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:

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 patiromer during Run-in Phase, and 878 of these subjects were randomized to receive patiromer 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
Arm title	Patiromer

Arm description:

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

Arm type	Experimental
Investigational medicinal product name	Patiromer
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 patiromer at the end of the Run-in Phase but were to be up- or down-titrated depending on local serum K+ 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+ management algorithms, patiromer was to be increased by 1 packet per day in intervals of at least 1 week (±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+ ≥4.0 mEq/l. Doses of patiromer were 0 packets/day, 1 packet/day, 2 packets/day, and 3 packets/day (maximum dose).

Arm title	Placebo

Arm description:

Randomized subjects who discontinued treatment with patiromer 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 patiromer at the end of the Run-in Phase but were to be

up- or down-titrated depending on local serum K+ 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+ management algorithms, placebo was to be increased by 1 packet per day in intervals of at least 1 week (±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+ ≥4.0 mEq/l. Doses of placebo were 0 packets/day, 1 packet/day, 2 packets/day, and 3 packets/day (maximum dose).

Number of subjects in period 1	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:	
Randomized subjects who received continued treatment with patiromer during the Treatment Phase.	
Reporting group title	Placebo
Reporting group description:	
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			
Units: Subjects			
<65 years	181	169	350
≥65 years	258	270	528
Age continuous			
Units: years			
arithmetic mean	66.6	67.1	
standard deviation	± 10.0	± 9.9	-
Gender categorical			
Units: Subjects			
Female	112	126	238
Male	327	313	640

End points

End points reporting groups

Reporting group title	Patiromer
Reporting group description:	
Randomized subjects who received continued treatment with patiromer during the Treatment Phase.	
Reporting group title	Placebo
Reporting group description:	
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:	
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:	
All subjects randomized to patiromer or placebo arm. As adviced 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 adviced 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:	
Adjusted mean changes in serum K+ from Baseline.	
End point type	Primary
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: 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

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 [1]
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 [2]
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 - For reporting 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/losser 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

Statistical analysis title	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/losser 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 - For reporting 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/losser 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 %

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

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported