
| Subject analysis set type  | Full analysis                         |
| Subject analysis set description:<br>All subjects randomized to patiromer or placebo arm.  |                                       |
| Subject analysis set title   | All subjects - For reporting purposes |
| Subject analysis set type  | Full analysis                         |
| Subject analysis set description:<br>All subjects randomized to patiromer or placebo arm.<br>As advised in the EudraCT Q&A, in order to report a statistical analysis related to a specific endpoint it is required to define at least two comparison groups. For the secondary endpoints Hyperkalemia-related Hard Outcomes Endpoints & RAASi Use Score there were no comparison groups since the results were reported for all subjects (N=878). Due to this fact, a workaround needs to be performed for reporting their statistical analyses. It is advised to create an additional "Subject analysis set" and then select both comparison groups in each "Endpoint definition" section. |                                       |

### Primary: Changes in serum K+ levels from Baseline

|  |  |
|--|--|
| End point title  | Changes in serum K+ levels from Baseline |
| End point description:<br>Adjusted mean changes in serum K+ from Baseline. |  |
| End point type   | Primary                                  |
| End point timeframe:<br>From Day 1/Baseline to the End of Study visit      |  |

| End point values                    | Patiromer       | Placebo         |  |  |
|-------------------------------------|-----------------|-----------------|--|--|
| Subject group type                  | Reporting group | Reporting group |  |  |
| Number of subjects analysed         | 439             | 439             |  |  |
| Units: mEq/l                        |                 |                 |  |  |
| least squares mean (standard error) | 0.029 (± 0.019) | 0.127 (± 0.019) |  |  |

### Statistical analyses

|                            |  |
|----------------------------|--|
| Statistical analysis title | Difference in adjusted mean changes (SE) |
| Comparison groups          | Patiromer v Placebo                      |

|   |  |
|---|--|
| Number of subjects included in analysis | 878                                      |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| P-value                                 | < 0.001                                  |
| Method                                  | Mixed model for repeated measures (MMRM) |
| Parameter estimate                      | Mean difference (final values)           |
| Point estimate                          | -0.097                                   |
| Confidence interval                     |  |
| level                                   | 95 %                                     |
| sides                                   | 2-sided                                  |
| lower limit                             | -0.128                                   |
| upper limit                             | -0.067                                   |
| Variability estimate                    | Standard error of the mean               |
| Dispersion value                        | 0.015                                    |

### Secondary: Time to First Hyperkalemia Event with Serum K+ Level >5.5 mEq/l

|  |   |
|--|---|
| End point title  | Time to First Hyperkalemia Event with Serum K+ Level >5.5 mEq/l |
| End point description:   |   |
| Time to the first event of hyperkalemia with a serum K+ value >5.5 mEq/l calculated as CIF Estimate (95% CI) from the measured values. CIF = cumulative incidence function |   |
| Number of subjects with Hyperkalemia was n=61 (13.9%) for Patiromer and n=85 (19.4%) for Placebo   |   |
| End point type   | Secondary   |
| End point timeframe:   |   |
| From Day 1/Baseline to week 90   |   |

| End point values                 | Patiromer           | Placebo             |  |  |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type               | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed      | 439                 | 439                 |  |  |
| Units: CIF estimate              |                     |                     |  |  |
| number (confidence interval 95%) |                     |                     |  |  |
| Week 1                           | 0.02 (0.01 to 0.04) | 0.04 (0.03 to 0.06) |  |  |
| Week 2                           | 0.04 (0.02 to 0.06) | 0.08 (0.06 to 0.11) |  |  |
| Week 6                           | 0.05 (0.03 to 0.07) | 0.10 (0.08 to 0.13) |  |  |
| Week 18                          | 0.08 (0.06 to 0.12) | 0.14 (0.11 to 0.18) |  |  |
| Week 30                          | 0.13 (0.10 to 0.17) | 0.20 (0.15 to 0.24) |  |  |
| Week 42                          | 0.17 (0.12 to 0.22) | 0.24 (0.19 to 0.29) |  |  |
| Week 54                          | 0.21 (0.15 to 0.27) | 0.29 (0.23 to 0.35) |  |  |
| Week 66                          | 0.25 (0.18 to 0.32) | 0.34 (0.26 to 0.42) |  |  |
| Week 78                          | 0.30 (0.22 to 0.40) | 0.34 (0.26 to 0.42) |  |  |



|         |                     |                     |  |  |
|---------|---------------------|---------------------|--|--|
| Week 90 | 0.34 (0.23 to 0.44) | 0.34 (0.26 to 0.42) |  |  |
|---------|---------------------|---------------------|--|--|

## Statistical analyses

|                                   |                                   |
|-----------------------------------|-----------------------------------|
| <b>Statistical analysis title</b> | Hazard Ratio patiromer vs placebo |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

HR = Hazard Ratio

The HR for the time to first hyperkalemia event for patiromer vs placebo was calculated. HR and p-value come from a Cox proportional regression model adjusted for geographic region, sex, Baseline T2DM status, Baseline K+ value, and Baseline eGFR.

|   |                        |
|---|------------------------|
| Comparison groups                       | Patiromer v Placebo    |
| Number of subjects included in analysis | 878                    |
| Analysis specification                  | Pre-specified          |
| Analysis type                           | superiority            |
| P-value                                 | = 0.006 <sup>[1]</sup> |
| Method                                  | Regression, Cox        |
| Parameter estimate                      | Hazard ratio (HR)      |
| Point estimate                          | 0.63                   |
| Confidence interval                     |                        |
| level                                   | 95 %                   |
| sides                                   | 2-sided                |
| lower limit                             | 0.45                   |
| upper limit                             | 0.87                   |

Notes:

[1] - The treatment difference between patiromer vs placebo was statistically significant.

## Secondary: Durable Enablement to Stay on MRA Target Dose

|                 |   |
|-----------------|---|
| End point title | Durable Enablement to Stay on MRA Target Dose |
|-----------------|---|

End point description:

MRA=mineralocorticoid receptor antagonist; CIF=cumulative incidence function

Time to reduction of the MRA dose below target dose calculated as CIF Estimate (95% CI) from the measured values.

Note: The reduction below the MRA target dose must last for at least 14 days (or less if at the end of study) to confirm this endpoint.

Number of subjects with MRA reduction was n=61 (13.9%) for Patiromer and n=83 (18.9%) for Placebo.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From Day 1/Baseline to week 102)

| End point values                 | Patiromer           | Placebo             |  |  |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type               | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed      | 439                 | 439                 |  |  |
| Units: CIF estimate              |                     |                     |  |  |
| number (confidence interval 95%) |                     |                     |  |  |
| Week 1                           | 0.02 (0.01 to 0.04) | 0.04 (0.03 to 0.07) |  |  |
| Week 2                           | 0.03 (0.02 to 0.05) | 0.08 (0.06 to 0.11) |  |  |
| Week 6                           | 0.06 (0.04 to 0.08) | 0.12 (0.09 to 0.15) |  |  |
| Week 18                          | 0.10 (0.08 to 0.14) | 0.15 (0.12 to 0.19) |  |  |
| Week 30                          | 0.14 (0.10 to 0.18) | 0.19 (0.15 to 0.23) |  |  |
| Week 42                          | 0.16 (0.12 to 0.21) | 0.23 (0.18 to 0.28) |  |  |
| Week 54                          | 0.19 (0.14 to 0.24) | 0.26 (0.20 to 0.32) |  |  |
| Week 66                          | 0.22 (0.16 to 0.29) | 0.27 (0.21 to 0.33) |  |  |
| Week 78                          | 0.27 (0.20 to 0.35) | 0.29 (0.22 to 0.36) |  |  |
| Week 90                          | 0.27 (0.20 to 0.35) | 0.29 (0.22 to 0.36) |  |  |

## Statistical analyses

| Statistical analysis title | Hazard Ratio patiromer vs placebo |
|----------------------------|-----------------------------------|
|----------------------------|-----------------------------------|

Statistical analysis description:

HR = Hazard Ratio

The HR for the time to first hyperkalemia event for patiromer vs placebo was calculated. HR and p-value come from a Cox proportional regression model adjusted for geographic region, sex, Baseline T2DM status, Baseline K+ value, and Baseline eGFR

|   |                        |
|---|------------------------|
| Comparison groups                       | Patiromer v Placebo    |
| Number of subjects included in analysis | 878                    |
| Analysis specification                  | Pre-specified          |
| Analysis type                           | superiority            |
| P-value                                 | = 0.006 <sup>[2]</sup> |
| Method                                  | Regression, Cox        |
| Parameter estimate                      | Hazard ratio (HR)      |
| Point estimate                          | 0.62                   |
| Confidence interval                     |                        |
| level                                   | 95 %                   |
| sides                                   | 2-sided                |
| lower limit                             | 0.45                   |
| upper limit                             | 0.87                   |

Notes:

[2] - The treatment difference between patiromer vs placebo was statistically significant.

## Secondary: Investigator-reported Events of Hyperkalemia

|                 |  |
|-----------------|--|
| End point title | Investigator-reported Events of Hyperkalemia |
|-----------------|--|

End point description:

Subject's follow-up is from the date of the first dose of randomized study medication up to the subject's end of study date or 24 Jun 2021, whichever comes first.

Annualized event rate per 100 subject-years= The total number of events for all subjects in the treatment group divided by the total subject-years of follow-up in that treatment group multiplied by 100.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From Day 1/Baseline to the End of Study visit

| End point values                            | Patiromer       | Placebo         |  |  |
|---|-----------------|-----------------|--|--|
| Subject group type                          | Reporting group | Reporting group |  |  |
| Number of subjects analysed                 | 439             | 439             |  |  |
| Units: Number (n)                           |                 |                 |  |  |
| number (not applicable)                     |                 |                 |  |  |
| Number of Hyperkalemia AEs,                 | 225             | 316             |  |  |
| Number of subjects with at least 1 event    | 137             | 198             |  |  |
| Number of subjects with more than 1 event   | 54              | 74              |  |  |
| Number of events per subject n=0            | 302             | 241             |  |  |
| Number of events per subject n=1            | 83              | 124             |  |  |
| Number of events per subject n=2            | 36              | 43              |  |  |
| Number of events per subject n ≥ 3          | 18              | 31              |  |  |
| Total subject-years of follow-up            | 273.1           | 275.6           |  |  |
| Annualized event rate per 100 subject-years | 82.38           | 114.65          |  |  |

## Statistical analyses

|                            |  |
|----------------------------|--|
| Statistical analysis title | NBMAC Annualized event RR patiromer vs placebo |
|----------------------------|--|

Statistical analysis description:

NBMAC=Negative binomial model adjusted for covariates; RR=Rate Ratio

NBMAC adjusted for geographical region, sex, Baseline T2DM status, Baseline K+ value, and Baseline eGFR. Rate ratio less than 1 favors patiromer.

|   |  |
|---|--|
| Comparison groups                       | Patiromer v Placebo                      |
| Number of subjects included in analysis | 878                                      |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| P-value                                 | < 0.001                                  |
| Method                                  | Negative binomial model adjusted for cov |
| Parameter estimate                      | Annualized event rate ratio              |
| Point estimate                          | 0.658                                    |
| Confidence interval                     |  |
| level                                   | 95 %                                     |
| sides                                   | 2-sided                                  |
| lower limit                             | 0.534                                    |
| upper limit                             | 0.81                                     |

## Secondary: Hyperkalemia-related Hard Outcomes Endpoints

|                 |  |
|-----------------|--|
| End point title | Hyperkalemia-related Hard Outcomes Endpoints |
|-----------------|--|

End point description:

Analyzed using Win Ratio approach with the following hierarchical components:

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 mEq/l

MHTE=More hyperkalemia toxicity events

MHE= More hyperkalemia events

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From Day 1/Baseline to the End of Study visit

| End point values                    | All subjects         | All subjects -<br>For reporting<br>purposes |  |  |
|-------------------------------------|----------------------|---|--|--|
| Subject group type                  | Subject analysis set | Subject analysis set                        |  |  |
| Number of subjects analysed         | 878                  | 878   |  |  |
| Units: Number                       |                      |   |  |  |
| CV death-placebo                    | 3491                 | 3491  |  |  |
| CV death-patiromer                  | 4609                 | 4609  |  |  |
| More CV hospitalizations-placebo    | 4539                 | 4539  |  |  |
| More CV hospitalizations-patiromer  | 4178                 | 4178  |  |  |
| MHTE with serum K+>6.5-placebo      | 419                  | 419   |  |  |
| MHTE with serum K+>6.5-patiromer    | 401                  | 401   |  |  |
| MHE with serum K+>6.0-6.5-placebo   | 4283                 | 4283  |  |  |
| MHE with serum K+>6.0-6.5-patiromer | 1446                 | 1446  |  |  |
| MHE with serum K+>5.0-6.0-placebo   | 55633                | 55633                                       |  |  |
| MHE with serum K+>5.0-6.0-patiromer | 34156                | 34156                                       |  |  |
| None of the above                   | 79566                | 79566                                       |  |  |
| Total number of pairs               | 192721               | 19272                                       |  |  |

## Statistical analyses

|                            |                         |
|----------------------------|-------------------------|
| Statistical analysis title | Win ratio for composite |
|----------------------------|-------------------------|

Statistical analysis description:

Subjects analyzed n=1756 refers to the sum of the two comparison groups below. Win ratio approach: Patients in the new treatment and control groups are formed into matched pairs based on their risk profiles. For each matched pair, the new treatment patient is labelled winner/loser depending on CV/hyperkalemia event first. The win ratio is the total number of winners divided by the total numbers of losers. Unmatched win ratio is presented for this endpoint. Win ratio above 1 favors patiromer.

|                   |  |
|-------------------|--|
| Comparison groups | All subjects v All subjects - For reporting purposes |
|-------------------|--|

|   |               |
|---|---------------|
| Number of subjects included in analysis | 1756          |
| Analysis specification                  | Pre-specified |
| Analysis type                           | superiority   |
| P-value                                 | < 0.001       |
| Method                                  | Win Ratio     |
| Parameter estimate                      | Win Ratio     |
| Point estimate                          | 1.526         |
| Confidence interval                     |               |
| level                                   | 95 %          |
| sides                                   | 2-sided       |
| lower limit                             | 1.231         |
| upper limit                             | 1.906         |

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Win ratio CV death and hospitalization |
|-----------------------------------|--|

Statistical analysis description:

Subjects analyzed n=1756 refers to the sum of the two comparison groups below. Win ratio approach: Patients in the new treatment and control groups are formed into matched pairs based on their risk profiles. For each matched pair, the new treatment patient is labelled winner/loser depending on CV/hyperkalemia event first. The win ratio is the total number of winners divided by the total numbers of losers. Unmatched win ratio is presented for this endpoint. Win ratio above 1 favors patiromer.

|   |  |
|---|--|
| Comparison groups                       | All subjects - For reporting purposes v All subjects |
| Number of subjects included in analysis | 1756   |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | superiority  |
| P-value                                 | = 0.744  |
| Method                                  | Win Ratio  |
| Parameter estimate                      | Win Ratio  |
| Point estimate                          | 0.914  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 0.526  |
| upper limit                             | 1.578  |

## Secondary: RAASi Use Score

|                 |                 |
|-----------------|-----------------|
| End point title | RAASi Use Score |
|-----------------|-----------------|

End point description:

RAASi use score (0 to 8 points) analyzed using the Win Ratio approach for each pair of subjects with the following additive components:

1. All-cause death
2. Occurrence of a CV hospitalization
3. HF medication use and dose for i) an ACEi/ARB/ARNi, ii) a MRA, and iii) a beta-blocker

Each subject in each comparison can have 0-8 points and all subjects are compared using this score at the respective appropriate follow-up time point.

RAASi = renin-angiotensin-aldosterone system inhibitor; ACE=angiotensin converting enzyme; ARB=angiotensin receptor blocker; ARNi=angiotensin receptor/neprilysin inhibitor; MRA=mineralocorticoid receptor antagonist.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From Day 1/Baseline to the End of Study visit

| End point values            | All subjects         | All subjects -<br>For reporting<br>purposes |  |  |
|-----------------------------|----------------------|---|--|--|
| Subject group type          | Subject analysis set | Subject analysis set                        |  |  |
| Number of subjects analysed | 878                  | 878   |  |  |
| Units: Number               |                      |   |  |  |
| Number of wins-patiromer    | 62073                | 62073                                       |  |  |
| Number of wins-placebo      | 49733                | 49733                                       |  |  |
| Number of ties              | 80915                | 80915                                       |  |  |
| Total number of pairs       | 192721               | 192721                                      |  |  |

## Statistical analyses

| Statistical analysis title | Win ratio for composite |
|----------------------------|-------------------------|
|----------------------------|-------------------------|

Statistical analysis description:

Subjects analyzed n=1756 refers to the sum of the two comparison groups below. Win ratio approach: Patients in the new treatment and control groups are formed into matched pairs based on their risk profiles. For each matched pair, the new treatment patient is labelled winner/loser depending on CV/hyperkalemia event first. The win ratio is the total number of winners divided by the total numbers of losers. Unmatched win ratio is presented for this endpoint. Win ratio above 1 favors patiromer.

|   |  |
|---|--|
| Comparison groups                       | All subjects v All subjects - For reporting purposes |
| Number of subjects included in analysis | 1756   |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | superiority  |
| P-value                                 | = 0.048  |
| Method                                  | Win Ratio  |
| Parameter estimate                      | Win Ratio  |
| Point estimate                          | 1.248  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 1.003  |
| upper limit                             | 1.564  |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Treatment Phase

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 23.0 |
|--------------------|------|

### Reporting groups

|                       |                     |
|-----------------------|---------------------|
| Reporting group title | Patiromer Continued |
|-----------------------|---------------------|

Reporting group description:

Randomized subjects who received continued treatment with patiromer during the Treatment Phase.

|                       |                              |
|-----------------------|------------------------------|
| Reporting group title | Placebo (withdraw patiromer) |
|-----------------------|------------------------------|

Reporting group description:

Randomized subjects who discontinued treatment with patiromer of the Run-in-Phase and received placebo during the Treatment Phase.

| Serious adverse events  | Patiromer Continued | Placebo (withdraw patiromer) |  |
|---|---------------------|------------------------------|--|
| Total subjects affected by serious adverse events                   |                     |                              |  |
| subjects affected / exposed   | 54 / 439 (12.30%)   | 58 / 439 (13.21%)            |  |
| number of deaths (all causes)                                       | 24                  | 18                           |  |
| number of deaths resulting from adverse events                      | 24                  | 18                           |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                     |                              |  |
| Pancoast's tumour   |                     |                              |  |
| subjects affected / exposed   | 0 / 439 (0.00%)     | 1 / 439 (0.23%)              |  |
| occurrences causally related to treatment / all                     | 0 / 0               | 0 / 1                        |  |
| deaths causally related to treatment / all                          | 0 / 0               | 0 / 0                        |  |
| Plasmacytoma  |                     |                              |  |
| subjects affected / exposed   | 0 / 439 (0.00%)     | 1 / 439 (0.23%)              |  |
| occurrences causally related to treatment / all                     | 0 / 0               | 0 / 1                        |  |
| deaths causally related to treatment / all                          | 0 / 0               | 0 / 0                        |  |
| Thyroid neoplasm  |                     |                              |  |
| subjects affected / exposed   | 0 / 439 (0.00%)     | 1 / 439 (0.23%)              |  |
| occurrences causally related to treatment / all                     | 0 / 0               | 0 / 1                        |  |
| deaths causally related to treatment / all                          | 0 / 0               | 0 / 0                        |  |
| Vascular disorders  |                     |                              |  |
| Peripheral ischaemia  |                     |                              |  |

|  |                  |                  |  |
|--|------------------|------------------|--|
| subjects affected / exposed                          | 1 / 439 (0.23%)  | 1 / 439 (0.23%)  |  |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Hypotension  |                  |                  |  |
| subjects affected / exposed                          | 1 / 439 (0.23%)  | 0 / 439 (0.00%)  |  |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Orthostatic hypotension                              |                  |                  |  |
| subjects affected / exposed                          | 0 / 439 (0.00%)  | 2 / 439 (0.46%)  |  |
| occurrences causally related to treatment / all      | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| General disorders and administration site conditions |                  |                  |  |
| Sudden death   |                  |                  |  |
| subjects affected / exposed                          | 10 / 439 (2.28%) | 10 / 439 (2.28%) |  |
| occurrences causally related to treatment / all      | 0 / 10           | 0 / 10           |  |
| deaths causally related to treatment / all           | 0 / 10           | 0 / 10           |  |
| Death  |                  |                  |  |
| subjects affected / exposed                          | 1 / 439 (0.23%)  | 0 / 439 (0.00%)  |  |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all           | 0 / 1            | 0 / 0            |  |
| Respiratory, thoracic and mediastinal disorders      |                  |                  |  |
| Acute pulmonary oedema                               |                  |                  |  |
| subjects affected / exposed                          | 1 / 439 (0.23%)  | 1 / 439 (0.23%)  |  |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 1            |  |
| Acute respiratory failure                            |                  |                  |  |
| subjects affected / exposed                          | 1 / 439 (0.23%)  | 1 / 439 (0.23%)  |  |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all           | 0 / 1            | 0 / 0            |  |
| Chronic obstructive pulmonary disease                |                  |                  |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 439 (0.23%) | 0 / 439 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory failure                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 439 (0.23%) | 0 / 439 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory arrest                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 439 (0.00%) | 1 / 439 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vocal cord dysfunction                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 439 (0.00%) | 1 / 439 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Investigations                                  |                 |                 |  |
| Ultrasound pancreas abnormal                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 439 (0.00%) | 1 / 439 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Injury, poisoning and procedural complications  |                 |                 |  |
| Road traffic accident                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 439 (0.23%) | 0 / 439 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Traumatic intracranial haemorrhage              |                 |                 |  |
| subjects affected / exposed                     | 0 / 439 (0.00%) | 1 / 439 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vascular procedure complication                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 439 (0.00%) | 1 / 439 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|   |                 |                  |  |
|---|-----------------|------------------|--|
| Cardiac disorders                               |                 |                  |  |
| Cardiac failure                                 |                 |                  |  |
| subjects affected / exposed                     | 9 / 439 (2.05%) | 15 / 439 (3.42%) |  |
| occurrences causally related to treatment / all | 0 / 10          | 0 / 18           |  |
| deaths causally related to treatment / all      | 0 / 2           | 0 / 2            |  |
| Angina unstable                                 |                 |                  |  |
| subjects affected / exposed                     | 3 / 439 (0.68%) | 3 / 439 (0.68%)  |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Acute left ventricular failure                  |                 |                  |  |
| subjects affected / exposed                     | 2 / 439 (0.46%) | 0 / 439 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Atrial fibrillation                             |                 |                  |  |
| subjects affected / exposed                     | 1 / 439 (0.23%) | 2 / 439 (0.46%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Acute coronary syndrome                         |                 |                  |  |
| subjects affected / exposed                     | 1 / 439 (0.23%) | 1 / 439 (0.23%)  |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Acute myocardial infarction                     |                 |                  |  |
| subjects affected / exposed                     | 1 / 439 (0.23%) | 1 / 439 (0.23%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Cardiac failure congestive                      |                 |                  |  |
| subjects affected / exposed                     | 1 / 439 (0.23%) | 1 / 439 (0.23%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Ventricular tachycardia                         |                 |                  |  |
| subjects affected / exposed                     | 1 / 439 (0.23%) | 1 / 439 (0.23%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Angina pectoris                                 |                 |                  |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 439 (0.23%) | 0 / 439 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Left ventricular failure                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 439 (0.23%) | 0 / 439 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Myocardial infarction                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 439 (0.23%) | 0 / 439 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Myocardial ischaemia                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 439 (0.23%) | 0 / 439 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Ventricular extrasystoles                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 439 (0.23%) | 0 / 439 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac arrest                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 439 (0.00%) | 1 / 439 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Cardiomyopathy                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 439 (0.00%) | 1 / 439 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Coronary artery disease                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 439 (0.00%) | 1 / 439 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulseless electrical activity                   |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 439 (0.00%) | 1 / 439 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac failure acute                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 439 (0.23%) | 4 / 439 (0.91%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 6           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac failure chronic                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 439 (0.23%) | 1 / 439 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nervous system disorders                        |                 |                 |  |
| Ischaemic stroke                                |                 |                 |  |
| subjects affected / exposed                     | 2 / 439 (0.46%) | 1 / 439 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 2           | 0 / 0           |  |
| Cerebral haemorrhage                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 439 (0.23%) | 0 / 439 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Cerebral infarction                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 439 (0.23%) | 0 / 439 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Transient ischaemic attack                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 439 (0.23%) | 0 / 439 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Brain injury                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 439 (0.00%) | 1 / 439 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Cerebrovascular accident                        |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 439 (0.00%) | 1 / 439 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Status epilepticus                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 439 (0.00%) | 1 / 439 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vascular encephalopathy                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 439 (0.00%) | 1 / 439 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Blood and lymphatic system disorders            |                 |                 |  |
| Anaemia   |                 |                 |  |
| subjects affected / exposed                     | 0 / 439 (0.00%) | 3 / 439 (0.68%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ear and labyrinth disorders                     |                 |                 |  |
| Vertigo   |                 |                 |  |
| subjects affected / exposed                     | 0 / 439 (0.00%) | 1 / 439 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal disorders                      |                 |                 |  |
| Intestinal pseudo-obstruction                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 439 (0.23%) | 0 / 439 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vomiting  |                 |                 |  |
| subjects affected / exposed                     | 1 / 439 (0.23%) | 0 / 439 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Inflammatory bowel disease                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 439 (0.00%) | 1 / 439 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Rectal haemorrhage                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 439 (0.00%) | 1 / 439 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Umbilical hernia                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 439 (0.00%) | 1 / 439 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatobiliary disorders                         |                 |                 |  |
| Cholecystitis acute                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 439 (0.00%) | 1 / 439 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Skin and subcutaneous tissue disorders          |                 |                 |  |
| Diabetic foot                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 439 (0.23%) | 1 / 439 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal and urinary disorders                     |                 |                 |  |
| Renal failure                                   |                 |                 |  |
| subjects affected / exposed                     | 2 / 439 (0.46%) | 0 / 439 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Acute kidney injury                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 439 (0.23%) | 1 / 439 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Calculus urinary                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 439 (0.23%) | 0 / 439 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| End stage renal disease                         |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 439 (0.00%) | 1 / 439 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |                 |                 |  |
| Muscle atrophy                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 439 (0.23%) | 0 / 439 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infections and infestations                     |                 |                 |  |
| Pneumonia                                       |                 |                 |  |
| subjects affected / exposed                     | 5 / 439 (1.14%) | 6 / 439 (1.37%) |  |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 6           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           |  |
| COVID-19  |                 |                 |  |
| subjects affected / exposed                     | 2 / 439 (0.46%) | 3 / 439 (0.68%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 2           |  |
| COVID-19 pneumonia                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 439 (0.23%) | 0 / 439 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Cellulitis                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 439 (0.23%) | 0 / 439 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gangrene  |                 |                 |  |
| subjects affected / exposed                     | 0 / 439 (0.00%) | 2 / 439 (0.46%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Endocarditis                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 439 (0.00%) | 1 / 439 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Metabolism and nutrition disorders              |                 |                 |  |
| Dehydration                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 439 (0.23%) | 1 / 439 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Decreased appetite                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 439 (0.23%) | 0 / 439 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypoglycaemia                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 439 (0.23%) | 0 / 439 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypokalaemia                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 439 (0.23%) | 0 / 439 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyperglycaemia                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 439 (0.00%) | 1 / 439 (0.23%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

Frequency threshold for reporting non-serious adverse events: 1 %

| <b>Non-serious adverse events</b>                     | Patiromer Continued | Placebo (withdraw patiromer) |  |
|---|---------------------|------------------------------|--|
| Total subjects affected by non-serious adverse events |                     |                              |  |
| subjects affected / exposed                           | 320 / 439 (72.89%)  | 325 / 439 (74.03%)           |  |
| Vascular disorders                                    |                     |                              |  |
| Hypotension   |                     |                              |  |
| subjects affected / exposed                           | 15 / 439 (3.42%)    | 13 / 439 (2.96%)             |  |
| occurrences (all)                                     | 17                  | 14                           |  |
| Hypertension  |                     |                              |  |
| subjects affected / exposed                           | 8 / 439 (1.82%)     | 2 / 439 (0.46%)              |  |
| occurrences (all)                                     | 8                   | 2                            |  |
| General disorders and administration                  |                     |                              |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| site conditions                                 |                  |                  |  |
| Asthenia  |                  |                  |  |
| subjects affected / exposed                     | 5 / 439 (1.14%)  | 8 / 439 (1.82%)  |  |
| occurrences (all)                               | 5                | 9                |  |
| Oedema peripheral                               |                  |                  |  |
| subjects affected / exposed                     | 2 / 439 (0.46%)  | 5 / 439 (1.14%)  |  |
| occurrences (all)                               | 2                | 5                |  |
| Reproductive system and breast disorders        |                  |                  |  |
| Gynaecomastia                                   |                  |                  |  |
| subjects affected / exposed                     | 6 / 439 (1.37%)  | 0 / 439 (0.00%)  |  |
| occurrences (all)                               | 6                | 0                |  |
| Respiratory, thoracic and mediastinal disorders |                  |                  |  |
| Hydrothorax                                     |                  |                  |  |
| subjects affected / exposed                     | 6 / 439 (1.37%)  | 2 / 439 (0.46%)  |  |
| occurrences (all)                               | 7                | 2                |  |
| Acute respiratory failure                       |                  |                  |  |
| subjects affected / exposed                     | 5 / 439 (1.14%)  | 0 / 439 (0.00%)  |  |
| occurrences (all)                               | 6                | 0                |  |
| Dyspnoea  |                  |                  |  |
| subjects affected / exposed                     | 4 / 439 (0.91%)  | 5 / 439 (1.14%)  |  |
| occurrences (all)                               | 4                | 7                |  |
| Investigations                                  |                  |                  |  |
| Glomerular filtration rate decreased            |                  |                  |  |
| subjects affected / exposed                     | 15 / 439 (3.42%) | 10 / 439 (2.28%) |  |
| occurrences (all)                               | 19               | 14               |  |
| Blood creatinine increased                      |                  |                  |  |
| subjects affected / exposed                     | 2 / 439 (0.46%)  | 5 / 439 (1.14%)  |  |
| occurrences (all)                               | 2                | 5                |  |
| Cardiac disorders                               |                  |                  |  |
| Cardiac failure                                 |                  |                  |  |
| subjects affected / exposed                     | 10 / 439 (2.28%) | 10 / 439 (2.28%) |  |
| occurrences (all)                               | 11               | 11               |  |
| Atrial fibrillation                             |                  |                  |  |
| subjects affected / exposed                     | 5 / 439 (1.14%)  | 3 / 439 (0.68%)  |  |
| occurrences (all)                               | 6                | 3                |  |
| Nervous system disorders                        |                  |                  |  |

|  |                        |                        |  |
|--|------------------------|------------------------|--|
| Headache<br>subjects affected / exposed<br>occurrences (all)   | 9 / 439 (2.05%)<br>9   | 11 / 439 (2.51%)<br>14 |  |
| Blood and lymphatic system disorders<br>Anaemia<br>subjects affected / exposed<br>occurrences (all)              | 11 / 439 (2.51%)<br>11 | 5 / 439 (1.14%)<br>6   |  |
| Iron deficiency anaemia<br>subjects affected / exposed<br>occurrences (all)                                      | 9 / 439 (2.05%)<br>9   | 7 / 439 (1.59%)<br>7   |  |
| Gastrointestinal disorders<br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all)                      | 19 / 439 (4.33%)<br>20 | 15 / 439 (3.42%)<br>15 |  |
| Constipation<br>subjects affected / exposed<br>occurrences (all)   | 11 / 439 (2.51%)<br>13 | 5 / 439 (1.14%)<br>5   |  |
| Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all)   | 2 / 439 (0.46%)<br>2   | 5 / 439 (1.14%)<br>5   |  |
| Renal and urinary disorders<br>Chronic kidney disease<br>subjects affected / exposed<br>occurrences (all)        | 5 / 439 (1.14%)<br>7   | 8 / 439 (1.82%)<br>8   |  |
| Renal impairment<br>subjects affected / exposed<br>occurrences (all)   | 5 / 439 (1.14%)<br>5   | 7 / 439 (1.59%)<br>7   |  |
| Musculoskeletal and connective tissue disorders<br>Back pain<br>subjects affected / exposed<br>occurrences (all) | 10 / 439 (2.28%)<br>11 | 6 / 439 (1.37%)<br>6   |  |
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)   | 6 / 439 (1.37%)<br>6   | 3 / 439 (0.68%)<br>3   |  |
| Infections and infestations  |                        |                        |  |

|                                    |                    |                    |  |
|------------------------------------|--------------------|--------------------|--|
| Pneumonia                          |                    |                    |  |
| subjects affected / exposed        | 7 / 439 (1.59%)    | 1 / 439 (0.23%)    |  |
| occurrences (all)                  | 8                  | 1                  |  |
| COVID-19                           |                    |                    |  |
| subjects affected / exposed        | 6 / 439 (1.37%)    | 6 / 439 (1.37%)    |  |
| occurrences (all)                  | 6                  | 8                  |  |
| Respiratory tract infection viral  |                    |                    |  |
| subjects affected / exposed        | 0 / 439 (0.00%)    | 6 / 439 (1.37%)    |  |
| occurrences (all)                  | 0                  | 6                  |  |
| Metabolism and nutrition disorders |                    |                    |  |
| Hyperkalaemia                      |                    |                    |  |
| subjects affected / exposed        | 197 / 439 (44.87%) | 238 / 439 (54.21%) |  |
| occurrences (all)                  | 335                | 412                |  |
| Hypokalaemia                       |                    |                    |  |
| subjects affected / exposed        | 66 / 439 (15.03%)  | 47 / 439 (10.71%)  |  |
| occurrences (all)                  | 75                 | 53                 |  |
| Hypomagnesaemia                    |                    |                    |  |
| subjects affected / exposed        | 19 / 439 (4.33%)   | 22 / 439 (5.01%)   |  |
| occurrences (all)                  | 20                 | 25                 |  |
| Hyperglycaemia                     |                    |                    |  |
| subjects affected / exposed        | 10 / 439 (2.28%)   | 3 / 439 (0.68%)    |  |
| occurrences (all)                  | 11                 | 3                  |  |
| Diabetes mellitus                  |                    |                    |  |
| subjects affected / exposed        | 7 / 439 (1.59%)    | 5 / 439 (1.14%)    |  |
| occurrences (all)                  | 7                  | 5                  |  |
| Iron deficiency                    |                    |                    |  |
| subjects affected / exposed        | 6 / 439 (1.37%)    | 2 / 439 (0.46%)    |  |
| occurrences (all)                  | 6                  | 2                  |  |
| Hyponatraemia                      |                    |                    |  |
| subjects affected / exposed        | 0 / 439 (0.00%)    | 5 / 439 (1.14%)    |  |
| occurrences (all)                  | 0                  | 5                  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 26 February 2019 | Version 1.0 to Version 1.1 - Global amendment    |
| 19 October 2020  | Version 2.0 - Global amendment                   |
| 23 June 2021     | Version 4.0 - Final version submitted worldwide. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported