Clinical trial results:
A Multicenter, Randomized, Double-blind, Placebo-Controlled, Parallel-Group, Multiple-Dose Study to Evaluate the Effects of RLY5016 in Heart Failure Patients

Summary

EudraCT number	2009-009983-29
Trial protocol	DE CZ
Global end of trial date	12 November 2009

Results information

Result version number	v1 (current)
This version publication date	06 August 2016
First version publication date	06 August 2016

Trial information

Trial identification

Sponsor protocol code	RLY5016–202

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00868439
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Relypsa, Inc.
Sponsor organisation address	100 Cardinal Way, Redwood City, United States, 994063
Public contact	Medical Information, Relypsa, Inc., medinfo@relypsa.com
Scientific contact	Medical Information, Relypsa, Inc., medinfo@relypsa.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	24 November 2009
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 November 2009
Global end of trial reached?	Yes
Global end of trial date	12 November 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study was to assess the effects of patiromer on serum potassium participants with heart failure. This study also assessed the safety and tolerability of patiromer in participants with heart failure.

Protection of trial subjects:

This study was conducted in accordance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 May 2009
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	Poland: 1
Country: Number of subjects enrolled	Czech Republic: 5
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	United States: 19
Country: Number of subjects enrolled	Russian Federation: 35
Country: Number of subjects enrolled	Ukraine: 12
Country: Number of subjects enrolled	Georgia: 28
Worldwide total number of subjects	105
EEA total number of subjects	11

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	31
From 65 to 84 years	72
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

120 subjects were randomized (60 to each treatment group). Of these, 120 randomized subjects, 105 received either patiromer (n = 56) or placebo (n = 49).

Pre-assignment

Screening details:

Eligible participants ≥ 18 y/o, had history of chronic HF, clinically initiated spironolactone therapy, serum K+ = 4.3 – 5.1 mEq/L at screening and baseline, and either had 1) CKD, w/ eGFR < 60 mL/min and receiving HF therapies or 2) documented history of hyperkalemia led to discontinuation w/ aldosterone antagonist w/in 6 months prior to baseline.

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, Monitor, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Patiromer

Arm description: -

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

Dosage and administration details:

Patiromer, 15 g, orally, twice a day for up to 28 days.

Spironolactone, 25 mg, orally, once a day for up to 28 days. Spironolactone was increased to 50 mg/day after 2 weeks if the participant’s serum potassium (based on local laboratory determination) was > 3.5 mEq/L and ≤ 5.1 mEq/L. The spironolactone dose remained at 25 mg/day if the serum potassium was > 5.1 mEq/L and ≤ 5.5 mEq/L. If, at any time, a participant’s serum potassium level was confirmed to be ≤ 3.5 mEq/L or > 5.5 mEq/L based on local laboratory data, the participant was to be discontinued from the study.

Arm title	Placebo

Arm description: -

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

Dosage and administration details:

Placebo, orally, twice a day for up to 28 days.

Spironolactone, 25 mg, orally, once a day for up to 28 days. Spironolactone was increased to 50 mg/day after 2 weeks if the participant’s serum potassium (based on local laboratory determination) was > 3.5 mEq/L and ≤ 5.1 mEq/L. The spironolactone dose remained at 25 mg/day if the serum potassium

was > 5.1 mEq/L and ≤ 5.5 mEq/L. If, at any time, a participant's serum potassium level was confirmed to be ≤ 3.5 mEq/L or > 5.5 mEq/L based on local laboratory data, the participant was to be discontinued from the study.

Number of subjects in period 1[1]	Patiromer	Placebo
Started	55	49
Completed	48	40
Not completed	7	9
Adverse event, serious fatal	-	1
Physician decision	1	-
Consent withdrawn by subject	-	1
Adverse event, non-fatal	4	3
Prot-Specified W/D Criteria (Serum K+)	2	3
Protocol deviation	-	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: One participant received one dose of patiromer and did not return to the clinic in a timely manner; the participant was terminated from the study for protocol noncompliance, and because the participant did not have post-treatment efficacy data, the participant was excluded from the Full Analysis Set but retained in the Safety Analysis Set.

Baseline characteristics

Reporting groups	
Reporting group title	Patiromer
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Patiromer	Placebo	Total
Number of subjects	55	49	104
Age categorical Units: Subjects			
Adults (18-64 years)	16	14	30
From 65-84 years	37	35	72
85 years and over	2	0	2
Age continuous Units: years			
arithmetic mean	68.3	68.2	
standard deviation	± 8.66	± 10.46	-
Gender categorical Units: Subjects			
Female	26	15	41
Male	29	34	63

End points

End points reporting groups

Reporting group title	Patiromer
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Primary: Change From Baseline in Serum Potassium to the End of the 28-day Treatment Period

End point title	Change From Baseline in Serum Potassium to the End of the 28-day Treatment Period
End point description:	
Analysis was determined using Last Observation Carried Forward (LOCF).	
End point type	Primary
End point timeframe:	
Baseline and Day 28	

End point values	Patiromer	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	49		
Units: milliequivalent(s)/litre				
least squares mean (standard error)	-0.21 (± 0.066)	0.23 (± 0.072)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Patiromer v Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA

Secondary: Proportion of Participants With a Serum Potassium Level During the 28-day Treatment Period That Was > 5.5 mEq/L.

End point title	Proportion of Participants With a Serum Potassium Level During the 28-day Treatment Period That Was > 5.5 mEq/L.
End point description:	
Analysis based on central laboratory data.	

End point type	Secondary
End point timeframe: 28 Days	

End point values	Patiromer	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	49		
Units: percent				
number (not applicable)	7.3	24.5		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Patiromer v Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.027
Method	Fisher exact

Secondary: Proportion of Participants Discontinuing the Study Due to Serum Potassium Elevation (Serum K+ > 5.5 mEq/L).

End point title	Proportion of Participants Discontinuing the Study Due to Serum Potassium Elevation (Serum K+ > 5.5 mEq/L).
End point description: Analysis based on local laboratory data.	
End point type	Secondary
End point timeframe: 28 Days	

End point values	Patiromer	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	49		
Units: percent				
number (not applicable)	0	6.1		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Patiromer v Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.101
Method	Fisher exact

Secondary: Proportion of Participants Whose Spironolactone Dose Was Increased.

End point title	Proportion of Participants Whose Spironolactone Dose Was Increased.

End point description:

End point type	Secondary

End point timeframe:

28 Days

End point values	Patiromer	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	49		
Units: percent				
number (not applicable)	90.9	73.5		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Patiromer v Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.022
Method	Fisher exact

Secondary: Proportion of Participants With an Increase in Serum Potassium Level From Baseline to the End of the 28-day Treatment Period That Was ≥ 0.5 mEq/L

End point title	Proportion of Participants With an Increase in Serum Potassium Level From Baseline to the End of the 28-day Treatment Period That Was ≥ 0.5 mEq/L

End point description:

Analysis was determined using LOCF.

End point type	Secondary

End point timeframe:
Baseline and Day 28

End point values	Patiromer	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	49		
Units: percent				
number (not applicable)	12.7	24.5		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Patiromer v Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.136
Method	Fisher exact

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Up to 7 days after Day 28 or last patiromer dose, whichever was earlier.	
Adverse event reporting additional description: Participants received at least one dose of trial medication.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	12.0

Reporting groups	
Reporting group title	Patiromer
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Patiromer	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 56 (3.57%)	2 / 49 (4.08%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events			
Cardiac disorders			
Coronary artery disease			
subjects affected / exposed	2 / 56 (3.57%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 56 (1.79%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 56 (1.79%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Sudden cardiac death			

subjects affected / exposed	0 / 56 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	0 / 56 (0.00%)	1 / 49 (2.04%)	
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: 5 %

Non-serious adverse events	Patiromer	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 56 (19.64%)	1 / 49 (2.04%)	
Investigations			
Blood urea increased			
subjects affected / exposed	3 / 56 (5.36%)	0 / 49 (0.00%)	
occurrences (all)	3	0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	3 / 56 (5.36%)	0 / 49 (0.00%)	
occurrences (all)	3	0	
Diarrhoea			
subjects affected / exposed	3 / 56 (5.36%)	1 / 49 (2.04%)	
occurrences (all)	3	1	
Flatulence			
subjects affected / exposed	4 / 56 (7.14%)	0 / 49 (0.00%)	
occurrences (all)	4	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 February 2009	RLY5016-202 Protocol Amendment 1: Substantial protocol amendment was in effect prior to actual start date of recruitment, 29 May 2009.
07 April 2009	RLY5016-202 Protocol Amendment 2: Substantial protocol amendment was in effect prior to actual start date of recruitment, 29 May 2009.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported