



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 patiomer on serum potassium participants with heart failure. This study also assessed the safety and tolerability of patiomer 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 (\pm 0.066) | 0.23 (\pm 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