**Sponsor**

Novartis

**Generic Drug Name**

Serelaxin

**Therapeutic Area of Trial**

Chronic heart failure (CHF)

**Approved Indication**

Investigational – in development for chronic heart failure (CHF)

**Protocol Number**

CRLX030A2202

**Title**

A multicenter, randomized, double-blind, parallel group, placebo-controlled study to evaluate the renal hemodynamic effects of RLX030 at a dose of 30 μg/kg/day or placebo infused for 24 hours in subjects with chronic heart failure (CHF)

**Study Phase**

Phase II

**Study Start/End Dates**

14 February 2012 to 20 December 2012

**Study Design/Methodology**

This was a multicenter, double-blind, randomized, parallel group, placebo-controlled study in patients with CHF, worsening symptoms and mild-to-moderate renal impairment. The duration of constant infusion with serelaxin was 24 hours at a dose rate of 30 μg/kg/day or placebo. Patients were randomized 1:1 to serelaxin, or matching placebo. Randomization was stratified according to the prescribed daily dose of furosemide or equivalent dose of other loop diuretics (furosemide dose ≥120 mg p.o. [high-dose stratum] or <120 mg p.o. [low-dose stratum]).

**Centers**

18 centers in 4 countries: The Netherlands (4), Germany (6), Poland (7), United States of America (1).

**Publication**

Not applicable.

**Test Product (s), Dose(s), and Mode(s) of Administration**

Intravenous infusion of serelaxin 30 μg/kg/day

**Statistical Methods**

As per the Reporting and Analysis Plan (RAP), RPF and GFR as measured by plasma PAH clearance and plasma IOTH clearance, respectively, during the 8-24 hour time interval, were the primary variables. Note it is stated in the protocol that RBF is the primary variable. However, since RPF results are predominantly presented in the literature and to facilitate cross study comparisons RPF instead of RBF was treated as the primary variable, as specified in the RAP that was finalized prior to database lock.

An Analysis of Covariance (ANCOVA) was performed for change from baseline RPF and GFR over 8-24 hours of the study drug infusion. Data were log transformed before analysis. Treatment and diuretic dose stratum were the classification factors and the corresponding log-transformed baseline was the covariate in the ANCOVA model. The treatment by diuretic dose stratum interaction term was also included in the model if the number of patients in each treatment and stratum combination was ≥7. If the interaction was significant, then a comparison between the two treatments was also performed separately for each stratum. The same ANCOVA was performed for change from baseline RPF and GFR over 0-24 hours and 24-28 hours. Both the Bayesian and Frequentist approaches were implemented. In addition, the ANCOVA (frequentist approach) was performed for change from baseline RPF and GFR at individual time points (2, 4, 6, 8, 20, 22, 24, 26 and 28 hours). ANCOVA similar to that for the primary variables was performed for FF (key secondary variable). Other variables and their change from baseline were summarized using descriptive statistics and confidence intervals. Summary and inferential statistics for percent change from baseline were based on those for ratio of geometric means (geomeans) by treatment and diuretic dose stratum, as appropriate.

Upon blinded review of the data prior to database lock, several outlier values significantly above or below the concentrations at other time points for the same patient and outside of the concentration range at the same time point for other patients were identified by visual inspection of the blinded data on a per-patient basis. It was concluded that the outlier values were not caused by analytical issues. The majority of outliers came from site 3004 (20 out of 21 total outlier patients for plasma PAH measurements were from site 3004). As the outlier profiles were biologically implausible for a constant infusion of PAH and IOTH with expected steady-state concentrations, for which there was no clear explanation, a decision was made to consider the PD analyses excluding the data from site 3004 (serelaxin: N=11; placebo: N=11) as the primary analysis. However, for transparency, both analyses with and without data from site 3004 are presented as planned in the RAP.

**Study Population: Inclusion/Exclusion Criteria and Demographics**

**Inclusion criteria**

1. Written informed consent was obtained before any assessment was performed.
2. Male and female heart failure patients ≥18 years of age, with body weight <160 kg, on standard therapy including a stable (≥4 weeks) dose of furosemide 40-240 mg/day p.o. or equivalent dose of loop diuretics.
    a. Reduced systolic function (left ventricular ejection fraction ≤45% - local measurement, measured within the previous 6 months assessed by echocardiogram, multiple gated acquisition scan, CT scan, magnetic resonance imaging or ventricular angiography).
    b. Brain natriuretic peptide (BNP) ≥100 pg/mL or N-terminal pro-BNP (NT-proBNP) of ≥400 pg/mL (determined locally).

c. New York Heart Association classification of heart failure severity (NYHA) Class II or III.

d. Worsening symptoms, e.g. fatigue, dyspnea, breathlessness within 3 months.

3. Impaired renal function defined as an eGFR on admission between 30-89 mL/min/1.73 $m^2$, calculated using the simplified Modification of Diet in Renal Disease equation.

**Exclusion criteria**

1. Systolic blood pressure (SBP) <110 mmHg at the time of randomization.
2. Administration of i.v. radiographic contrast agent within 72 hours prior to randomization or acute contrast-induced nephropathy at the time of randomization.
3. Current use of non-steroidal anti-inflammatory drugs (NSAIDs).
4. Current or planned (through the completion of study drug infusion) treatment with any i.v. therapies, including vasodilators (including neseritide), positive inotropic agents, vasopressors, levosimendan or mechanical support (intra-aortic balloon pump, endotracheal intubation, mechanical ventilation, or any ventricular assist device).
5. Clinically significant hepatic impairment defined as hepatic encephalopathy of any degree or total bilirubin >50 μmol/L (3 mg/dL) or, if the patient was not on warfarin therapy, international normalized ratio > 2.0 (or prothrombin time > 2 times the upper limit of normal)
6. Other protocol-defined inclusion/exclusion criteria were applied.

**Patient disposition – n (%) of patients**

| | Serelaxin N=39 | Placebo N=48 | Total N=87 |
|---|---|---|---|
| **Patients** | | | |
| Completed | 39 (100) | 48 (100) | 87 (100) |

## Baseline Characteristics (all sites)

| | | Serelaxin Total N=39 | Placebo Total N=48 | Total Total N=87 |
|---|---|---|---|---|
| Age (years) | Mean (SD) | 69.9 (9.76) | 67.7 (9.31) | 68.7 (9.52) |
| | Median | 70.0 | 66.5 | 68.0 |
| | Range | 49, 86 | 44, 85 | 44, 86 |
| Sex – n (%) | Male | 32 (82.1) | 39 (81.3) | 71 (81.6) |
| | Female | 7 (17.9) | 9 (18.8) | 16 (18.4) |
| Race – n (%) | Caucasian | 38 (97.4) | 47 (97.9) | 85 (97.7) |
| | Black | 0 (0.0) | 1 (2.1) | 1 (1.1) |
| | Other | 1 (2.6) | 0 (0.0) | 1 (1.1) |
| Ethnicity – n (%) | Hispanic/Latino | 1 (2.6) | 2 (4.2) | 3 (3.4) |
| | Mixed ethnicity | 1 (2.6) | 0 (0.0) | 1 (1.1) |
| | Other | 37 (94.9) | 46 (95.8) | 83 (95.4) |
| Weight (kg) | Mean (SD) | 85.40 (17.082) | 86.32 (14.917) | 85.91 (15.835) |
| | Median | 84.00 | 86.50 | 85.00 |
| | Range | 49.7, 122.0 | 54.5, 117.8 | 49.7, 122.0 |
| Height (cm) | Mean (SD) | 170.5 (8.55) | 173.4 (10.15) | 172.1 (9.53) |
| | Median | 170.0 | 174.0 | 172.0 |
| | Range | 150, 188 | 150, 198 | 150, 198 |

| | | Serelaxin Total N=39 | Placebo Total N=48 | Total Total N=87 |
|---|---|---|---|---|
| Body mass index ($kg/m^2$) | Mean (SD) | 29.34 (5.356) | 28.62 (3.970) | 28.94 (4.628) |
| | Median | 29.41 | 28.07 | 28.41 |
| | Range | 20.7, 40.4 | 22.4, 41.7 | 20.7, 41.7 |
| eGFR[¥] ($mL/min/1.73m^2$) | Mean (SD) | 57.700 (16.1808) | 58.097 (16.5979) | 57.917 (16.3149) |
| | Median | 56.000 | 57.000 | 56.000 |
| | Range | 32.00, 89.00 | 33.00, 86.30 | 32.00, 89.00 |
| eGFR[*] ($mL/min/1.73m^2$) | Mean (SD) | 66.237 (25.6459) | 65.701 (19.9166) | 65.943 (22.5462) |
| | Median | 61.860 | 62.654 | 61.962 |
| | Range | 32.09, 152.70 | 33.22, 107.87 | 32.09, 152.70 |
| Brachial SBP (mmHg) | Mean (SD) | 131.5 (18.40) | 126.1 (15.28) | 128.5 (16.87) |
| Brachial DBP (mmHg) | Mean (SD) | 79.4 (9.93) | 77.8 (8.43) | 78.5 (9.11) |

Note: Weight and height were taken from Screening vital signs evaluations.

[¥] Value reported on the baseline eCRF based on local laboratory serum creatinine.

[*] Value derived from the central laboratory baseline serum creatinine.

Brachial SBP and DBP is the value measured just before study drug infusion was started.

## Baseline Characteristics (excluding site 3004)

| | | Serelaxin Total N=28 | Placebo Total N=37 | Total Total N=65 |
|---|---|---|---|---|
| Age (years) | Mean (SD) | 68.9 (10.08) | 67.1 (9.80) | 67.9 (9.89) |
| | Median | 68.5 | 66.0 | 68.0 |
| | Range | 49, 85 | 44, 85 | 44, 85 |
| Sex – n (%) | Male | 25 (89.3) | 33 (89.2) | 58 (89.2) |
| | Female | 3 (10.7) | 4 (10.8) | 7 (10.8) |
| Race – n (%) | Caucasian | 27 (96.4) | 36 (97.3) | 63 (96.9) |
| | Black | 0 (0.0) | 1 (2.7) | 1 (1.5) |
| | Other | 1 (3.6) | 0 (0.0) | 1 (1.5) |
| Ethnicity – n (%) | Hispanic/Latino | 1 (3.6) | 2 (5.4) | 3 (4.6) |
| | Mixed ethnicity | 1 (3.6) | 0 (0.0) | 1 (1.5) |
| | Other | 26 (92.9) | 35 (94.6) | 61 (93.8) |
| Weight (kg) | Mean (SD) | 88.60 (15.841) | 88.48 (14.345) | 88.53 (14.887) |
| | Median | 85.75 | 88.00 | 86.00 |
| | Range | 63.0, 122.0 | 64.0, 117.8 | 63.0, 122.0 |
| Height (cm) | Mean (SD) | 173.3 (7.19) | 176.0 (9.29) | 174.8 (8.50) |
| | Median | 172.0 | 175.0 | 174.0 |
| | Range | 160, 188 | 158, 198 | 158, 198 |

| | | Serelaxin Total N=28 | Placebo Total N=37 | Total Total N=65 |
|---|---|---|---|---|
| Body mass index ($kg/m^2$) | Mean (SD) | 29.54 (5.027) | 28.51 (3.788) | 28.95 (4.358) |
| | Median | 29.33 | 27.77 | 28.41 |
| | Range | 20.8, 39.0 | 22.7, 41.7 | 20.8, 41.7 |
| eGFR[¥] ($mL/min/1.73m^2$) | Mean (SD) | 56.796 (15.7221) | 56.738 (17.4320) | 56.763 (16.5758) |
| | Median | 56.000 | 52.900 | 55.500 |
| | Range | 33.00, 88.80 | 33.00, 86.30 | 33.00, 88.80 |
| eGFR[*] ($mL/min/1.73m^2$) | Mean (SD) | 63.861 (18.9102) | 64.956 (20.1159) | 64.484 (19.4621) |
| | Median | 63.291 | 61.795 | 62.130 |
| | Range | 32.09, 112.33 | 33.22, 107.87 | 32.09, 112.33 |

Note: Weight and height were taken from Screening vital signs evaluations.

[¥] Value reported on the baseline eCRF based on local laboratory serum creatinine.

[*] Value derived from the central laboratory baseline serum creatinine.

## Outcome Measures

## Primary Outcome Result(s)

### Statistical analysis of Renal plasma flow (RPF) (mL/min) change from baseline – PD analysis set

| | All Sites | | | | Excluding Site 3004 | | | |
|---|---|---|---|---|---|---|---|---|
| **Time Point/ Interval** | **Serelaxin LS-Geomean Ratio to Baseline (SE)** | **Placebo LS-Geomean Ratio to Baseline (SE)** | **Ratio of LS-Geomean Ratios# (95% CI)** | **P-value** | **Serelaxin LS-Geomean Ratio to Baseline (SE)** | **Placebo LS-Geomean Ratio to Baseline (SE)** | **Ratio of LS-Geomean Ratios# (95% CI)** | **P-value** |
| 0-24 hr | 1.06 (1.14) | 0.97 (1.12) | 1.10 (0.79, 1.54) | 0.5681 | 1.31 (1.05) | 1.13 (1.04) | 1.16 (1.05, 1.28) | 0.0042 |
| 8-24 hr | 1.03 (1.14) | 1.01 (1.12) | 1.02 (0.73, 1.43) | 0.8969 | 1.29 (1.05) | 1.14 (1.05) | 1.13 (1.01, 1.27) | 0.0386 |
| 24-28 hr | 1.50 (1.16) | 1.09 (1.14) | 1.38 (0.93, 2.04) | 0.1074 | 1.35 (1.05) | 1.16 (1.05) | 1.16 (1.03, 1.30) | 0.0115 |

All sites: N=39 (serelaxin); N=48 (placebo); Excluding site 3004: N=28 (serelaxin); N=37 (placebo). LS-Geomean=geometric least-squares mean.

# serelaxin to placebo

Results are from an ANCOVA model with terms for treatment, stratum, baseline, and treatment*stratum interaction. When site 3004 was excluded the treatment*stratum interaction term was not included in the model as the sample size was not large enough. Values are log-transformed prior to analysis. Baseline is the value at Time 0.

Results for the combined strata are presented. For the analysis of all sites, the treatment*stratum interaction was not statistically significant.

### Statistical analysis of GFR (mL/min) change from baseline – PD analysis set

| | All Sites | | | | Excluding Site 3004 | | | |
|---|---|---|---|---|---|---|---|---|
| **Time Point/ Interval** | **Serelaxin LS-Geomean Ratio to Baseline (SE)** | **Placebo LS-Geomean Ratio to Baseline (SE)** | **Ratio of LS-Geomean Ratios# (95% CI)** | **P-value** | **Serelaxin LS-Geomean Ratio to Baseline (SE)** | **Placebo LS-Geomean Ratio to Baseline (SE)** | **Ratio of LS-Geomean Ratios# (95% CI)** | **P-value** |
| 0-24 hrs | 1.76 (1.07) | 1.54 (1.06) | 1.14 (0.96, 1.35) | 0.1247 | 1.60 (1.04) | 1.66 (1.04) | 0.96 (0.88, 1.06) | 0.4336 |
| 8-24 hrs | 2.01 (1.08) | 1.74 (1.06) | 1.16 (0.96, 1.40) | 0.1329 | 1.78 (1.06) | 1.87 (1.05) | 0.95 (0.84, 1.07) | 0.3932 |
| 24-28 hrs | 2.35 (1.08) | 1.83 (1.07) | 1.28 (1.05, 1.57) | 0.0151 | 1.92 (1.06) | 2.13 (1.05) | 0.90 (0.79, 1.03) | 0.1371 |

All sites: N=39 (serelaxin); N=48 (placebo); Excluding site 3004: N=28 (serelaxin); N=37 (placebo)

# serelaxin to placebo

Results are from an ANCOVA model with terms for treatment, stratum, baseline, and treatment*stratum interaction. When site 3004 was excluded the treatment*stratum interaction term was not included in the model as the sample size was not large enough. Values are log-transformed prior to analysis. Baseline is the value at Time 0.

Results for the combined strata are presented.

## Secondary Outcome Result(s)

### Statistical analysis of FF (%) change from baseline – PD analysis set

| | All Sites | | | | Excluding Site 3004 | | | |
|---|---|---|---|---|---|---|---|---|
| **Time Point/ Interval** | **Serelaxin LS-Geomean Ratio to Baseline (SE)** | **Placebo LS-Geomean Ratio to Baseline (SE)** | **Ratio of LS-Geomean Ratios# (95% CI)** | **P-value** | **Serelaxin LS-Geomean Ratio to Baseline (SE)** | **Placebo LS-Geomean Ratio to Baseline (SE)** | **Ratio of LS-Geomean Ratios# (95% CI)** | **P-value** |
| 0-24 hrs | 1.64 (1.10) | 1.61 (1.08) | 1.02 (0.80, 1.30) | 0.8820 | 1.20 (1.05) | 1.44 (1.04) | 0.84 (0.76, 0.92) | 0.0004 |
| 8-24 hrs | 1.95 (1.11) | 1.75 (1.09) | 1.11 (0.85, 1.45) | 0.4370 | 1.36 (1.05) | 1.62 (1.05) | 0.84 (0.75, 0.94) | 0.0019 |
| 24-28 hrs | 1.55 (1.13) | 1.70 (1.11) | 0.91 (0.66, 1.25) | 0.5693 | 1.41 (1.06) | 1.81 (1.05) | 0.78 (0.69, 0.88) | <0.0001 |

All sites: N=39 (serelaxin); N=48 (placebo); Excluding site 3004: N=28 (serelaxin); N=37 (placebo)

# serelaxin to placebo

Results are from an ANCOVA model with terms for treatment, stratum, baseline, and treatment*stratum interaction. When site 3004 was excluded the treatment*stratum interaction term was not included in the model as the sample size was not large enough. Values are log-transformed prior to analysis. Baseline is the value at Time 0.

Results for the combined strata are presented. FF is calculated as GFR (based on plasma clearance of IOTH) divided by RPF (based on plasma clearance of PAH).

## Brachial SBP, brachial DBP and CASP (mmHg) – PD analysis set

| Time point | Serelaxin mean (SD) | Placebo mean (SD) |
|---|---|---|
| **SBP at:** | | |
| 0 h | 131.5 (18.40) | 126.1 (15.28) |
| 2 h | 120.3 (16.97) | 118.9 (16.38) |
| 4 h | 122.8 (18.38) | 121.6 (16.24) |
| 8 h | 121.1 (19.13) | 122.8 (17.53) |
| 12 h | 122.6 (12.51) | 119.4 (16.23) |
| 16 h | 108.1 (10.45) | 116.6 (14.90) |
| 20 h | 120.5 (17.77) | 120.3 (15.57) |
| 24 h | 118.4 (17.01) | 117.4 (17.68) |
| 24.5 h | 118.2 (13.34) | 117.5 (12.08) |
| 28 h | 123.4 (11.49) | 121.6 (12.69) |
| 48 h | 120.2 (14.88) | 120.1 (16.47) |
| **DBP at:** | | |
| 0 h | 79.4 (9.93) | 77.8 (8.43) |
| 2 h | 72.1 (10.64) | 73.9 (8.38) |
| 4 h | 72.1 (9.93) | 75.6 (7.92) |
| 8 h | 71.6 (7.53) | 75.8 (9.70) |
| 12 h | 78.9 (12.10) | 73.7 (8.90) |
| 16 h | 69.5 (8.50) | 72.7 (9.51) |
| 20 h | 73.4 (13.28) | 75.7 (9.32) |
| 24 h | 73.0 (12.20) | 73.6 (9.97) |
| 24.5h | 75.3 (11.81) | 76.5 (9.81) |
| 28 h | 78.9 (7.23) | 76.6 (8.70) |
| 48 h | 72.8 (8.02) | 74.9 (8.32) |
| **CASP at:** | | |
| 0 h | 121.8 (18.13) | 117.3 (14.16) |
| 2 h | 110.6 (17.05) | 111.0 (15.18) |
| 4 h | 112.5 (17.45) | 113.6 (15.73) |
| 8 h | 111.3 (18.40) | 114.0 (17.38) |
| 12 h | 117.9 (9.72) | 107.2 (11.36) |
| 16 h | 102.2 (7.12) | 106.2 (12.42) |
| 20 h | 111.1 (17.03) | 112.4 (15.52) |
| 24 h | 109.1 (17.45) | 109.5 (16.72) |
| 24.5 h | 110.8 (13.46) | 111.2 (11.44) |
| 28 h | 114.6 (13.44) | 112.9 (12.87) |
| 48 h | 110.4 (14.53) | 110.9 (15.77) |

## Radial augmentation index

| | RLX030<br>RLX030 as intravenous infusion for 24 hours. | | Placebo<br>Placebo as intravenous infusion for 24 hours. | |
|---|---|---|---|---|
| Number of Participants Analyzed: | 39 | | 48 | |
| **Radial augmentation index<br>Units: Percent** | **Mean** | **Standard Deviation** | **Mean** | **Standard Deviation** |
| 0 hour (n=36, 45) | 92.0 | 25.46 | 93.3 | 27.46 |
| 24 hours post dose (n=37,42) | 99.8 | 48.86 | 90.3 | 25.40 |

## Fractional sodium clearance (natriuresis)

| | RLX030<br>RLX030 as intravenous infusion for 24 hours. | | Placebo<br>Placebo as intravenous infusion for 24 hours. | |
|---|---|---|---|---|
| Number of Participants Analyzed: | 39 | | 48 | |
| **Fractional sodium clearance (natriuresis)<br>Units: Percent** | **Median** | **IQR** | **Median** | **IQR** |
| -3-0 hours (n=36,42) | 0.98 | 0.49, 1.76 | 0.60 | 0.37, 1.00 |
| 0-24 hours (n=35,37) | 1.42 | 1.05, 2.09 | 1.75 | 1.30, 2.27 |
| 8-24 hours (n=36,41) | 1.14 | 0.92, 1.80 | 1.69 | 1.27, 2.18 |
| 24-28 hours (n=34,43) | 1.12 | 0.71, 1.54 | 1.47 | 1.01, 2.36 |

## Calculated creatinine clearance

| | RLX030<br>RLX030 as intravenous infusion for 24 hours. | | Placebo<br>Placebo as intravenous infusion for 24 hours. | |
|---|---|---|---|---|
| Number of Participants Analyzed: | 39 | | 48 | |
| **Calculated creatinine clearance<br>Units: mL/min** | **Median** | **IQR** | **Median** | **IQR** |
| -3-0 hours (n=36,42) | 80.54 | 50.66, 111.59 | 92.50 | 69.25, 123.46 |
| 0-24 hours (n=35,37) | 79.23 | 56.02, 96.52 | 83.72 | 69.80, 110.39 |
| 8-24 hours (n=36,41) | 77.81 | 55.83, 100.07 | 78.09 | 64.69, 106.65 |
| 24-28 hours (n=34,43) | 92.06 | 60.64, 126.04 | 81.06 | 59.41, 132.49 |

**Diuresis (Urinary flow rate)**

| | RLX030<br>RLX030 as intravenous infusion for 24 hours. | | Placebo<br>Placebo as intravenous infusion for 24 hours. | |
|---|---|---|---|---|
| Number of Participants Analyzed: | 39 | | 48 | |
| **Change over time in Diuresis<br>Units: mL/hr** | **Geometric Mean** | **95% CI** | **Geometric Mean** | **95% CI** |
| -3-0 hours (n=37,45) | 75.49 | 58.05, 98.17 | 67.49 | 54.03, 84.30 |
| 0-24 hours (n=37,41) | 110.55 | 98.05, 124.63 | 136.78 | 121.68, 153.76 |
| 8-24 hours (n=38,42) | 93.04 | 81.05, 106.81 | 125.41 | 112.87, 139.34 |
| 24-28 hours (n=36,45) | 105.28 | 86.78, 127.72 | 125.97 | 104.54, 151.78 |

## Safety Results

| | Serelaxin<br>N=39<br>n (%) | Placebo<br>N=48<br>n (%) | Total<br>N=87<br>n (%) |
|---|---|---|---|
| **Patients with AE(s)** | **8 (20.5)** | **12 (25.0)** | **20 (23.0)** |
| SOC: | | | |
| Vascular disorders | 4 (10.3) | 1 (2.1) | 5 (5.7) |
| General disorders and administration site conditions | 0 (0.0) | 4 (8.3) | 4 (4.6) |
| Gastrointestinal disorders | 0 (0.0) | 3 (6.3) | 3 (3.4) |
| Investigations | 1 (2.6) | 2 (4.2) | 3 (3.4) |
| Blood and lymphatic system disorders | 1 (2.6) | 0 (0.0) | 1 (1.1) |
| Cardiac disorders | 1 (2.6) | 0 (0.0) | 1 (1.1) |
| Infections and infestations | 0 (0.0) | 1 (2.1) | 1 (1.1) |
| Injury, poisoning and procedural complications | 0 (0.0) | 1 (2.1) | 1 (1.1) |
| Metabolism and nutrition disorders | 1 (2.6) | 0 (0.0) | 1 (1.1) |
| Nervous system disorders | 0 (0.0) | 1 (2.1) | 1 (1.1) |
| Respiratory, thoracic and mediastinal disorders | 0 (0.0) | 1 (2.1) | 1 (1.1) |

N=number of patients studied; n=number of patients with at least one treatment-emergent AE in the category.

AEs by SOC are presented in descending order of frequency in the Total column.

## Incidence of AEs by preferred term – safety analysis set

| | Serelaxin N=39 n (%) | Placebo N=48 n (%) | Total N=87 n (%) |
|---|---|---|---|
| **Patients with AE(s)** | **8 (20.5)** | **12 (25.0)** | **20 (23.0)** |
| Preferred term: | | | |
| Nausea | 0 (0.0) | 3 (6.3) | 3 (3.4) |
| Hypotension | 1 (2.6) | 1 (2.1) | 2 (2.3) |
| Infusion site edema | 0 (0.0) | 2 (4.2) | 2 (2.3) |
| Anemia | 1 (2.6) | 0 (0.0) | 1 (1.1) |
| Blood creatinine increased | 0 (0.0) | 1 (2.1) | 1 (1.1) |
| Blood glucose increased | 0 (0.0) | 1 (2.1) | 1 (1.1) |
| Blood pressure decreased | 1 (2.6) | 0 (0.0) | 1 (1.1) |
| Bradycardia | 1 (2.6) | 0 (0.0) | 1 (1.1) |
| Extravasation | 0 (0.0) | 1 (2.1) | 1 (1.1) |
| Flushing | 1 (2.6) | 0 (0.0) | 1 (1.1) |
| Hydrothorax | 0 (0.0) | 1 (2.1) | 1 (1.1) |
| Hyperemia | 1 (2.6) | 0 (0.0) | 1 (1.1) |
| Hyperkalemia | 1 (2.6) | 0 (0.0) | 1 (1.1) |
| Infusion related reaction | 0 (0.0) | 1 (2.1) | 1 (1.1) |
| Infusion site cellulitis | 0 (0.0) | 1 (2.1) | 1 (1.1) |
| Infusion site erythema | 0 (0.0) | 1 (2.1) | 1 (1.1) |
| Ischemic stroke | 0 (0.0) | 1 (2.1) | 1 (1.1) |
| Thrombophlebitis | 1 (2.6) | 0 (0.0) | 1 (1.1) |
| Vomiting | 0 (0.0) | 1 (2.1) | 1 (1.1) |

## Summary of SAEs during the study - safety analysis set

| Study Day | Preferred Term | Severity | Relationship To Study Drug | Action Taken |
|---|---|---|---|---|
| **Serelaxin Group** | | | | |
| 2 | Flushing* | Moderate | Not suspected | Hospitalization |
| **Placebo Group** | | | | |
| 2 | Nausea† | Moderate | Suspected | Study drug permanently discontinued, non-drug therapy given, hospitalization |
| 2 | Hypotension† | Moderate | Suspected | Study drug permanently discontinued, non-drug therapy given, hospitalization |
| 2 | Hydrothorax | Mild | Not suspected | Hospitalization |
| 10 | Ischemic stroke | Severe | Not suspected | Hospitalization |

* The patient received an inadvertent bolus of IOTH and PAH after completing the serelaxin infusion. The investigator reported that the inadvertent bolus was a possible contributory factor to the event.
† SAEs of nausea and hypotension occurred in the same patient

Due to the nature of the study population and the many patients with atrial fibrillation, ventricular pacing and left bundle branch block, only a limited number of patients was available for analysis.

**Summary of treatment-emergent notable Holter ECG QTcF values - safety analysis set**

| | Serelaxin N=8 n (%) | Placebo N=12 n (%) |
|---|---|---|
| Decrease from baseline: | | |
| > 30 ms | 1 (12.5) | 1 (8.3) |
| > 60 ms | 0 | 1 (8.3) |
| Increase from baseline | | |
| > 30 ms | 2 (25.0) | 1 (8.3) |
| > 60 ms | 0 | 0 |
| Post-baseline value: | | |
| > 450 ms | 5 (62.5) | 8 (66.7) |
| > 480 ms | 2 (25.0) | 2 (16.7) |
| > 500 ms | 0 | 1 (8.3) |

n (%)=number (percentage) of patients.

**Summary statistics of PK parameters – PK analysis set**

**Combined strata**

| Statistic | Actual delivered dose rate (µg/kg/day) | AUClast / dose (h.ng/mL) /(µg/kg) | C24h /(dose rate) (ng/mL)/ (µg/kg/day) | AUClast (h.ng/mL) | C24h (ng/mL) | CL (mL/h/kg) |
|---|---|---|---|---|---|---|
| n | 38 | 36 | 36 | 36 | 36 | 36 |
| Mean (SD) | 36.4 (3.45) | 12.9 (4.03) | 0.453 (0.134) | 474 (144) | 16.6 (4.77) | 104 (56.3) |
| CV% mean | 9.5 | 31.2 | 29.6 | 30.5 | 28.7 | 53.9 |
| Geomean | 36.2 | 12.3 | 0.430 | 454 | 15.9 | 96.9 |
| CV% geomean | 12.8 | 31.2 | 36.2 | 30.1 | 35.1 | 36.2 |
| Median | 36.9 | 11.8 | 0.431 | 433 | 15.5 | 96.6 |
| Range | 17.4, 41.4 | 6.20, 21.9 | 0.103, 0.729 | 237, 823 | 3.96, 27.5 | 57.1, 403 |

Note: Patients 3001003 and 2003002 are not included in the summary statistics due to short infusion duration (3001003) and dose reduction (2003002).

Actual delivered dose rate = (weight-adjusted volume of drug (mL) *Serelaxin stock solution concentration (µg/mL) *infusion flow rate (mL/hr) * 24 hr) / (275.9 + weight-adjusted volume of drug)(mL) / baseline body weight (kg)).

CV% = Coefficient of variation (%) = SD/mean*100. CV% geo mean = sqrt(exp(variance for log-transformed data)-1) * 100.

**Other Relevant Findings**

None

**Date of Clinical Trial Report**

7 May 2013

**Date Inclusion on Novartis Clinical Trial Results Database**

20 December 2013

**Date of Latest Update**