Clinical trial results:
A Randomized, Double-Blind, Placebo controlled, Parallel Group Study of Patiromer for the Enablement of Spironolactone Use for Blood Pressure Control in Patients with Resistant Hypertension and Chronic Kidney Disease: Evaluation of Safety and Efficacy (AMBER)

Summary

EudraCT number	2016-002657-38
Trial protocol	HU DE HR BG
Global end of trial date	27 November 2018

Results information

Result version number	v1 (current)
This version publication date	18 December 2019
First version publication date	18 December 2019

Trial information

Trial identification

Sponsor protocol code	RLY5016-207

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03071263
WHO universal trial number (UTN)	-
Other trial identifiers	US IND Number: 75,615

Notes:

Sponsors

Sponsor organisation name	Relypsa, Inc.
Sponsor organisation address	100 Cardinal Way, Redwood City, United States, CA 94063
Public contact	Clive Burge, Clinical Support & Regulatory Intelligence, Regulatory Affairs Director. , Vifor Pharma Inc., +1 250 708 4296, Clive.Burge@viforpharma.com
Scientific contact	Udo-Michael Göhring, Head of Global Clinical Development, Corporate Strategy, Vifor Pharma Inc., +41 58 851 81 26, Udo-Michael.Goehring@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	27 November 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 November 2018
Global end of trial reached?	Yes
Global end of trial date	27 November 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine if patiromer treatment of chronic kidney disease (CKD) subjects receiving spironolactone for the treatment of resistant hypertension will result in:
• More persistent use of spironolactone through prevention of hyperkalemia
• Improved blood pressure control through more persistent use of spironolactone

Protection of trial subjects:

This study was conducted in accordance with United States (US) Food and Drug Administration (FDA) regulations, the International Council for Harmonisation (ICH) E6 guidelines for Good Clinical Practice (GCP), the Declaration of Helsinki, and IRB or IEC requirements. The study was also conducted in accordance with the European Union (EU) Clinical Trials Directive 2001/20/EC for sites in the EU and all other applicable local and national laws and regulations governing the conduct of human clinical studies.

In compliance with GCP guidelines, all subjects were informed of the purpose of the research, the possible risks, and their right to withdraw at any time from the study without prejudice and without jeopardy to their future medical care at the center.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 January 2017
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	United States: 11
Country: Number of subjects enrolled	South Africa: 3
Country: Number of subjects enrolled	Ukraine: 70
Country: Number of subjects enrolled	Georgia: 92
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Croatia: 13
Country: Number of subjects enrolled	Bulgaria: 30
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Hungary: 73
Worldwide total number of subjects	295
EEA total number of subjects	119

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)	93
From 65 to 84 years	202
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted under the sponsorship of Relypsa, Inc. at 56 sites worldwide.

Pre-assignment

Screening details:

Purpose of Screening: to ensure that all enrolled subjects were on stable doses of baseline medications, did not have white coat hypertension, could demonstrate proper and reliable use of the home blood pressure monitoring device prior to study treatment, and that they met all study inclusion/exclusion criteria. It consisted of 4 Screening Visits.

Period 1

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

Blinding implementation details:

Randomization to patiromer or placebo (Day 0) in a 1:1 ratio was performed at the Randomization Visit using the Interactive Web Response System (IWRS), with stratification on the basis of serum potassium and history of diabetes as described previously.
All subjects were instructed to begin treatment with assigned patiromer or placebo and spironolactone 25 mg once daily (QD) on the day after randomization to patiromer/placebo (Day 1).

Arms

Are arms mutually exclusive?	Yes
Arm title	Patiromer

Arm description:

spironolactone + blinded patiromer

Arm type	Experimental
Investigational medicinal product name	Patiromer
Investigational medicinal product code	
Other name	Veltassa, RLY5016 for Oral Suspension, Patiromer for Oral Suspension
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

The starting dose of patiromer/placebo was 2 packets once daily (QD) taken with food for randomized subjects. Based upon the patiromer/placebo treatment algorithm, patiromer/placebo was increased in 2 packet per day increments for serum potassium >5.1 mEq/L at intervals of at least 1 week. Doses of patiromer/placebo were 2 packets, 4 packets, and 6 packets (maximum dose). Patiromer/placebo was to be decreased by at least 2 packets per day for serum potassium <4.0 mEq/L. The minimum daily dose of patiromer/placebo was 0 packets.
All subjects started spironolactone 25 mg QD on Day 1. At the Week 3 visit (or after), the spironolactone dose was increased to 50 mg QD for subjects with AOBP SBP ≥120 mmHg and potassium ≤5.1 mEq/L. For subjects with potassium >5.1 mEq/L, 25 mg daily dose of spironolactone was continued until the first subsequent visit when potassium was ≤5.1 mEq/L (and AOBP SBP ≥120 mmHg), at which time spironolactone was to be increased to 50 mg QD.

Arm title	Placebo

Arm description:

Spironolactone + Blinded Placebo

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

The starting dose of patiromer/placebo was 2 packets once daily (QD) taken with food for randomized subjects. Based upon the patiromer/placebo treatment algorithm, patiromer/placebo was increased in 2 packet per day increments for serum potassium >5.1 mEq/L at intervals of at least 1 week. Doses of patiromer/placebo were 2 packets, 4 packets, and 6 packets (maximum dose). Patiromer/placebo was to be decreased by at least 2 packets per day for serum potassium <4.0 mEq/L. The minimum daily dose of patiromer/placebo was 0 packets.
All subjects started spironolactone 25 mg QD on Day 1. At the Week 3 visit (or after), the spironolactone dose was increased to 50 mg QD for subjects with AOBP SBP ≥120 mmHg and potassium ≤5.1 mEq/L. For subjects with potassium >5.1 mEq/L, 25 mg daily dose of spironolactone was continued until the first subsequent visit when potassium was ≤5.1 mEq/L (and AOBP SBP ≥120 mmHg), at which time spironolactone was to be increased to 50 mg QD.

Number of subjects in period 1	Patiromer	Placebo
Started	147	148
Completed	144	141
Not completed	3	7
Adverse event, serious fatal	-	1
Consent withdrawn by subject	1	3
Physician decision	1	-
Adverse event, non-fatal	1	2
Subject moved to another city	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Patiromer
Reporting group description: spironolactone + blinded patiromer	
Reporting group title	Placebo
Reporting group description: Spironolactone + Blinded Placebo	

Reporting group values	Patiromer	Placebo	Total
Number of subjects	147	148	295
Age categorical Units: Subjects			
<=18 years	0	0	0
Between 18 and 65 years	49	44	93
>=65 years	98	104	202
Age continuous Units: years			
arithmetic mean	67.8	68.5	
standard deviation	± 12.24	± 11.13	-
Gender categorical Units: Subjects			
Female	71	71	142
Male	76	77	153
Ethnicity Units: Subjects			
Hispanic or Latino	7	16	23
Not Hispanic or Latino	140	131	271
Unknown or Not Reported	0	1	1
Race Units: Subjects			
White	145	145	290
Black	2	2	4
Asian	0	0	0
Other	0	1	1
Baseline central laboratory serum potassium Units: Subjects			
Baseline serum potassium <4.3 mEq/L	7	17	24
Baseline serum potassium 4.3-<4.7 mEq/L	55	52	107
Baseline serum potassium 4.7-5.1 mEq/L	65	65	130
Baseline serum potassium >5.1 mEq/L	20	14	34
Antihypertensive Medications at Baseline: Agents Acting on the Renin-Angiotensin System			
Measure Description: Antihypertensive Medications at Baseline by Preferrerd Drug Name for ≥10% of			

the total subjects. Agents Acting on the Renin-Angiotensin System (AARAS): Perindopril, Valsartan, Losartan.			
Units: Subjects			
Subjects who were on AARAS Drugs	147	147	294
Subjects who were not on AARAS Drugs	0	1	1
Antihypertensive Medications at Baseline: Diuretics			
Measure Description: Antihypertensive Medications at Baseline by Preferrerd Drug Name for ≥10% of the total subjects. Diuretics: Indapamide, Hydrochlorothiazide, Furosemide, Torasemide.			
Units: Subjects			
Subjects who were on Diuretic Drugs	146	145	291
Subjects who were not on Diuretic Drugs	1	3	4
Antihypertensive Medications at Baseline: Calcium Channel Blockers			
Measure Description: Antihypertensive Medications at Baseline by Preferrerd Drug Name for ≥10% of the total subjects. Calcium Channel Blockers (CCB): Amlodipine, Lercanidipine.			
Units: Subjects			
Subjects who were on CCB drugs	107	106	213
Subjects who were not on CCB drugs	40	42	82
Antihypertensive Medications at Baseline: Beta Blocking Agents			
Measure Description: Antihypertensive Medications at Baseline by Preferrerd Drug Name for ≥10% of the total subjects. Beta Blocking Agents (BBA): Bisoprolol, Nebivolol.			
Units: Subjects			
Subjects who were on BBA drugs	87	86	173
Subjects who were not on BBA drugs	60	62	122
Antihypertensive Medications at Baseline: Other Antihypertensives			
Measure Description: Antihypertensive Medications at Baseline by Preferrerd Drug Name for ≥10% of the total subjects. Other antihypertensives not listed before (OA): Moxonidine, Rilmenidine, Doxazosin, Clonidine, Prazosin, Urapidil, Dihydralazine, Hydralazine, Reserpine, Terazosin.			
Units: Subjects			
Subjects who were on OA	40	31	71
Subjects who were not on OA	107	117	224
Baseline eGFR			
eGFR=Estimated glomerular filtration range. eGFR was calculated using CKD Epidemiology Collaboration (CKD-EPI) formula.			
Units: mL/ min/1.73m^2			
arithmetic mean	35.37	36.08	
standard deviation	± 7.274	± 7.597	-
Systolic blood pressure as measured using automated office blood pressure device			
Units: mmHg			
arithmetic mean	143.3	144.9	

standard deviation	± 6.48	± 7.01	-

End points

End points reporting groups

Reporting group title	Patiromer
Reporting group description: spironolactone + blinded patiromer	
Reporting group title	Placebo
Reporting group description: Spironolactone + Blinded Placebo	

Primary: Number of Subjects Remaining on Spironolactone at Week 12

End point title	Number of Subjects Remaining on Spironolactone at Week 12

End point description:

The proportion of subjects remaining on spironolactone at Week 12 will be compared between treatment groups (spironolactone/patiromer versus spironolactone/placebo). Subjects who discontinued from the study early or discontinued study spironolactone prior to Week 12, for any reason, were considered as not having remained on spironolactone until Week 12.

Analysis Population Description:
Intent-to-Treat population (ITT): The ITT population included all participants who were randomized and who took at least 1 dose of spironolactone and at least 1 dose of patiromer/placebo.

End point type	Primary
End point timeframe: At week 12	

End point values	Patiromer	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	148		
Units: Subjects				
Subjects Remaining on Spironolactone Week 12	126	98		
Subjects Not Remaining on Spironolactone Week 12	21	50		

Statistical analyses

Statistical analysis title	Subjects Remaining on Spironolactone at Week 12

Statistical analysis description:

A sample size of 280 subjects has 90% power to detect a difference between treatment groups of 20% or more in the proportion of subjects remaining on spironolactone at Week 12, at $\alpha = 0.05$.

Comparison groups	Patiromer v Placebo

Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	Cochran-Mantel-Haenszel

Notes:

[1] - α-level 0.05. Stratified by baseline potassium category (4.3-<4.7 mEq/L or 4.7-5.1 mEq/L) and history of Type 1 or Type 2 diabetes mellitus (Yes or No) as randomized.

Secondary: Change in AOBP SBP (Systolic blood pressure as measured using automated office blood pressure device) From Baseline to Week 12 or Last Available AOBP SBP Prior to Addition of Any New BP Medications or Increase From Any Baseline BP Medications

End point title	Change in AOBP SBP (Systolic blood pressure as measured using automated office blood pressure device) From Baseline to Week 12 or Last Available AOBP SBP Prior to Addition of Any New BP Medications or Increase From Any Baseline BP Medications

End point description:

AOBP: Automated Office Blood Pressure SBP: Systolic Blood Pressure BP: Blood Pressure.

Analysis Population Description
Intent-to-Treat population (ITT): The ITT population included all participants who were randomized and who took at least 1 dose of spironolactone and at least 1 dose of patiromer/placebo.

End point type	Secondary

End point timeframe:

From baseline to Week 12.

End point values	Patiromer	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	144	141		
Units: mmHg				
arithmetic mean (standard deviation)	-11.3 (± 14.11)	-11.0 (± 15.34)		

Statistical analyses

Statistical analysis title	Change in AOBP SBP From Baseline to Week 12

Statistical analysis description:

Statistical Analysis for Change in AOBP SBP From Baseline to Week 12 or Last Available AOBP SBP Prior to Addition of Any New BP Medications or Increase From Any Baseline BP Medications.

Comparison groups	Placebo v Patiromer
Number of subjects included in analysis	285
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5757 [2]
Method	ANCOVA

Notes:

[2] - Baseline AOBP SBP as a covariate and treatment group, baseline serum potassium (K+ 4.3-<4.7 or 4.7-5.1 mEq/L), and history of Type 1 or Type 2 diabetes mellitus (Yes or No) as factors in the model.

Other pre-specified: Change in AOBP SBP From Baseline to Week 12 Regardless of Increase in Antihypertensives

End point title	Change in AOBP SBP From Baseline to Week 12 Regardless of Increase in Antihypertensives

End point description:

AOBP SBP: Automated Office Systolic Blood Pressure

Analysis Population Description
Intent-to-Treat population (ITT): The ITT population included all participants who were randomized and who took at least 1 dose of spironolactone and at least 1 dose of patiromer/placebo.

End point type	Other pre-specified

End point timeframe:

From baseline to Week 12

End point values	Patiromer	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	144	141		
Units: mmHg				
arithmetic mean (standard deviation)				
Change in AOBP SBP From Baseline to Week 12	-11.3 (± 14.11)	-11.2 (± 15.04)		

Statistical analyses

Statistical analysis title	Change in AOBP SBP From Baseline to Week 12

Statistical analysis description:

Statistical Analysis for Change in AOBP SBP From Baseline to Week 12 Regardless of Increase in Antihypertensives.

Comparison groups	Placebo v Patiromer
Number of subjects included in analysis	285
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.6367 [4]
Method	ANCOVA

Notes:

[3] - The p-value is from a test comparing the difference between two groups in the mean change in AOBP SBP from baseline.
[4] - Baseline AOBP SBP as a covariate and treatment group, baseline serum potassium (K+ 4.3-<4.7 or 4.7-5.1 mEq/L), and history of Type 1 or Type 2 diabetes mellitus as factors in the model.

Other pre-specified: Central Serum Potassium Change From Baseline to Week 12 by Baseline Serum Potassium Category

End point title	Central Serum Potassium Change From Baseline to Week 12 by Baseline Serum Potassium Category

End point description:

The two baseline potassium subgroups, 4.3-<4.7 mEq/L versus 4.7-5.1 mEq/L, are based on central laboratory data. If a subject's serum potassium result is not in one of these two subgroups, the subject's

potassium stratum at randomization was used.

Analysis Population Description
Intent-to-Treat population (ITT): The ITT population included all participants who were randomized and who took at least 1 dose of spironolactone and at least 1 dose of patiromer/placebo.

Reported results only include participants with Baseline Serum Potassium values according to the ranges defined below.

See attached Table (Central Serum Potassium Change from Baseline to Week 12 by Baseline Serum Potassium) to see the the number of subjects analysed in each categroy.

End point type	Other pre-specified

End point timeframe:

From baseline to Week 12

End point values	Patiromer	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	144	140		
Units: mEq/L				
arithmetic mean (standard deviation)				
Baseline Central Serum Potassium 4.3-<4.7 mEq/L	0.16 (± 0.468)	0.40 (± 0.494)		
Baseline Central Serum Potassium 4.7-<5.1 mEq/L	-0.09 (± 0.442)	0.03 (± 0.468)		
Overall	0.02 (± 0.469)	0.20 (± 0.514)		

Attachments (see zip file)	Serum Potassium change from Baseline to Week 12/Central

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Proportion of Subjects With Central Serum Potassium <5.5 mEq/L Over Time

End point title	Proportion of Subjects With Central Serum Potassium <5.5 mEq/L Over Time

End point description:

Baseline Central Serum Potassium: BCSP.

Analysis Population Description
Intent-to-Treat population (ITT): The ITT population included all participants who were randomized and who took at least 1 dose of spironolactone and at least 1 dose of patiromer/placebo.

Reported results only include participants with Central Serum Potassium values according to the ranges defined below.

Category Titles
W= Week

See attached Table (Central Serum Potassion Over Time) to see the the number of subjects analysed in each categroy.

End point type	Other pre-specified

End point timeframe:
From baseline to Week 12

End point values	Patiromer	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	148		
Units: Subjects				
Baseline Serum Potassium 4.3-<4.7 mEq/L ≤W1	60	62		
Baseline Serum Potassium 4.3-<4.7 mEq/L >W1-≤W2	57	57		
Baseline Serum Potassium 4.3-<4.7 mEq/L >W2-≤W3	59	63		
Baseline Serum Potassium 4.3-<4.7 mEq/L >W3-≤W4	61	60		
Baseline Serum Potassium 4.3-<4.7 mEq/L >W4-≤W6	61	61		
Baseline Serum Potassium 4.3-<4.7 mEq/L >W6-≤W8	61	58		
Baseline Serum Potassium 4.3-<4.7 mEq/L >W8-≤W10	58	58		
Baseline Serum Potassium 4.3-<4.7 mEq/L >W10-≤W12	61	61		
Baseline Serum Potassium 4.7-<5.1 mEq/L ≤W1	75	66		
Baseline Serum Potassium 4.7-<5.1 mEq/L >W1-≤W2	74	65		
Baseline Serum Potassium 4.7-<5.1 mEq/L >W2-≤W3	74	65		
Baseline Serum Potassium 4.7-<5.1 mEq/L >W3-≤W4	74	61		
Baseline Serum Potassium 4.7-<5.1 mEq/L >W4-≤W6	79	64		
Baseline Serum Potassium 4.7-<5.1 mEq/L >W6-≤W8	74	66		
Baseline Serum Potassium 4.7-<5.1 mEq/L >W8-≤W10	72	66		
Baseline Serum Potassium 4.7-<5.1 mEq/L >W10-≤W12	80	65		
Overall : ≤Week 1	135	128		
Overall : > Week 1 and ≤Week 2	131	122		
Overall : >Week 2 and ≤Week 3	133	128		
Overall : >Week 3 and ≤Week 4	135	121		
Overall : >Week 4 and ≤Week 6	140	125		
Overall : >Week 6 and ≤Week 8	135	124		
Overall : >Week 8 and ≤Week 10	130	124		
Overall : >Week 10 and ≤Week 12	141	126		

Attachments (see zip file)	Subjects with Serum Potassium <5.5 mEq/L Over Time/Central

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Proportion of Subjects Having Spironolactone Titrations Over Time

End point title	Proportion of Subjects Having Spironolactone Titrations Over Time

End point description:

Analysis Population Description
Intent-to-Treat population (ITT): The ITT population included all participants who were randomized and who took at least 1 dose of spironolactone and at least 1 dose of patiromer/placebo.

Reported results only include the proportion of participants having spironolactone titrations over time according to the classification defined below.

See attached Table (Proportion of Subjects Having Spironolactone Titrations over Time) to see the the number of subjects analysed in each categroy.

End point type	Other pre-specified

End point timeframe:

From baseline to Week 12

End point values	Patiromer	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	148		
Units: Subjects				
Up : ≤Week 1	0	0		
Up : >Week 1 and ≤Week 2	0	0		
Up : >Week 2 and ≤Week 3	88	77		
Up : >Week 3 and ≤Week 4	27	21		
Up : >Week 4 and ≤Week 6	10	11		
Up : >Week 6 and ≤Week 8	6	6		
Up : >Week 8 and ≤Week 10	6	7		
Up : >Week 10 and ≤Week 12	1	0		
Down : ≤Week 1	1	2		
Down : >Week 1 and ≤Week 2	2	0		
Down : >Week 2 and ≤Week 3	2	2		
Down : >Week 3 and ≤Week 4	6	5		
Down : >Week 4 and ≤Week 6	8	7		
Down : >Week 6 and ≤Week 8	5	8		
Down : >Week 8 and ≤Week 10	4	7		
Down : >Week 10 and ≤Week 12	3	1		

Attachments (see zip file)	Subjects Having Spironolactone Titrations/Proportion of

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects by Spironolactone Dose Prescribed at Each Visit

End point title	Number of Subjects by Spironolactone Dose Prescribed at Each Visit

End point description:

Analysis Population Description
Intent-to-Treat population (ITT): The ITT population included all participants who were randomized and who took at least 1 dose of spironolactone and at least 1 dose of patiromer/placebo.

QD=Once daily; QOD=Once every other day.

End point type	Other pre-specified

End point timeframe:

From baseline to Week 10

End point values	Patiromer	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	148		
Units: Subjects				
50 mg QD : Baseline	0	0		
50 mg QD : Week 1	0	0		
50 mg QD : Week 2	0	0		
50 mg QD : Week 3	86	76		
50 mg QD : Week 4	105	94		
50 mg QD : Week 6	106	96		
50 mg QD : Week 8	106	85		
50 mg QD : Week 10	106	80		
25 mg QD : Baseline	147	148		
25 mg QD : Week 1	145	144		
25 mg QD : Week 2	140	142		
25 mg QD : Week 3	49	57		
25 mg QD : Week 4	27	34		
25 mg QD : Week 6	25	28		
25 mg QD : Week 8	26	24		
25 mg QD : Week 10	19	20		
25 mg QOD : Baseline	0	0		
25 mg QOD : Week 1	1	2		
25 mg QOD : Week 2	3	1		
25 mg QOD : Week 3	3	2		
25 mg QOD : Week 4	3	3		
25 mg QOD : Week 6	2	2		
25 mg QOD : Week 8	1	4		
25 mg QOD : Week 10	2	4		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Shifts in Selected Laboratory Tests From Baseline to End of Treatment

End point title	Shifts in Selected Laboratory Tests From Baseline to End of Treatment

End point description:

The end of treatment value is defined as the last non-missing value on or prior to the last spironolactone dose date (from End of Treatment - Case report form) + 3 days

Analysis Population Description
Safety Population

LLN=Lower limit of the normal range. ULN=Upper limit of the normal range. EoT=End of Treatment

End point type	Other pre-specified

End point timeframe:

From Baseline to End of Treatment

End point values	Patiromer	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	146	147		
Units: Subjects				
Magnesium - Baseline Value <LLN : EoT Value<LLN	9	4		
Magnesium - Baseline Value <LLN : EoT Value Normal	3	8		
Magnesium - Baseline Value <LLN : EoT Value >ULN	0	0		
Magnesium - Baseline Value Normal : EoT Value <LLN	12	7		
Magnesium- Baseline Value Normal: EoT Value Normal	103	109		
Magnesium - Baseline Value Normal : EoT Value >ULN	6	10		
Magnesium - Baseline Value >ULN : EoT Value <LLN	0	0		
Magnesium - Baseline Value >ULN : EoT Value Normal	10	6		
Magnesium - Baseline Value >ULN : EoT Value >ULN	3	3		
Phosphate - Baseline Value <LLN : EoT Value <LLN	0	1		
Phosphate - Baseline Value <LLN : EoT Value Normal	1	3		
Phosphate - Baseline Value <LLN : EoT Value >ULN	0	0		
Phosphate - Baseline Value Normal : EoT Value <LLN	0	1		
Phosphate- Baseline Value Normal: EoT Value Normal	136	125		
Phosphate - Baseline Value Normal : EoT Value >ULN	2	8		
Phosphate - Baseline Value >ULN : EoT Value <LLN	0	0		
Phosphate - Baseline Value >ULN : EoT Value Normal	5	4		
Phosphate - Baseline Value >ULN : EoT Value >ULN	2	5		

Calcium - Baseline Value <LLN : EoT Value <LLN	2	4		
Calcium - Baseline Value <LLN : EoT Value Normal	5	1		
Calcium - Baseline Value <LLN : EoT Value >ULN	0	0		
Calcium - Baseline Value Normal : EoT Value <LLN	4	6		
Calcium - Baseline Value Normal : EoT Value Normal	133	133		
Calcium - Baseline Value Normal : EoT Value >ULN	0	0		
Calcium - Baseline Value >ULN : EoT Value <LLN	0	0		
Calcium - Baseline Value >ULN : EoT Value Normal	2	1		
Calcium - Baseline Value >ULN : EoT Value >ULN	0	2		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Spironolactone Dose Level at End of 12 Weeks of Study Treatment

End point title	Spironolactone Dose Level at End of 12 Weeks of Study Treatment

End point description:

Analysis Population Description
Intent-to-Treat population (ITT): The ITT population included all participants who were randomized and who took at least 1 dose of spironolactone and at least 1 dose of patiromer/placebo.

Category title:
Participants not completing 12W of study treatment: Participants who had not completed 12 weeks of study treatment.

End point type	Other pre-specified

End point timeframe:

12 Weeks of Study Treatment

End point values	Patiromer	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	148		
Units: Subjects				
50 mg QD	102	76		
25 mg QD	22	19		
25 mg QOD	2	3		
Participants not completing 12W of study treatment	21	50		

Statistical analyses

No statistical analyses for this end point

Post-hoc: Number of Subjects Requiring Additional New Antihypertensive Medications or Increases to Baseline Antihypertensive Medications

End point title	Number of Subjects Requiring Additional New Antihypertensive Medications or Increases to Baseline Antihypertensive Medications

End point description:

Row Titles:
• AM: Antihypertensive Medication(s)
• New AM: Participants who required additional new antihypertensive medication(s)
• Increases to baseline AM: Participants who required increases to baseline antihypertensive medication(s)
• Addition new (or increase) AM: Participants who required addition of new antihypertensive medication(s) and/or
increases to baseline antihypertensive medications
• At any time during the study: During study
• While on study medication: On medication

End point type	Post-hoc

End point timeframe:

From baseline to Week 12/Early Termination visit

End point values	Patiromer	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	148		
Units: Subjects				
New AM : At any time during the study	0	3		
New AM : On medication	0	1		
Increases to baseline AM: During study	0	2		
Increases to baseline AM: On medication	0	1		
Addition new (or increases) AM: During study	0	4		
Addition new (or increases) AM : On medication	0	2		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

During Treatment Period (12 weeks); until Follow-up Visit 2 weeks after the Week 12 Visit (or Early Termination Visit).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Patiromer

Reporting group description:

spironolactone + blinded patiromer

Reporting group title	Placebo

Reporting group description:

Spironolactone + Blinded Placebo

Serious adverse events	Patiromer	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 147 (0.68%)	4 / 148 (2.70%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0		
Vascular disorders			
Aortic rupture			
subjects affected / exposed	0 / 147 (0.00%)	1 / 148 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 147 (0.00%)	1 / 148 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	0 / 147 (0.00%)	1 / 148 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			

subjects affected / exposed	0 / 147 (0.00%)	1 / 148 (0.68%)	
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			
Humerus fracture			
subjects affected / exposed	1 / 147 (0.68%)	0 / 148 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Patiromer	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	81 / 147 (55.10%)	75 / 148 (50.68%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	9 / 147 (6.12%)	6 / 148 (4.05%)	
occurrences (all)	9	6	
Nervous system disorders			
Headache			
subjects affected / exposed	9 / 147 (6.12%)	11 / 148 (7.43%)	
occurrences (all)	9	13	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	9 / 147 (6.12%)	8 / 148 (5.41%)	
occurrences (all)	9	9	
Renal and urinary disorders			
Renal impairment			
subjects affected / exposed	13 / 147 (8.84%)	10 / 148 (6.76%)	
occurrences (all)	15	11	
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	7 / 147 (4.76%)	13 / 148 (8.78%)	
occurrences (all)	11	17	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 October 2016	• Automated office BP, AOBP, (rather than 7dHBP) to be used for screening, study drug dosing and discontinuation decisions, clinical decision making, and BP analyses • The lower end of the range to define hypertension as measured by AOBP SBP is changed to 135 mmHg • AOBP (automated office BP) – defined as BP measured at the office (i.e., clinical site) using an automatic oscillometric device with the capability of performing automatic multiple measurements after the study staff has left the room (unwitnessed measurement after the subject has been sitting quietly for 5 minutes) • Removed the requirement for evidence of elevated BP during a routine standard of care visit within past 3 months • Changed to allow a single AOBP SBP to be <135 mmHg at either S2 or S3 if AOBP SBP is 135-160 mmHg at the other Screening Visits • Triamterene and amiloride are added to the prohibited medications list • Additional text explaining that a sample size of 290 allows for up to 10 subjects who are randomized but do not receive treatment. Change also removes the statements regarding power for the secondary endpoint • Added 'After discontinuation of spironolactone and patiromer/placebo, hyperkalemia may be treated using standard of care per the Investigator's judgment.' • Added further instructions 'The site will be notified regarding out-of-range HBP and subject noncompliance with performing HBP.' • Removed the following urine assessments due to an error: - Calcium - Phosphate - Potassium from 24-hour urine collection - Added leukocyte esterase to urine assessment
04 November 2016	• Clarified that it is subjects with untreated secondary causes of hypertension that should be excluded • Clarified that BP measurements should be done before BP medications are administered on the morning of the visit • Clarified the order of visit activities

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported