# Clinical trial results:
# Prospective, Double-Blind, Multicenter Study Evaluating the Safety of Repeat Doses of IV Serelaxin in Subjects with Chronic Heart Failure

**Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.novfor complete trial results.**

## Summary

| | |
|---|---|
| EudraCT number | 2013-002781-39 |
| Trial protocol | DE IT FI ES SE NO RO NL CZ |
| Global end of trial date | 23 September 2015 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 06 July 2018 |
| First version publication date | 06 July 2018 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | CRLX030A2209 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01982292 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Novartis Pharma AG |
| Sponsor organisation address | CH-4002, Basel, Switzerland, |
| Public contact | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, |
| Scientific contact | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, |

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 | 23 September 2015 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 23 September 2015 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To assess the proportion of patients with CHF who develop anti-serelaxin antibodies at any time following repeat administration of three IV continuous infusions of serelaxin administered for up to 48 hours in four week intervals.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial. The Investigator could prescribe any medications and/or supportive care during the study based on clinical needs.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 12 May 2014 |
| 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 | Australia: 3 |
| Country: Number of subjects enrolled | Czech Republic: 41 |
| Country: Number of subjects enrolled | Germany: 120 |
| Country: Number of subjects enrolled | Italy: 12 |
| Country: Number of subjects enrolled | Netherlands: 13 |
| Country: Number of subjects enrolled | Norway: 5 |
| Country: Number of subjects enrolled | Romania: 24 |
| Country: Number of subjects enrolled | Russian Federation: 12 |
| Country: Number of subjects enrolled | Spain: 25 |
| Country: Number of subjects enrolled | Sweden: 5 |
| Country: Number of subjects enrolled | Turkey: 23 |
| Country: Number of subjects enrolled | United States: 40 |
| Worldwide total number of subjects | 323 |
| 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) | 127 |
| From 65 to 84 years | 190 |
| 85 years and over | 6 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

A total of 323 patients were randomized to the serelaxin or placebo treatment in a 2:1 ratio. 2 patients from serelaxin were mis-randomized, hence 321 received study drug.

### Period 1

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | RLX030 (serelaxin) |

Arm description:

Randomized patients received an IV infusion of 30 µg/kg/day of serelaxin for 48 hours at randomization and at Weeks 4 and 8

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | serelaxin |
| Investigational medicinal product code | RLX030 |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

RLX030 (serelaxin) was administered according to a weight-range adjusted dosing regimen at a nominal dose of 30 µg/kg/day as a continuous IV infusion for 48 hours.

| | |
|---|---|
| **Arm title** | Placebo |

Arm description:

Randomized patients received an IV infusion of placebo of serelaxin for 48 hours at randomization and at Weeks 4 and 8

| | |
|---|---|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo of RLX030 (serelaxin) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Matching placebo of serelaxin was administered as a continuous IV infusion for 48 hours.

| **Number of subjects in period 1** | RLX030 (serelaxin) | Placebo |
|---|---|---|
| Started | 215 | 108 |
| Full analaysis set (FAS) | 213 | 108 |
| Safety set | 212 | 108 |
| Completed | 203 | 107 |
| Not completed | 12 | 1 |
| Adverse event, serious fatal | 1 | - |
| Adverse event, non-fatal | 2 | - |
| Protocol Deviation | 1 | - |
| Patient/Guardian Decision | 3 | 1 |
| Technical Problems | 2 | - |
| Non-Compliance With Study Treatment | 1 | - |
| Lost to follow-up | 2 | - |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | RLX030 (serelaxin) |
| Reporting group description: | |
| Randomized patients received an IV infusion of 30 µg/kg/day of serelaxin for 48 hours at randomization and at Weeks 4 and 8 | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Randomized patients received an IV infusion of placebo of serelaxin for 48 hours at randomization and at Weeks 4 and 8 | |

| Reporting group values | RLX030 (serelaxin) | Placebo | Total |
|---|---|---|---|
| Number of subjects | 215 | 108 | 323 |
| Age categorical<br>Units: Subjects | | | |
| Adults (18-64 years) | 79 | 48 | 127 |
| From 65-84 years | 133 | 57 | 190 |
| 85 years and over | 3 | 3 | 6 |
| Gender, Male/Female<br>Units: Subjects | | | |
| Female | 46 | 26 | 72 |
| Male | 169 | 82 | 251 |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | RLX030 (serelaxin) |
| Reporting group description: | |
| Randomized patients received an IV infusion of 30 µg/kg/day of serelaxin for 48 hours at randomization and at Weeks 4 and 8 | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Randomized patients received an IV infusion of placebo of serelaxin for 48 hours at randomization and at Weeks 4 and 8 | |

### Primary: Percentage of participants with chronic heart failure (CHF) who develop anti-serelaxin antibodies at any time following repeat administration of IV continuous infusions of serelaxin administered for up to 48 hours in 16 weeks

| | |
|---|---|
| End point title | Percentage of participants with chronic heart failure (CHF) who develop anti-serelaxin antibodies at any time following repeat administration of IV continuous infusions of serelaxin administered for up to 48 hours in 16 weeks |
| End point description: | |
| A patient is considered antibody positive during the study if he/she had at least two infusions and had at least one evaluable measurement to test for anti-serelaxin antibodies after each infusion and all evaluable antibody test results were positive. A patient is considered antibody negative during the study if he/she had at least two infusions and had at least one evaluable measurement to test for anti-serelaxin antibodies after each infusion and all evaluable antibody test results were negative. A patient's antibody status is considered to be undetermined during the study if it is not defined as positive or negative. | |
| End point type | Primary |
| End point timeframe: | |
| 16 weeks | |

| End point values | RLX030 (serelaxin) | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 200 | 106 | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 90%) | | | | |
| Positive | 0.5 (0.03 to 2.35) | 0 (0 to 2.79) | | |
| Negative | 99.5 (97.65 to 99.97) | 100 (97.21 to 100) | | |

### Statistical analyses

| Statistical analysis title | Difference in % of pts with +ve antibody status |
|---|---|
| Statistical analysis description: | |
| Difference in percentage of patients with positive antibody status | |
| Comparison groups | RLX030 (serelaxin) v Placebo |

| | |
|---|---|
| Number of subjects included in analysis | 306 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | > 0.9999 |
| Method | Fisher exact |
| Parameter estimate | Difference in percentage |
| Point estimate | 0.5 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -9.38 |
| upper limit | 10.38 |

| | |
|---|---|
| **Statistical analysis title** | Difference in % of pts with - ve antibody status |
| Statistical analysis description: | |
| Difference in percentage of patients with negative antibody status | |
| Comparison groups | RLX030 (serelaxin) v Placebo |
| Number of subjects included in analysis | 306 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Difference in percentage |
| Point estimate | -0.5 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -10.38 |
| upper limit | 9.38 |

## Secondary: Percentage of participants with chronic heart failure who develop positive anti-serelaxin antibodies after a single infusion of serelaxin over time up to week 16

| | |
|---|---|
| End point title | Percentage of participants with chronic heart failure who develop positive anti-serelaxin antibodies after a single infusion of serelaxin over time up to week 16 |

End point description:

A patient is considered antibody positive during the study if he/she had at least two infusions and had at least one evaluable measurement to test for anti-serelaxin antibodies after each infusion and all evaluable antibody test results were positive. Each time period is defined as the time frame from study drug initiation (or the visit if there is no infusion) to prior to study drug initiation of the next period (or the visit if no there is no infusion). n= The total number of subjects with evaluable antibody status during the defined period.

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

End point timeframe:

Randomization to Week 4, Week 4 to Week 8, Week 8 to Week 12, week 12 to week 16

| End point values | RLX030 (serelaxin) | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 212 | 108 | | |
| Units: Percentage of patients | | | | |
| number (confidence interval 90%) | | | | |
| Randomization to week 4 (n= 209, 107) | 0.48 (0.02 to 2.25) | 0 (0 to 2.76) | | |
| Week 4 to week 8 (n= 204, 108) | 0.49 (0.03 to 2.3) | 0 (0 to 2.74) | | |
| Week 8 to week 12 (n= 204, 107) | 0.49 (0.03 to 2.3) | 0 (0 to 2.76) | | |
| Week 12 to week 16 (n= 2, 2) | 0 (0 to 0) | 0 (0 to 0) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Antibody titers in participants with chronic heart failure who develop anti-serelaxin antibodies (neutralizing, non-neutralizing or both) at any time following 3 repeated infusions and at Week 4, Week 8 and Week 12.

| End point title | Antibody titers in participants with chronic heart failure who develop anti-serelaxin antibodies (neutralizing, non-neutralizing or both) at any time following 3 repeated infusions and at Week 4, Week 8 and Week 12. |
|---|---|

End point description:

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

End point timeframe:

Week 4, Week 8, Week 12

| End point values | RLX030 (serelaxin) | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1[1] | 0[2] | | |
| Units: In international Units | | | | |
| arithmetic mean (standard deviation) | 9999 (± 99.99) | () | | |

Notes:

[1] - Antibody titers unavailable as positive anti-bodies patients were very low in number

[2] - Antibody titers is unavailable because there was no positive anti-body patient

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of participants with chronic heart failure with positive antibody status who develop non-neutralizing anti-serelaxin antibodies following 3 repeated infusions (i.e. at Week 4, Week 8, and Week 12)

| End point title | Percentage of participants with chronic heart failure with positive antibody status who develop non-neutralizing anti- |
|---|---|

| | |
|---|---|
| | serelaxin antibodies following 3 repeated infusions (i.e. at Week 4, Week 8, and Week 12) |

End point description:

A patient is considered antibody positive during the study if he/she had at least two infusions and had at least one evaluable measurement to test for anti-serelaxin antibodies after each infusion and all evaluable antibody test results were positive. n = the total number of subjects with evaluable antibody status after specified number of infusions

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

End point timeframe:

At Week 4, Week 8, Week 12

| **End point values** | RLX030 (serelaxin) | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 212 | 108 | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 90%) | | | | |
| after 1 infusion (at week 4) [n=209,108] | 0.48 (0.02 to 2.25) | 0 (0 to 2.74) | | |
| after 2 infusions (at week 8) [n=200,106] | 0.5 (0.03 to 2.35) | 0 (0 to 2.79) | | |
| after 3 infusions (at week 12) [n=184, 102] | 0.54 (0.03 to 2.55) | 0 (0 to 2.89) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of participants with adverse events such as adjudicated potential hypersensitivity or infusion reactions

| | |
|---|---|
| End point title | Number of participants with adverse events such as adjudicated potential hypersensitivity or infusion reactions |

End point description:

Incidence rate of special interest, indicative of hypersensitivity reactions which occur during and after administration of repeated infusions of serelaxin relative to placebo in subjects with chronic heart failure is reported. Hypersensitivity reactions or infusion reactions can be headache, nausea, fever, chills, dizziness, flush, pruritus, chest and/or back pain.

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

End point timeframe:

16 weeks

| **End point values** | RLX030 (serelaxin) | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 212 | 108 | | |
| Units: Participants | | | | |
| Submitted for adjudication | 32 | 14 | | |

| | | | | |
|---|---|---|---|---|
| Confirmed with no hypersensitivity reactions | 32 | 14 | | |
| Hypersensitivity reactions confirmed | 0 | 0 | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Pharmacokinetics of RLX030: Area under the plasma concentration time curve from time zero up to 48 hours post dose (AUC 0-48)

| End point title | Pharmacokinetics of RLX030: Area under the plasma concentration time curve from time zero up to 48 hours post dose (AUC 0-48)[3] |
|---|---|

End point description:

Due to sparse PK sampling, AUC 0-48 hours was not analyzed.

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

End point timeframe:

pre-infusion and 8, 24 and 48 hours post each infusion.

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: PK gets measured on study drug, not on placebo

| End point values | RLX030 (serelaxin) | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 0[4] | | | |
| Units: h*ng/mL | | | | |
| arithmetic mean (standard deviation) | () | | | |

Notes:

[4] - Due to sparse PK sampling, AUC 0-48 hours was not analyzed.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Pharmacokinetics of RLXL030: actual concentrations at steady state (Css)

| End point title | Pharmacokinetics of RLXL030: actual concentrations at steady state (Css)[5] |
|---|---|

End point description:

Concentration at steady state (Css) was estimated using C48 or C24 for patients who received the intended rate of infusion for at least 24hours. n: Number of patients with valid PK parameters available

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

End point timeframe:

pre-infusion and 24, 48 hours post each infusion

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: PK gets measured on study drug, not on placebo

| End point values | RLX030 (serelaxin) | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 211 | | | |
| Units: ng/ml | | | | |
| arithmetic mean (standard deviation) | | | | |
| First infusion (n=174) | 31.6 (± 70.1) | | | |
| Second Infusion (n=174) | 53.5 (± 234) | | | |
| Third (n = 181) | 38.9 (± 95.2) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Pharmacokinetics of RLX030: Cmax steady state (Cmaxss) concentration at 48 hours

| End point title | Pharmacokinetics of RLX030: Cmax steady state (Cmaxss) concentration at 48 hours[6] |
|---|---|

End point description:

This analysis was not done due to sparse PK sampling.

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

End point timeframe:

48 hours post each infusion

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: PK gets measured on study drug, not on placebo

| End point values | RLX030 (serelaxin) | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 0[7] | | | |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | () | | | |

Notes:

[7] - This analysis was not done due to sparse PK sampling.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Pharmacokinetics of RLX030: clearance of serelaxin (CL)

| End point title | Pharmacokinetics of RLX030: clearance of serelaxin (CL)[8] |
|---|---|

End point description:

Clearance (CL) was calculated using concentration at steady state (Css) and the actual delivered dose rate. n: Number of patients with valid PK parameters available within 48 hours post each infusion.

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

End point timeframe:

48 hours post each infusion

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: PK gets measured on study drug, not on placebo

| **End point values** | RLX030 (serelaxin) | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 211 | | | |
| Units: mL/hr/kg | | | | |
| arithmetic mean (standard deviation) | | | | |
| First Infusion (n= 173) | 106 (± 55.8) | | | |
| Second Infusion (n=173) | 97.4 (± 41.4) | | | |
| Third Infusion (n= 180) | 202 (± 1290) | | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse events are reported in this record from First Patient First Treatment until Last Patient Last Visit.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 18.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Placebo |

Reporting group description:

Randomized patients received an IV infusion of placebo of serelaxin for 48 hours at randomization and at Weeks 4 and 8

| | |
|---|---|
| Reporting group title | Serelaxin |

Reporting group description:

Randomized patients received an IV infusion of 30 µg/kg/day of serelaxin for 48 hours at randomization and at Weeks 4 and 8

| Serious adverse events | Placebo | Serelaxin | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 15 / 108 (13.89%) | 30 / 212 (14.15%) | |
| number of deaths (all causes) | 0 | 1 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| SQUAMOUS CELL CARCINOMA OF SKIN | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 212 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| BASAL CELL CARCINOMA | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 212 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| HYPOTENSION | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 108 (0.93%) | 0 / 212 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HYPERTENSIVE EMERGENCY | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | 0 / 212 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PERIPHERAL ARTERIAL OCCLUSIVE DISEASE | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | 0 / 212 (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 | | | |
| MEDICAL DEVICE SITE PAIN | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | 0 / 212 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| MULTI-ORGAN FAILURE | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 212 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| SYSTEMIC INFLAMMATORY RESPONSE SYNDROME | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 212 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| ACUTE RESPIRATORY DISTRESS SYNDROME | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | 0 / 212 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CHRONIC OBSTRUCTIVE PULMONARY DISEASE | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 108 (0.00%) | 2 / 212 (0.94%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| EPISTAXIS | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 212 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| RESPIRATORY FAILURE | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 2 / 212 (0.94%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Psychiatric disorders | | | |
| ACUTE PSYCHOSIS | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 212 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SUICIDAL IDEATION | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 212 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| ALCOHOL POISONING | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 212 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| POST PROCEDURAL HAEMORRHAGE | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | 0 / 212 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| ACUTE MYOCARDIAL INFARCTION | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 212 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| CARDIAC FAILURE CHRONIC | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | 2 / 212 (0.94%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ATRIOVENTRICULAR BLOCK SECOND DEGREE | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 212 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CARDIAC FAILURE | | | |
| subjects affected / exposed | 2 / 108 (1.85%) | 4 / 212 (1.89%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CARDIAC FAILURE ACUTE | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | 1 / 212 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ATRIAL FIBRILLATION | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | 2 / 212 (0.94%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ANGINA UNSTABLE | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 212 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ATRIAL FLUTTER | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 212 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CARDIAC FAILURE CONGESTIVE | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 2 / 212 (0.94%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CARDIOGENIC SHOCK | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 212 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| VENTRICULAR TACHYCARDIA | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | 2 / 212 (0.94%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| SYNCOPE | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 2 / 212 (0.94%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CAROTID ARTERY STENOSIS | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | 0 / 212 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| VOCAL CORD PARALYSIS | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | 0 / 212 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| ANAEMIA | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | 1 / 212 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| HAEMORRHOIDAL HAEMORRHAGE | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | 0 / 212 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DIARRHOEA | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | 0 / 212 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Renal and urinary disorders | | | |
| ACUTE KIDNEY INJURY | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | 1 / 212 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HYDRONEPHROSIS | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 212 (0.47%) | |
| 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 | | | |
| OSTEOARTHRITIS | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | 0 / 212 (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 | | | |
| DIARRHOEA INFECTIOUS | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | 0 / 212 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| BRONCHITIS | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | 0 / 212 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| APPENDICITIS | | | |
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 212 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| EPIDIDYMITIS | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | 0 / 212 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| OSTEOMYELITIS | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 108 (0.93%) | 0 / 212 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| GASTROENTERITIS | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | 1 / 212 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| GANGRENE | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | 0 / 212 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PERITONSILLAR ABSCESS | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | 0 / 212 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PNEUMONIA STREPTOCOCCAL | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | 0 / 212 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PNEUMONIA | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | 3 / 212 (1.42%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| URINARY TRACT INFECTION | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | 0 / 212 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| STREPTOCOCCAL SEPSIS | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | 0 / 212 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SEPSIS | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 108 (0.00%) | 1 / 212 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |

Frequency threshold for reporting non-serious adverse events: 2 %

| **Non-serious adverse events** | Placebo | Serelaxin | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 39 / 108 (36.11%) | 65 / 212 (30.66%) | |
| Vascular disorders | | | |
| HYPERTENSION | | | |
| subjects affected / exposed | 5 / 108 (4.63%) | 7 / 212 (3.30%) | |
| occurrences (all) | 6 | 8 | |
| Nervous system disorders | | | |
| HEADACHE | | | |
| subjects affected / exposed | 3 / 108 (2.78%) | 9 / 212 (4.25%) | |
| occurrences (all) | 4 | 10 | |
| DIZZINESS | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | 10 / 212 (4.72%) | |
| occurrences (all) | 1 | 10 | |
| Blood and lymphatic system disorders | | | |
| ANAEMIA | | | |
| subjects affected / exposed | 2 / 108 (1.85%) | 6 / 212 (2.83%) | |
| occurrences (all) | 2 | 6 | |
| General disorders and administration site conditions | | | |
| INFUSION SITE EXTRAVASATION | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | 5 / 212 (2.36%) | |
| occurrences (all) | 1 | 6 | |
| OEDEMA PERIPHERAL | | | |
| subjects affected / exposed | 3 / 108 (2.78%) | 4 / 212 (1.89%) | |
| occurrences (all) | 3 | 4 | |
| NON-CARDIAC CHEST PAIN | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | 6 / 212 (2.83%) | |
| occurrences (all) | 1 | 8 | |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|---|---|---|---|
| DYSPNOEA | | | |
| subjects affected / exposed | 3 / 108 (2.78%) | 3 / 212 (1.42%) | |
| occurrences (all) | 3 | 3 | |
| Psychiatric disorders | | | |
| INSOMNIA | | | |
| subjects affected / exposed | 3 / 108 (2.78%) | 3 / 212 (1.42%) | |
| occurrences (all) | 5 | 5 | |
| Musculoskeletal and connective tissue disorders | | | |
| MUSCLE SPASMS | | | |
| subjects affected / exposed | 3 / 108 (2.78%) | 4 / 212 (1.89%) | |
| occurrences (all) | 3 | 5 | |
| BACK PAIN | | | |
| subjects affected / exposed | 4 / 108 (3.70%) | 1 / 212 (0.47%) | |
| occurrences (all) | 4 | 1 | |
| Infections and infestations | | | |
| PNEUMONIA | | | |
| subjects affected / exposed | 3 / 108 (2.78%) | 1 / 212 (0.47%) | |
| occurrences (all) | 3 | 1 | |
| NASOPHARYNGITIS | | | |
| subjects affected / exposed | 8 / 108 (7.41%) | 18 / 212 (8.49%) | |
| occurrences (all) | 8 | 21 | |
| BRONCHITIS | | | |
| subjects affected / exposed | 4 / 108 (3.70%) | 2 / 212 (0.94%) | |
| occurrences (all) | 4 | 2 | |
| Metabolism and nutrition disorders | | | |
| HYPOKALAEMIA | | | |
| subjects affected / exposed | 5 / 108 (4.63%) | 3 / 212 (1.42%) | |
| occurrences (all) | 6 | 4 | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 11 January 2014 | This amendment issued before the study initiation (first patient first visit), introduced the following changes:<br>- Addition of the brand name for the infusion filter<br>- A sentence was added to clarify that the use of other 250 mL infusion bags containing 5% dextrose were permitted<br>-the liver monitoring sections of the protocol were updated to match the program and company standard wording and process |
| 21 March 2014 | This amendment issued before the study initiation (first patient first visit), introduced the following change(s):<br>- One exclusion criteria was corrected to indicate that women of child-bearing potential must use highly effective methods of contraception.<br>- A section in the protocol was modified to clarify the various methods utilized to ensure protocol and GCP compliance and the quality/integrity of the sites' data.<br>- Per request of German Health Authority as part of additional safety measures to avoid any<br>potential risk of hypotension with the infusion of serelaxin, particular section of the protocol clarified that an infusion pump, a drip or any other controllable infusion system would be used to ensure a constant infusion rate of serelaxin at 10 mL/hr. |
| 28 July 2014 | This amendment issued when less than 20 patients were randomized introduced the following change(s):<br>- One exclusion criteria was modified with following sentence "The exception to this exclusion criteria are the low potency topical corticosteroids and inhaled glucocorticoids used for anti-inflammatory effect, e.g. asthma, contact dermatitis, etc". The rationale for allowing low potency topical corticosteroids and inhaled glucocorticoids used for antiinflammatory effects was that these products had no known or negligible systemic effects if used in accordance to approved dosing and in line with medical recommendation. Since the immunomodulating/immunosuppressive actions were minimal and were not expected to affect the objectives of this study, patients requiring such treatment could be enrolled into the study as long as all other inclusion and exclusion criteria have been fulfilled.<br>- One exclusion criteria was modified by adding 'Visit 2' for clarity.<br>- Tables and appendices were updated and modified for clarity. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.novfor complete trial results.

Notes: