Sponsor

Novartis

Generic Drug Name

Serelaxin

Therapeutic Area of Trial

Acute Heart Failure (AHF)

Approved Indication

Investigational

Protocol Number

CRLX030A2201

Title

A multicenter, double blind, randomized, parallel group, placebo-controlled study to evaluate the hemodynamic responses to intravenous RLX030 infusion in subjects with acute heart failure

Study Phase

Phase II

Study Start/End Dates

05 Mar 2012 to 18 Jan 2013

Study Design/Methodology

This was a multi-center, randomized, double-blind, parallel-group, placebo-controlled study in patients with AHF. The duration of constant infusion with serelaxin at a dose rate of 30

μg/kg/day or placebo was 20 hours following an initial period of stabilization after admission. Patients were randomized 1:1 to serelaxin, or matching placebo.

Centers

17 centers in 6 countries: Argentina (2), Germany (5), Italy (1), Poland (2), Russia (6), The Netherlands (1)

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

Serelaxin, 30 μg/kg/day, or matching placebo as an i.v. infusion for 20 hours

Statistical Methods

An Analysis of Covariance (ANCOVA) was performed for peak change from baseline in PCWP and CI over 8 hours of infusion. Both the Bayesian and Frequentist's approaches were implemented. The time weighted average change from baseline (AUEC/time-baseline, 0-8 hr, 8-20 hr, 0-20 hr, 20-24 hr) and change from baseline in PCWP/CI for each scheduled time point (30 min, 2 hr, 4 hr, 6 hr, 8 hr, 12 hr, 16 hr, 20 hr, 20.5 hr, 21 hr, 22 hr, 24 hr) were also analyzed using the ANCOVA model described above (Frequentist's approach). ANCOVA similar to that for the primary variables was performed for the secondary hemodynamic and PD variables. 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, as appropriate.

Study Population: Inclusion/Exclusion Criteria and Demographics

Key Inclusion Criteria:

- Male or female patients ≥18 years of age, with body weight <160 kg who had been admitted to hospital with AHF or in the opinion of the investigator required admission to hospital for management of AHF. AHF was defined as new onset or worsening of signs and symptoms of heart failure requiring urgent therapy (e.g. dyspnea at rest or on minimal exertion, and pulmonary congestion at the time of presentation).
- All patients were to be stabilized on furosemide 40-120 mg/day i.v. (or equivalent) at the time of randomization and per investigator not requiring any i.v. vasodilator or a change in diuretic dose 4 hours before and up to 8 hours after randomization.
- Patients were required to have a mean PCWP ≥18 mmHg and a Swan-Ganz catheter in place at least 1 hour before randomization,

- Systolic blood pressure (SBP) ≥115 mmHg,
- Estimated glomerular filtration rate (eGFR) ≥30 ml/min 1.73m2,

Key Exclusion Criteria:

- No current or planned i.v. therapies (inotropes, vasopressors, levosimendan, nesiritide or analogues), mechanical support, ultrafiltration, hemofiltration or dialysis;
- No i.v. radiographic contrast agent within 72 hours before screening or acute contrast-induced nephropathy;
- No significant dyspnea of non-cardiac origin;
- No non-cardiac pulmonary edema;
- No known significant valvular disease as specified;
- No clinical diagnosis of acute coronary syndrome within 45 days before screening;
- No AHF due to significant arrhythmias as specified and
- No acute myocarditis, hypertrophic obstructive, restrictive or constrictive cardiomyopathy.

Other protocol-defined inclusion/exclusion criteria applied.

Participant Flow

Out of a total of 120 patients screened, 71 patients were randomized.

Patient disposition – n (%) of patients (Safety Analysis Set)

	RLX030 30 µg/kg/day N=34 n (%)	Placebo N=37 n (%)	Total N=71 n (%)
Number of Patients			
Completed	27 (79.4)	34 (91.9)	61 (85.9)
Discontinued	7 (20.6)	3 (8.1)	10 (14.1)
Main cause of discontinuation			
Protocol deviation	0 (0)	1 (2.7)	1 (1.4)
Death	2 (5.9)	2 (5.4)	4 (5.6)
Administrative problems	1 (2.9)	0 (0)	1 (1.4)
Lost to follow-up	1 (2.9)	0 (0)	1 (1.4)
Patient withdrew consent	3 (8.8)	0 (0)	3 (4.2)

Baseline Characteristics

Demographic and baseline characteristics summary by treatment group – Safety analysis set

Demographic Variable	RLX030 30 µg/kg/day N=34	Placebo N=37	Total N=71
Age (years)			
mean (SD)	66.6 (11.15)	70.4 (12.41)	68.6 (11.89)
median (min-max)	68.0 (38-86)	74.0 (22-87)	70.0 (22-87)
*Height (cm)			
mean (SD)	169.9 (7.80)	168.3 (9.39)	169.1 (8.64)
median (min-max)	169.5 (155-188)	170.0 (147-187)	170.0 (147-188)
*Weight (kg)			
mean (SD)	89.16 (20.215)	85.95 (21.123)	87.49 (20.608)
median	84.65 (64.0-158.4)	82.00 (58.6-159.0)	83.40 (58.6-159.0)
Sex; n (%)			
Male	27 (79.4)	26 (70.3)	53 (74.6)
Female	7 (20.6)	11 (29.7)	18 (25.4)
Predominant Race; n (%)			
Caucasian	34 (100)	37 (100)	71 (100)
Ethnicity; n (%)			
Hispanic/Latino	2 (5.9)	2 (5.4)	4 (5.6)
Mixed ethnicity	2 (5.9)	0	2 (2.8)
Other	30 (88.2)	35 (94.6)	65 (91.5)
Body Mass Index (kg/m^2)			
mean (SD)	31.06 (7.562)	30.59 (9.012)	30.81 (8.293)
median (min-max)	28.63 (22.2-53.5)	29.79 (18.1-71.6)	29.31 (18.1-71.6)
eGFR (mL/min/1.73 m^2)			
mean (SD)	71.73 (23.657)	67.76 (24.076)	69.67 (23.789)
median (min-max)	68.91 (30.7-115.2)	64.88 (31.6-130.9)	66.79 (30.7-130.9)
Baseline mean SBP (SD) (mmHg)	131.1 (14.69)	131.6 (17.09)	131.3 (15.89)
Baseline mean DBP (SD) (mmHg)	84.3 (10.74)	84.3 (13.03)	84.3 (11.92)

* Weight and height are taken from Screening vital signs evaluations.

(BMI) [kg/m^2] = weight[kg] /(height[m]**2);eGFR (mL/min/1.73 m2) = 175 × (SerumCr)^(-1.154) × (Age)^-(0.203) × (0.742 if female) × (1.212 if African American).

Outcome Measures

Primary Outcome Results

- **Pulmonary Capillary Wedge Pressure (PCWP**
- **Cardiac Index (CI)**

Statistical analysis of PCWP (mmHg) – Pharmacodynamic-analysis set

	RLX030 30 µg/kg/day LS Mean (SE) (mmHg) (N=32)	Placebo LSMean (SE) (mmHg) (N=31)	Difference (mmHg) [95% CI]	P value
Change from baseline in peak PCWP over 8 hours	-6.69 (0.59)	-4.25 (0.60)	-2.44 [-4.10, -0.78]	0.0040
Time weighted average change from baseline in PCWP				
0-8 hours based on AUEC0-8h	-3.79 (0.50)	-1.08 (0.51)	-2.70 [-4.10, -1.31]	0.0001
8-20 hours based on AUEC8-20h	-4.90 (0.73)	-2.67 (0.74)	-2.24 [-4.28, -0.19]	0.0322
0-20 hours based on AUEC0-20h	-4.46 (0.59)	-2.04 (0.60)	-2.42 [-4.08, -0.76]	0.0042
20-24 hours based on AUEC20-24h	-4.41 (0.83)	-3.11 (0.85)	-1.30 [-3.63, 1.03]	0.2733
Change from baseline in PCWP				
at 0.5 hours	-2.17 (0.50)	-1.15 (0.51)	-1.01 [-2.41, 0.39]	0.1564
at 2 hours	-4.02 (0.60)	-1.62 (0.60)	-2.40 [-4.06, -0.73]	0.0048
at 4 hours	-4.36 (0.75)	-0.43 (0.74)	-3.93 [-6.00, -1.86]	0.0002
at 6 hours	-3.84 (0.70)	-1.23 (0.71)	-2.61 [-4.57, -0.65]	0.0092
at 8 hours	-5.03 (0.78)	-1.50 (0.80)	-3.53 [-5.72, -1.35]	0.0015
at 20 hours	-4.98 (0.89)	-4.09 (0.90)	-0.89 [-3.38, 1.59]	0.4815
at 21 hours	-5.08 (0.84)	-3.22 (0.85)	-1.86 [-4.21, 0.49]	0.1210
at 22 hours	-4.54 (0.91)	-2.70 (0.89)	-1.85 [-4.34, 0.65]	0.1471
at 24 hours	-3.74 (1.07)	-3.41 (1.06)	-0.33 [-3.28, 2.62]	0.8260

Results are from an ANCOVA model with treatment as the classification factor and baseline as a covariate

PCWP = pulmonary capillary wedge pressure. AUEC = area under the effect curve.

Statistical analysis of CI (L/min/m^2) – Pharmacodynamic (PD)-analysis set

	RLX030 30 µg/kg/day LSmean (SE) (L/min/m^2) (N=32)	Placebo LSmean (SE) (L/min/m^2) (N=31)	Difference [95% CI]	P value
Change from baseline in peak CI over 8 hours	0.32 (0.05)	0.30 (0.05)	0.02 [-0.13, 0.16]	0.7936
Time weighted average change from baseline in CI				
0-8 hours based on AUEC0-8h	0.12 (0.04)	0.07 (0.04)	0.04 [-0.07, 0.15]	0.4754
8-20 hours based on AUEC8-20h	0.05 (0.05)	0.07 (0.05)	-0.02 [-0.15, 0.12]	0.8001
0-20 hours based on AUEC0-20h	0.08 (0.04)	0.07 (0.04)	0.01 [-0.11, 0.12]	0.9213
20-24 hours based on AUEC20-24h	0.08 (0.05)	0.03 (0.05)	0.05 [-0.09, 0.20]	0.4621
Change from baseline in CI				
at 0.5 hours	0.15 (0.04)	0.06 (0.04)	0.09 [-0.02, 0.20]	0.1012
at 2 hours	0.14 (0.05)	0.10 (0.05)	0.04 [-0.08, 0.17]	0.5021
at 4 hours	0.13 (0.06)	0.06 (0.05)	0.07 [-0.08, 0.23]	0.3386
at 6 hours	0.09 (0.06)	0.08 (0.06)	0.01 [-0.17, 0.18]	0.9346
at 8 hours	0.03 (0.05)	0.07 (0.05)	-0.04 [-0.18, 0.10]	0.5991
at 20 hours	0.09 (0.06)	0.09 (0.06)	0.00 [-0.15, 0.16]	0.9717
at 21 hours	0.10 (0.07)	0.02 (0.07)	0.08 [-0.10, 0.26]	0.3958
at 22 hours	0.09 (0.06)	0.03 (0.06)	0.06 [-0.10, 0.23]	0.4381
at 24 hours	0.08 (0.06)	0.03 (0.06)	0.05 [-0.11, 0.22]	0.5375

Results are from an ANCOVA model with treatment as the classification factor and baseline as a covariate

CI = Cardiac index. AUEC = area under the effect curve.

Secondary Outcome Results

- **Cardiac Output (CO)**
- **Systemic vascular resistance (SVR)**
- **Right atrial pressure (RAP)**
- **Pulmonary arterial pressure (PAP) – mean PAP**
- **Pulmonary vascular resistance (PVR)**
- **Oxygen saturation**
- **Central Aortic Systolic Pressure (CASP), Brachial Blood Pressure (BP), and radial Augmentation Index (rAI)**

Statistical analysis of CO (L/min) - PD-analysis set

Parameter (unit)	RLX030 30 µg/kg/day LSMean (SE) (L/min) (N=32)	Placebo LSMean (SE) (L/min) (N=31)	Difference [95% CI]	P Value
Change from baseline in peak CO over 8 hours	0.62 (0.11)	0.59 (0.11)	0.04 [-0.26, 0.33]	0.8105
Time weighted average change from baseline in CO				
0-8 hours based on AUEC0-8h	0.23 (0.08)	0.15 (0.08)	0.07 [-0.15, 0.30]	0.5178
8-20 hours based on AUEC8-20h	0.10 (0.10)	0.15 (0.10)	-0.05 [-0.32, 0.22]	0.7177
0-20 hours based on AUEC0-20h	0.15 (0.08)	0.15 (0.08)	0.00 [-0.24, 0.24]	0.9989
20-24 hours based on AUEC20-24h	0.16 (0.10)	0.06 (0.10)	0.09 [-0.19, 0.37]	0.5136
Change from baseline in CO				
at 0.5 hours	0.29 (0.08)	0.11 (0.08)	0.18 [-0.04, 0.39]	0.1025
at 2 hours	0.30 (0.09)	0.19 (0.09)	0.11 [-0.13, 0.36]	0.3683
at 4 hours	0.26 (0.11)	0.12 (0.11)	0.13 [-0.17, 0.43]	0.3850
at 6 hours	0.17 (0.13)	0.19 (0.13)	-0.02 [-0.37, 0.33]	0.9282
at 8 hours	0.05 (0.10)	0.15 (0.10)	-0.10 [-0.38, 0.18]	0.4926
at 20 hours	0.18 (0.11)	0.17 (0.11)	0.00 [-0.31, 0.31]	0.9887
at 21 hours	0.20 (0.13)	0.04 (0.13)	0.16 [-0.20, 0.52]	0.3879
at 22 hours	0.18 (0.12)	0.07 (0.11)	0.11 [-0.21, 0.42]	0.5154
at 24 hours	0.15 (0.12)	0.08 (0.12)	0.08 [-0.25, 0.41]	0.6540

CO = Cardiac output. AUEC = area under the effect curve.

Results are from an ANCOVA model with treatment as the classification factor and baseline as a covariate.

Statistical analysis of SVR (dynes*sec/cm^5) - PD-analysis set

Parameter (unit)	RLX030 30 µg/kg/day LSMean (SE) (dynes*sec/cm^5) (N=32)	Placebo LSMean (SE) (dynes*sec/cm^5) (N=31)	Difference [95% CI]	P Value
Change from baseline in peak SVR over 8 hours	-368.06 (45.92)	-284.62 (45.92)	-83.44 [-211.72, 44.85]	0.2024
Time weighted average change from baseline in SVR				
0-8 hours based on AUEC0-8h	-166.15 (44.73)	-29.24 (44.73)	-136.91 [-261.89, -11.93]	0.0318
8-20 hours based on AUEC8-20h	-158.82 (57.04)	-27.20 (57.04)	-131.62 [-291.00, 27.76]	0.1055
0-20 hours based on AUEC0-20h	-161.75 (48.44)	--28.02 (48.44)	-133.74 [-269.09, 1.62]	0.0528
20-24 hours based on AUEC20-24h	-181.94 (67.36)	70.01 (67.36)	-251.95 [-440.15, -63.75]	0.0087
Change from baseline in SVR				
at 0.5 hours	-181.20 (50.80)	-53.50 (49.91)	-127.70 [-267.81, 12.40]	0.0740
at 2 hours	-217.23 (51.63)	-118.84 (50.77)	-98.39 [-241.44, 44.65]	0.1776
at 4 hours	-162.65 (59.04)	56.01 (57.07)	-218.66 [-380.73, -56.60]	0.0082
at 6 hours	-170.63 (69.10)	-19.08 (67.96)	-151.55 [-342.63, 39.54]	0.1201
at 8 hours	-144.37 (57.97)	-66.41 (57.97)	-77.96 [-240.01, 84.08]	0.3457
at 20 hours	-187.52 (74.29)	6.73 (74.29)	-194.25 [-401.42, 12.92]	0.0661
at 21 hours	-190.52 (56.71)	-19.14 (56.71)	-171.38 [-329.15, -13.60]	0.0333
at 22 hours	-232.07 (93.81)	114.22 (92.21)	-346.28 [-605.86, -86.70]	0.0089
at 24 hours	-178.42 (68.11)	60.70 (65.86)	-239.12 [-425.67, -52.58]	0.0120

SVR (Systemic vascular resistance) = [80 * (MAP – Mean RAP)]/CO. AUEC = area under the effect curve.

Results are from an ANCOVA model with treatment as the classification factor and baseline as a covariate

Summary statistics of RAP- PD analysis set

Parameter (unit)	Parameter	RLX030 30 ug/kg/day (N=32)	Placebo (N=31)
Change from baseline in peak RAP over 8 hours (mmHg)	LSMeans (SE)	-3.24 (0.36)	-2.07 (0.36)
	Difference vs. Placebo	-1.16	
	95% CI	[-2.16, -0.17]	
	p-value	0.0216	
Time weighted average change from baseline over 0-8 hours based on AUEC0-8h (mmHg)	LSMeans (SE)	-1.12 (0.36)	-0.23 (0.36)
	Difference vs. Placebo	-0.89	
	95% CI	[-1.89, 0.12]	
	p-value	0.0838	
Time weighted average change from baseline over 0-20 hours based on AUEC0-20h (mmHg)	LSMeans (SE)	-1.12 (0.45)	-0.47 (0.45)
	Difference vs. Placebo	-0.65	
	95% CI	[-1.89, 0.59]	
	p-value	0.3053	

RAP = Right atrial pressure. AUEC = area under the effect curve. Results are from an ANCOVA model with treatment as the classification factor and baseline as a covariate. Baseline is the mean of the last 3 pre-dose values

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Statistical analysis of Mean PAP (mmHg) - PD-analysis set.

Parameter (unit)	RLX030 30 µg/kg/day LSMean (SE) (mmHg) (N=32)	Placebo LSMean (SE) (mmHg) (N=31)	Difference [95% CI]	P Value
Change from baseline in peak mean PAP over 8 hours	-7.56 (0.72)	-3.63 (0.74)	-3.93 [-5.96, -1.90]	0.0001
Time weighted average change from baseline in mean PAP				
0-8 hours based on AUEC0-8h	-3.98 (0.65)	0.06 (0.66)	-4.04 [-5.86, -2.22]	<0.0001
8-20 hours based on AUEC8-20h	-4.56 (0.88)	-0.80 (0.89)	-3.76 [-6.22, -1.29]	0.0028
0-20 hours based on AUEC0-20h	-4.32 (0.72)	-0.45 (0.73)	-3.87 [-5.89, -1.86]	0.0002
20-24 hours based on AUEC20-24h	-4.29 (0.96)	-1.67 (0.98)	-2.62 [-5.31, 0.07]	0.0561
Change from baseline in mean PAP				
at 0.5 hours	-2.51 (0.79)	0.50 (0.79)	-3.01 [-5.20, -0.81]	0.0072
at 2 hours	-5.58 (0.75)	-0.56 (0.76)	-5.02 [-7.13, -2.92]	<0.0001
at 4 hours	-4.59 (0.84)	0.58 (0.83)	-5.17 [-7.49, -2.86]	<0.0001
at 6 hours	-2.97 (0.89)	-0.28 (0.91)	-2.69 [-5.18, -0.19]	0.0349
at 8 hours	-4.76 (0.98)	0.40 (1.00)	-5.16 [-7.92, -2.41]	0.0002
at 20 hours	-4.38 (1.03)	-2.00 (1.03)	-2.38 [-5.23, 0.47]	0.1021
at 21 hours	-4.84 (1.17)	-1.24 (1.19)	-3.60 [-6.89, -0.31]	0.0317
at 22 hours	-4.51 (1.05)	-1.68 (1.03)	-2.83 [-5.71, 0.05]	0.0543
at 24 hours	-3.42 (1.18)	-1.87 (1.16)	-1.55 [-4.80, 1.70]	0.3485

PAP = Pulmonary arterial pressure. AUEC = area under the effect curve.

Results are from an ANCOVA model with treatment as the classification and baseline as a covariate

Statistical analysis of PVR (dynes*sec/cm^5)- PD-analysis set.

Parameter (unit)	RLX030 30 µg/kg/day LSMean (SE) (dynes*sec/cm$^{5)}$ (N=32)	Placebo LSMean (SE) (dynes*sec/cm^5) (N=31)	Difference [95% CI]	P Value
Change from baseline in peak PVR over 8 hours	-77.73 (10.01)	-52.69 (10.01)	-25.04 [-52.86, 2.78]	0.0777
Time weighted average change from baseline in PVR				
0-8 hours based on AUEC0-8h	-20.30 (9.91)	18.69 (9.91)	-38.99 [-66.53, -11.44]	0.0055
8-20 hours based on AUEC8-20h	-12.27 (12.28)	30.45 (12.28)	-42.73 [-76.85, -8.60]	0.0141
0-20 hours based on AUEC0-20h	-15.48 (10.08)	25.75 (10.08)	-41.23 [-69.25, -13.21]	0.0039
20-24 hours based on AUEC20-24h	-10.15 (16.20)	30.14 (16.20)	-40.28 [-85.31, 4.74]	0.0795
Change from baseline in PVR				
at 0.5 hours	-23.81 (15.45)	27.83 (14.92)	-51.64 [-93.83, -9.46]	0.0164
at 2 hours	-49.75 (11.31)	6.46 (11.31)	-56.22 [-87.64, -24.80]	0.0005
at 4 hours	-26.07 (15.62)	24.16 (15.36)	-50.23 [-93.27, -7.19]	0.0222
at 6 hours	4.99 (15.84)	15.91 (15.84)	-10.93 [-54.96, 33.10]	0.6266
at 8 hours	-10.64 (14.98)	27.68 (15.23)	-38.33 [-80.35, 3.69]	0.0738
at 20 hours	-14.41 (17.82)	29.97 (17.82)	-44.37 [-93.94, 5.19]	0.0793
at 21 hours	-0.31 (21.97)	33.65 (21.97)	-33.96 [-95.08, 27.16]	0.2762
at 22 hours	-14.40 (17.86)	20.70 (17.57)	-35.10 [-84.33, 14.12]	0.1622
at 24 hours	-8.80 (17.80)	40.51 (17.51)	-49.32 [-98.37, -0.26]	0.0488

PVR (Pulmonary vascular resistance) = [80 * (Mean PAP - PCWP)] / CO. AUEC = area under the effect curve.
Results are from an ANCOVA model with treatment as the classification factor and baseline as a covariate.

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Summary statistics of SvO2 - PD analysis set

Parameter (unit)	Parameter	RLX030 30 ug/kg/day (N=32)	Placebo (N=31)
Change from baseline in peak SvO2 over 8 hours (%)	LSMeans (SE)	5.10 (1.05)	3.22 (1.03)
	Difference vs. Placebo	1.88	
	95% CI	[-1.05, 4.80]	
	p-value	0.2081	
Time weighted average change from baseline over 0-8 hours based on AUEC0-8h (%)	LSMeans (SE)	0.36 (0.99)	-1.68 (0.99)
	Difference vs. Placebo	2.05	
	95% CI	[-0.72, 4.81]	
	p-value	0.1474	
Time weighted average change from baseline over 0-20 hours based on AUEC0-20h (%)	LSMeans (SE)	0.13 (1.06)	-1.00 (1.06)
	Difference vs. Placebo	1.13	
	95% CI	[-1.86, 4.11]	
	p-value	0.4601	
Time weighted average change from baseline over 20-24 hours based on AUEC20-24h (%)	LSMeans (SE)	0.02 (1.33)	-0.45 (1.33)
	Difference vs. Placebo	0.46	
	95% CI	[-3.27, 4.20]	
	p-value	0.8085	

SvO2 = Mixed venous oxygen saturation. AUEC = area under the effect curve.
Results are from an ANCOVA model with treatment as the classification factor and baseline as a covariate.
Baseline is the mean of the last 3 pre-dose values.

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Summary statistics of SaO2 - PD analysis set

Parameter (unit)	Parameter	RLX030 30 ug/kg/day (N=32)	Placebo (N=31)
Change from baseline in peak SaO2 over 8 hours (%)	LSMeans (SE)	1.70 (0.24)	1.90 (0.24)
	Difference vs. Placebo	-0.20	
	95% CI	[-0.86, 0.45]	
	p-value	0.5413	
Time weighted average change from baseline over 0-8 hours based on AUEC0-8h (%)	LSMeans (SE)	-0.26 (0.24)	0.26 (0.24)
	Difference vs. Placebo	-0.53	
	95% CI	[-1.20, 0.15]	
	p-value	0.1273	
Time weighted average change from baseline over 0-20 hours based on AUEC0-20h (%)	LSMeans (SE)	0.06 (0.26)	0.45 (0.26)
	Difference vs. Placebo	-0.39	
	95% CI	[-1.11, 0.33]	
	p-value	0.2842	
Time weighted average change from baseline over 20-24 hours based on AUEC20-24h (%)	LSMeans (SE)	0.13 (0.27)	0.83 (0.27)
	Difference vs. Placebo	-0.70	
	95% CI	[-1.45, 0.05]	
	p-value	0.0658	

SaO2 = Peripheral arterial oxygen saturation. AUEC = area under the effect curve. Results are from an ANCOVA model with treatment as the classification factor and baseline as a covariate. Baseline is the mean of the last 3 pre-dose values.

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Statistical Analysis of change from baseline in CASP - Safety analysis set

Timepoint	RLX030 30 ug/kg/day LSMeans(SE)	Placebo LSMeans(SE)	RLX030 versus placebo in change from baseline		
			Difference	95% CI	p-value
Change from baseline in CASP (mmHg) at:					
0.5 hr	-1.91(1.821)	1.39(1.821)	-3.30	(-8.45, 1.85)	0.2054
2 hr	-9.33(1.668)	-2.28(1.576)	-7.05	(-11.63, -2.47)	0.0031
4 hr	-6.09(2.115)	-1.62(2.025)	-4.47	(-10.31, 1.38)	0.1320
6 hr	-6.30(2.008)	-1.27(1.896)	-5.04	(-10.55, 0.48)	0.0727
8 hr	-6.70(2.234)	-1.68(2.139)	-5.02	(-11.19, 1.16)	0.1096
12 hr	-9.37(2.433)	-3.94(1.733)	-5.43	(-14.20, 3.35)	0.1728
20 hr	-7.77(2.460)	-1.54(2.288)	-6.23	(-12.94, 0.48)	0.0682
21 hr	-10.68(1.989)	-3.45(1.875)	-7.23	(-12.69, -1.77)	0.0102
22 hr	-9.81(2.642)	-2.13(2.491)	-7.68	(-14.93, -0.43)	0.0382
24 hr	-9.31(2.125)	-2.53(1.976)	-6.78	(-12.58, -0.99)	0.0225
27 hr	-14.12(1.480)	-4.77(1.415)	-9.35	(-13.40, -5.30)	<.0001
44 hr	-9.43(2.745)	-4.96(2.583)	-4.47	(-12.01, 3.07)	0.2409
720 hr	-8.03(3.114)	-7.49(2.710)	-0.54	(-8.81, 7.74)	0.8972

Results for each timepoint are obtained from an ANCOVA model with baseline and treatment as covariates.

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Statistical Analysis of change from baseline in brachial SBP - Safety analysis set

Timepoint	RLX030 30 ug/kg/day LSMeans(SE)	Placebo LSMeans(SE)	RLX030 versus placebo in change from baseline		
			Difference	95% CI	p-value
Change from baseline in SBP (mmHg) at:					
0.5 hr	-1.87(1.765)	0.72(1.739)	-2.59	(-7.53, 2.36)	0.3005
2 hr	-8.58(1.990)	-2.14(1.880)	-6.43	(-11.90, -0.97)	0.0218
4 hr	-6.42(2.211)	-1.71(2.088)	-4.71	(-10.78, 1.36)	0.1261
6 hr	-6.69(2.120)	-2.27(2.002)	-4.42	(-10.24, 1.40)	0.1347
8 hr	-6.46(2.278)	-1.51(2.181)	-4.95	(-11.25, 1.34)	0.1211
12 hr	-10.70(5.023)	-3.75(3.594)	-6.96	(-25.00, 11.09)	0.3671
20 hr	-7.75(2.597)	-1.87(2.453)	-5.88	(-13.01, 1.25)	0.1047
21 hr	-11.19(2.220)	-4.09(2.093)	-7.11	(-13.20, -1.01)	0.0230
22 hr	-10.95(2.839)	-3.25(2.676)	-7.70	(-15.50, 0.09)	0.0526
24 hr	-9.98(2.344)	-2.91(2.180)	-7.07	(-13.46, -0.68)	0.0308
27 hr	-14.58(2.334)	-4.02(2.232)	-10.57	(-17.02, -4.11)	0.0017
44 hr	-10.98(2.774)	-5.14(2.615)	-5.84	(-13.45, 1.78)	0.1308
720 hr	-9.63(3.325)	-8.36(2.893)	-1.27	(-10.11, 7.57)	0.7744

Results for each timepoint are obtained from an ANCOVA model with baseline and treatment as covariates.

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Statistical Analysis of change from baseline in brachial DBP- Safety analysis set

Timepoint	RLX030 30 ug/kg/day LSMeans(SE)	Placebo LSMeans(SE)	RLX030 versus placebo in change from baseline		
			Difference	95% CI	p-value
Change from baseline in DBP (mmHg) at:					
0.5 hr	-4.18(1.549)	-0.21(1.527)	-3.96	(-8.31, 0.38)	0.0730
2 hr	-7.97(1.858)	-2.72(1.755)	-5.25	(-10.35, -0.15)	0.0438
4 hr	-5.86(1.855)	0.67(1.752)	-6.52	(-11.62, -1.43)	0.0129
6 hr	-5.57(1.702)	-0.34(1.607)	-5.23	(-9.90, -0.55)	0.0289
8 hr	-5.16(2.396)	0.69(2.294)	-5.85	(-12.47, 0.78)	0.0827
12 hr	-8.21(2.449)	-2.97(1.831)	-5.24	(-13.59, 3.12)	0.1681
20 hr	-7.53(2.034)	1.48(1.920)	-9.01	(-14.60, -3.43)	0.0020
21 hr	-9.13(1.550)	-1.18(1.461)	-7.95	(-12.21, -3.70)	0.0004
22 hr	-9.48(1.963)	0.27(1.850)	-9.75	(-15.14, -4.36)	0.0006
24 hr	-7.35(1.793)	-0.20(1.668)	-7.16	(-12.04, -2.27)	0.0048
27 hr	-9.79(1.815)	-3.22(1.735)	-6.57	(-11.59, -1.55)	0.0111
44 hr	-8.72(2.168)	-1.76(2.044)	-6.96	(-12.91, -1.01)	0.0227
720 hr	-5.18(2.638)	-2.59(2.295)	-2.59	(-9.60, 4.42)	0.4625

Results for each timepoint are obtained from an ANCOVA model with baseline and treatment as covariates.

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Summary of CASP measurements – radial Augmentation Index (rAI) - Safety analysis set

Treatment: RLX030 30 µg/h

Hours post dose		rAI (%)
-4	n	32
	mean	84.811
	95% CI of mean	88.867
	SD	11.2504
	minimum	65.50
	median	83.165
	maximum	119.00
20	n	32
	mean	85.865
	95% CI of mean	92.484
	SD	18.3592
	minimum	64.67
	median	84.000
	maximum	169.00
44	n	31
	mean	87.258
	95% CI of mean	97.177
	SD	27.0407
	minimum	48.00
	median	85.000
	maximum	219.00

Treatment: Placebo

Hours post dose		rAI (%)
-4	n	37
	mean	86.240
	95% CI of mean	93.124
	SD	20.6485
	minimum	44.00
	median	85.330
	maximum	156.50
20	n	30
	mean	86.544
	95% CI of mean	92.334
	SD	15.5045
	minimum	70.33
	median	81.000
	maximum	134.33
44	n	34
	mean	87.529
	95% CI of mean	98.446
	SD	31.2868
	minimum	41.00
	median	80.500
	maximum	201.00

Safety Results

Incidence of AEs by primary system organ class - Safety analysis set

	RLX030 30 µg/kg/day N=34 n (%)	Placebo N=37 n (%)	Total N=71 n (%)
Patients with AE(s)	21 (61.8)	28 (75.7)	49 (69.0)
System organ class			
Metabolism and nutrition disorders	8 (23.5)	8 (21.6)	16 (22.5)
Gastrointestinal disorders	5 (14.7)	9 (24.3)	14 (19.7)
General disorders and administration site conditions	6 (17.6)	7 (18.9)	13 (18.3)
Investigations	4 (11.8)	6 (16.2)	10 (14.1)
Cardiac disorders	3 (8.8)	5 (13.5)	8 (11.3)
Infections and infestations	3 (8.8)	4 (10.8)	7 (9.9)
Renal and urinary disorders	4 (11.8)	3 (8.1)	7 (9.9)
Respiratory, thoracic and mediastinal disorders	3 (8.8)	4 (10.8)	7 (9.9)
Vascular disorders	5 (14.7)	2 (5.4)	7 (9.9)
Psychiatric disorders	3 (8.8)	3 (8.1)	6 (8.5)
Musculoskeletal and connective tissue disorders	3 (8.8)	2 (5.4)	5 (7.0)
Nervous system disorders	0 (0.0)	5 (13.5)	5 (7.0)
Blood and lymphatic system disorders	2 (5.9)	1 (2.7)	3 (4.2)
Skin and subcutaneous tissue disorders	1 (2.9)	2 (5.4)	3 (4.2)
Injury, poisoning and procedural complications	0 (0.0)	2 (5.4)	2 (2.8)
Endocrine disorders	1 (2.9)	0 (0.0)	1 (1.4)
Eye disorders	1 (2.9)	0 (0.0)	1 (1.4)
Hepatobiliary disorders	1 (2.9)	0 (0.0)	1 (1.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0.0)	1 (2.7)	1 (1.4)
Surgical and medical procedures	0 (0.0)	1 (2.7)	1 (1.4)

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

Incidence of AEs by preferred term (at least 2 patients - Safety analysis set

Preferred term	RLX030 30 µg/kg/day N=34 n (%)	Placebo N=37 n (%)	Total N=71 n (%)
Patients with AE(s)	21 (61.8)	28 (75.7)	49 (69.0)
Hypokalemia	8 (23.5)	6 (16.2)	14 (19.7)
Hematuria	4 (11.8)	1 (2.7)	5 (7.0)
Hypotension	3 (8.8)	1 (2.7)	4 (5.6)
Blood pressure decreased	2 (5.9)	1 (2.7)	3 (4.2)
Constipation	1 (2.9)	3 (8.1)	4 (5.6)
Headache	0 (0.0)	3 (8.1)	3 (4.2)
Dry mouth	1 (2.9)	2 (5.4)	3 (4.2)
Nausea	1 (2.9)	2 (5.4)	3 (4.2)
Pyrexia	1 (2.9)	2 (5.4)	3 (4.2)
Ventricular tachycardia	1 (2.9)	2 (5.4)	3 (4.2)
Agitation	2 (5.9)	0 (0.0)	2 (2.8)
Urinary tract infection	2 (5.9)	0 (0.0)	2 (2.8)
Dyspnea	1 (2.9)	1 (2.7)	2 (2.8)
Electrocardiogram QT prolonged	1 (2.9)	1 (2.7)	2 (2.8)
Gastritis erosive	1 (2.9)	1 (2.7)	2 (2.8)
Hypocalcemia	1 (2.9)	1 (2.7)	2 (2.8)
Pneumonia	1 (2.9)	1 (2.7)	2 (2.8)
Pruritus	1 (2.9)	1 (2.7)	2 (2.8)
Renal impairment	1 (2.9)	1 (2.7)	2 (2.8)
Cardiac failure	0 (0.0)	2 (5.4)	2 (2.8)
Cardiac failure congestive	0 (0.0)	2 (5.4)	2 (2.8)
Chronic obstructive pulmonary disease	0 (0.0)	2 (5.4)	2 (2.8)
Coronary artery disease	0 (0.0)	2 (5.4)	2 (2.8)
Puncture site pain	0 (0.0)	2 (5.4)	2 (2.8)
Vomiting	0 (0.0)	2 (5.4)	2 (2.8)

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

Summary of SAEs during the study-Safety analysis set

Study Day	Preferred Term	Severity	Action Taken
RLX030 Group			
2	Acute pulmonary edema†	Severe	Concomitant medication taken
6	Sick sinus syndrome	Moderate	Non-drug therapy given, hospitalization
8	Acute myocardial infarction†	Severe	No action taken
Placebo Group			
3	Implantable defibrillator insertion	Moderate	Hospitalization
8	Chronic obstructive pulmonary disease	Moderate	Concomitant medication taken, hospitalization
12	Cardiac failure	Mild	Hospitalization
14	Cerebrovascular insufficiency	Severe	Concomitant medication taken
17	Pneumonia	Moderate	Concomitant medication taken, hospitalization
20	Spinal column injury†	Severe	Hospitalization
23	Pulmonary edema†	Severe	No action taken
31	Hypotension	Severe	Concomitant medication taken

† Fatal SAEs

Other Relevant Findings:

- **Pharmacokinetics (PK)**
- **Creatinine clearance**
- **Urine flow rate**

Summary statistics of PK parameters –PK analysis set

Statistic	Actual delivered dose rate (µg/kg/day)	AUCinf / dose (hr.ng/mL) /(µg/kg)	AUClast / dose (hr.ng/mL) /(µg/kg)	C20h /(dose rate) (ng/mL)/ (µg/kg/day)	AUCinf (hr.ng/mL)	AUClast (hr.ng/mL)	C20h (ng/mL)	MRT (hr)	CL (mL/hr/kg)	Vss (mL/kg)
n	33	24	29	29	24	29	29	24	24	24
Mean (SD)	36.8 (1.40)	9.88 (2.38)	11.4 (7.21)	0.364 (0.108)	306 (76.3)	354 (225)	13.4 (3.97)	6.87 (2.61)	107 (26.6)	747 (410)
CV% mean	3.8	24.1	63.0	29.8	24.9	63.5	29.7	37.9	24.9	54.9
Geomean	36.8	9.61	10.3	0.345	297	318	12.7	6.19	104	644
CV% geomean	3.8	24.4	42.9	35.4	25.7	43.7	35.5	58.2	24.4	70.1
Median	36.7	9.40	9.31	0.356	295	287	13.5	7.16	106	691
[Min; Max]	[34.4;39.3]	[5.36;14.8]	[5.25;37.6]	[0.142;0.575]	[161;463]	[158;1180]	[5.26;21.5]	[0.924;12.2]	[67.3;187]	[63.5;2270]

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% geomean = sqrt(exp(variance for log transformed data)-1) * 100.

Statistical Analysis of Creatinine clearance (mL/min) – PD analysis set

Collection period	Parameter	RLX030 30ug/kg/day (N=32)	Placebo (N=31)
0-8 hour	n	27	26
	LSMean ratio to baseline (SE)	1.12 (1.11)	0.87 (1.12)
	Ratio of ratio to baseline#	1.29	
	95% CI	[0.95, 1.74]	
	p-value	0.0988	
0-20 hour	n	26	26
	LSMean ratio to baseline (SE)	1.13 (1.10)	0.82 (1.10)
	Ratio of ratio to baseline#	1.39	
	95% CI	[1.07, 1.81]	
	p-value	0.0143	
0-24 hour	n	24	26
	LSMean ratio to baseline (SE)	1.07 (1.10)	0.85 (1.10)
	Ratio of ratio to baseline#	1.26	
	95% CI	[0.97, 1.63]	
	p-value	0.0899	

Ratio of RLX030 to Placebo Results are from an ANCOVA model on log-transformed change from baseline with treatment as the classification factor and log(baseline) as a covariate. Baseline is the -4 to 0 hours collection value..

Summary of Derived PD endpoints: Urine flow rate – PD analysis set

Parameter: Urine flow rate (mL/hr)

Hours post dose	Parameter	Change from baseline RLX030 30 ug/kg/day	Change from baseline Placebo	Change from baseline Total
20-24	n	27	27	54
	Mean (SD)	-146.53 (172.334)	-164.17 (181.856)	-155.35 (175.705)
	95% CI for Mean	-214.70, -78.35	-236.11, -92.23	-203.31, -107.39
	Geo-mean	0.44	0.38	0.41
	95% CI for GeoMean	0.29, 0.67	0.25, 0.59	0.31, 0.55
	Median	-155.00	-170.00	-160.00
	Min, Max	-697.5, 62.5	-487.5, 177.5	-697.5, 177.5
0-20	n	29	27	56
	Mean (SD)	-117.64 (158.162)	-179.28 (163.258)	-147.36 (162.174)
	95% CI for Mean	-177.80, -57.48	-243.86, -114.70	-190.79, -103.93
	Geo-mean	0.61	0.41	0.50
	95% CI for GeoMean	0.43, 0.86	0.31, 0.54	0.40, 0.63
	Median	-131.50	-145.00	-135.00
	Min, Max	-605.9, 115.3	-495.5, 22.5	-605.9, 115.3

Baseline is the collection period prior to dosing (-4 to 0 hours). Values reported as <LLOQ are imputed as 0.5*LLOQ. For change from baseline geo-means, a ratio to baseline is used by first calculating in the log domain and then back transforming using exponentiation.

Date of Clinical Trial Report

03-May-2013

Date Inclusion on Novartis Clinical Trial Results Database

Date: 17-Jan-2014

Date of Latest Update