NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Serelaxin

Trial Indication(s)

Acute heart failure

Protocol Number

CRLX030A3301

Protocol Title

A multicenter, prospective, randomized, open-label study to assess the effect of serelaxin versus Standard of Care in Acute Heart Failure (AHF) patients

Clinical Trial Phase

Phase 3

Phase of Drug Development

Phase 3

Study Start/End Dates

Study Start Date: January 2014 (Actual)
Primary Completion Date: March 2017 (Actual)
Study Completion Date: April 2017 (Actual)

Reason for Termination (If applicable)

Study was terminated based on results from pivotal adult AHF study CRLX030A2301

Study Design/Methodology

This was a multinational, multicenter, randomized, open-label study to confirm and expand the efficacy, safety and tolerability evidence of 48 hours intravenous infusion of serelaxin (30 micrograms/kg/day) when added to Standard of Care (SoC) in patients admitted to hospital for Acute Heart Failure (AHF).

Centers

369 centers in 25 countries: Slovakia (Slovak Republic)(6), Switzerland(4), France(43), Romania(7), Austria(9), Belgium(13), Spain(40), Slovenia(4), Germany(87), Italy(35), Czech Republic(11), Russia(32), Hungary(13), Bulgaria(7), United Kingdom(10), Latvia(1), Greece(6), Lithuania(4), Poland(14), Portugal(8), Estonia(2), Croatia(5), Serbia(6), Finland(1), Iceland(1)

Objectives:

The primary objective of the study was to evaluate the effect of serelaxin as add-on therapy to standard of care (SOC) versus SOC alone in reducing in-hospital worsening HF (WHF) requiring rescue therapy or all-cause death, from randomization through Day 5.

The secondary objectives of the study were:

- To assess the effect of serelaxin as add-on therapy to SOC versus SOC alone in reducing in-hospital WHF requiring rescue therapy or all-cause death or readmission for heart failure, from randomization through Day 14.
- To assess the effect of serelaxin as add-on therapy to SOC versus SOC alone in reducing the number of patients with persistent symptoms or signs of HF / not showing an improvement versus baseline conditions from randomization through Day 5 (persisting need of IV therapy for HF).
- To evaluate the effect of serelaxin as add-on therapy to SOC versus SOC alone in reducing the rate of renal deterioration (defined as $\geq$ 0.3 mg/dL increase in serum creatinine), from randomization through Day 5.

- To evaluate the effect of serelaxin as add-on therapy to SOC versus SOC alone in modifying the index length of stay (LOS) by location (e.g., ICU, CCU, cardiology department) in days and hours (ICU).
- To evaluate the safety and tolerability of intravenous serelaxin in AHF patients during a period of 30 days following exposure.
- To collect data on health-related quality of life (HRQoL) and economic burden to provide a more comprehensive analysis of the burden of HF, beyond the clinical outcomes.

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

Serelaxin was supplied in individual 6 ml glass vials each containing 3.5 mL of 1 mg/mL serelaxin solution (20 mM sodium acetate solution, pH 5.0).
Study drug was administered according to a weight-range adjusted dosing regimen at a nominal dose of 30 μg/kg/day, as a continuous intravenous infusion for 48 hours. Serelaxin was withdrawn from the vials contained in the kits, injected into a 250 mL intravenous bag of 5% dextrose solution and then infused through a dedicated IV line or port, using compatible tubing, infusion filters and IV bags.

Statistical Methods

The primary statistical hypothesis was:
H_0: $\lambda_2/\lambda_1 \geq 1$, i.e., the rate of primary event of in-hospital WHF or all cause death is greater or equal in the serelaxin group relative to the standard of care group versus the one-sided alternative H_A: $\lambda_2/\lambda_1 < 1$, i.e., the rate of in-hospital WHF or all cause death is smaller in the serelaxin group relative to the standard of care group, where λ_1 and λ_2 are the hazard rates for in-hospital WHF or all cause death in the standard of care group and serelaxin group, respectively. The ratio λ_2/λ_1 is the hazard ratio of serelaxin to standard of care.
The hypothesis was tested based on the Full Analysis Set (FAS) with a Gehan's generalized Wilcoxon test at a significance level of 0.025 (one-sided).

Analysis of secondary variable(s):
Standard descriptive statistics were presented for each treatment group at each time point that the endpoint was measured. Two-sided p-values <0.05 were considered statistically significant; no adjustment for multiple comparisons was adopted.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:
- Systolic blood pressure ≥ 125 mmHg
- Admitted for Acute Heart Failure (AHF)
- Received intravenous furosemide (or equivalent) at any time between presentation and the start of screening
- eGFR on admission: ≥ 25 and ≤75 mL/min/1.73 m^2

Exclusion Criteria:
- Dyspnea (non-cardiac causes)
- T > 38.5°C
- Clinical evidence of acute coronary syndrome currently or within 30 days prior to enrollment.
- Significant left ventricular outflow obstruction, uncorrected, such as obstructive hypertrophic cardiomyopathy or severe aortic stenosis (i.e., aortic valve area <1.0 cm^2 or mean gradient >50 mmHg on prior or current echocardiogram), severe aortic regurgitation and severe mitral stenosis.
- AHF due to significant arrhythmias
- Acute myocarditis or hypertrophic obstructive, restrictive, or constrictive cardiomyopathy (does not include restrictive mitral filling patterns seen on Doppler echocardiographic assessments of diastolic function).

Participant Flow Table

Overall Study

	Serelaxin + Standard of Care	Standard of Care (SOC)
Started	1756	894
Full Analysis Set	1756	894
Safety Set	1729[1]	894
Per Protocol Set	1155	627

Completed	1722	881
Not Completed	34	13
Lost to Follow-up	14	8
Physician Decision	1	0
Withdrawal by Subject	14	3
Technical Problems or Missing	5	2

[1] The Safety Set includes one patient not randomized but treated with serelaxin

Baseline Characteristics

	Serelaxin + Standard of Care	Standard of Care (SOC)	Total
Number of Participants [units: participants]	1756	894	2650
Age Continuous (units: Years) Mean ± Standard Deviation			
	75.24±10.349	75.95±9.905	75.48±10.205
Sex: Female, Male (units: Participants) Count of Participants (Not Applicable)			
Female	760	383	1143
Male	996	511	1507
Race/Ethnicity, Customized			

(units:)
Count of Participants (Not Applicable)

Caucasian	1706	869	2575
Black	4	4	8
Asian	5	2	7
Unknown	16	7	23
Other	25	12	37

Summary of Efficacy

Primary Outcome Result(s)

Worsening heart failure (WHF) / all cause of deaths through day 5

	Serelaxin + Standard of Care	Standard of Care (SOC)
Number of Participants Analyzed [units: participants]	1756	894
Worsening heart failure (WHF) / all cause of deaths through day 5 (units: Percentage of Participants)		
	4.95	6.94

Statistical Analysis

Groups	Serelaxin + Standard of Care,

	Standard of Care (SOC)	
P Value	0.0172	One-sided p-value
Method	Other Gehan's generalized Wilcoxon test	
Hazard Ratio (HR)	0.71	
95 % Confidence Interval 2-Sided	0.51 to 0.98	

Secondary Outcome Result(s)

In-hospital worsening heart failure/all-cause death/readmission for heart failure through day 14

	Serelaxin + Standard of Care	Standard of Care (SOC)
Number of Participants Analyzed [units: participants]	1756	894
In-hospital worsening heart failure/all-cause death/readmission for heart failure through day 14 (units: Percentage of Patients)		
	8.49	10.63

Statistical Analysis

Groups	Serelaxin + Standard of Care,

	Standard of Care (SOC)	
P Value	0.0634	Two-sided p-value
Method	Other Gehan's generalized Wilcoxon test	
Hazard Ratio (HR)	0.79	
95 % Confidence Interval 2-Sided	0.61 to 1.02	

Persistent sign or symptoms of heart failure / non-improvement at any post baseline visit through day 5

	Serelaxin + Standard of Care	Standard of Care (SOC)
Number of Participants Analyzed [units: participants]	1744	894
Persistent sign or symptoms of heart failure / non-improvement at any post baseline visit through day 5 (units: Percentage of Participants) Number (95% Confidence Interval)		
	86 (84 to 87)	91 (89 to 93)

Statistical Analysis

Groups	Serelaxin + Standard of Care, Standard of Care (SOC)

P Value	<0.0001
Method	Chi-squared

Renal deterioration at any post baseline visit through day 14

	Serelaxin + Standard of Care	Standard of Care (SOC)
Number of Participants Analyzed [units: participants]	1740	889
Renal deterioration at any post baseline visit through day 14 (units: Percentage of Participants) Number (95% Confidence Interval)		
	36 (34 to 38)	44 (40 to 47)

Statistical Analysis

Groups	Serelaxin + Standard of Care, Standard of Care (SOC)
P Value	0.0002
Method	Chi-squared

Length of index hospital stay

	Serelaxin + Standard of Care	Standard of Care (SOC)
Number of Participants	1756	894

Analyzed [units: participants]		
Length of index hospital stay (units: hours) Mean ± Standard Deviation		
	251.28 ± 162.368	243.59 ± 160.270

Statistical Analysis

Groups	Serelaxin + Standard of Care, Standard of Care (SOC)
P Value	0.1392
Method	Wilcoxon (Mann-Whitney)

Number of patients reported with adverse events as assessment of safety and tolerability of Serelaxin in AHF patients

	Serelaxin + Standard of Care	Standard of Care (SOC)
Number of Participants Analyzed [units: participants]	1729	894
Number of patients reported with adverse events as assessment of safety and tolerability of Serelaxin in AHF patients (units: Percentage of participants)		
Patients with any AE through Day 5	58.13	56.04
Patients with any SAE through Day 14	12.38	11.97

All cause deaths through Day 5	0.58	0.67
All cause deaths through Day 14	1.91	2.01
All cause deaths through Day 30	3.30	4.25

Change from baseline in Health-related quality of life index value, assessed by EuroQoL EQ-5D-5L questionnaire.

	Serelaxin + Standard of Care	Standard of Care (SOC)
Number of Participants Analyzed [units: participants]	1545	793
Change from baseline in Health-related quality of life index value, assessed by EuroQoL EQ-5D-5L questionnaire. (units: Points) Mean ± Standard Deviation		
Day 5	0.28 ± 0.298	0.27 ± 0.292
Day 14	0.32 ± 0.328	0.31 ± 0.317

Statistical Analysis

Groups	Serelaxin + Standard of Care, Standard of Care (SOC)	Day 5
P Value	0.3115	
Method	Mixed Models Analysis	

Statistical Analysis

Groups	Serelaxin + Standard of Care,	Day 14

	Standard of Care (SOC)
P Value	0.1236
Method	Mixed Models Analysis

Summary of Safety

Safety Results

All-Cause Mortality

	Serelaxin + Standard of Care N = 1729	Standard of Care (SOC) N = 894
Total participants affected	43 (2.49%)	25 (2.80%)

Serious Adverse Events by System Organ Class

Time Frame	Serious Adverse Events: 14 days Other non-serious Adverse Events (AEs): 5 days
Additional Description	All AEs were collected through Day 5, and all serious adverse events were collected through Day 14. All cause mortality (43 in "Serelaxin + SOC" and 25 in "SOC") is presented in "total number affected" only if a corresponding (S)AE was recorded. 38 additional deaths (20 in "Serelaxin + SOC" and 18 in "SOC") were recorded outside the reporting period of (S)AE. So in total 106 deaths occurred in the study, 63 patients in the "Serelaxin + SOC" group and 43 patients in the "SOC" group.
Source Vocabulary for Table Default	MedDRA (20.0)
Assessment Type for Table Default	Systematic Assessment

	Serelaxin + Standard of Care N = 1729	Standard of Care (SOC) N = 894
Total participants affected	214 (12.38%)	107 (11.97%)
Blood and lymphatic system disorders		
Anaemia	1 (0.06%)	1 (0.11%)
Microcytic anaemia	1 (0.06%)	0 (0.00%)
Cardiac disorders		
Acute coronary syndrome	1 (0.06%)	0 (0.00%)
Acute left ventricular failure	1 (0.06%)	0 (0.00%)
Acute myocardial infarction	6 (0.35%)	4 (0.45%)
Angina pectoris	0 (0.00%)	2 (0.22%)
Angina unstable	1 (0.06%)	4 (0.45%)
Aortic valve incompetence	0 (0.00%)	1 (0.11%)
Aortic valve stenosis	1 (0.06%)	3 (0.34%)
Atrial fibrillation	6 (0.35%)	1 (0.11%)
Atrioventricular block complete	3 (0.17%)	0 (0.00%)
Atrioventricular block second degree	0 (0.00%)	1 (0.11%)
Bradyarrhythmia	2 (0.12%)	0 (0.00%)

Bradycardia	7 (0.40%)	2 (0.22%)
Bundle branch block left	0 (0.00%)	1 (0.11%)
Cardiac arrest	6 (0.35%)	2 (0.22%)
Cardiac failure	38 (2.20%)	26 (2.91%)
Cardiac failure acute	6 (0.35%)	2 (0.22%)
Cardiac failure chronic	2 (0.12%)	1 (0.11%)
Cardiac failure congestive	2 (0.12%)	1 (0.11%)
Cardiac hypertrophy	0 (0.00%)	1 (0.11%)
Cardiac ventricular thrombosis	0 (0.00%)	1 (0.11%)
Cardiogenic shock	3 (0.17%)	2 (0.22%)
Cardiopulmonary failure	1 (0.06%)	0 (0.00%)
Cardiorenal syndrome	1 (0.06%)	0 (0.00%)
Cardio-respiratory arrest	1 (0.06%)	0 (0.00%)
Cardiovascular insufficiency	1 (0.06%)	0 (0.00%)
Congestive cardiomyopathy	1 (0.06%)	0 (0.00%)
Coronary artery disease	7 (0.40%)	4 (0.45%)
Coronary artery stenosis	0 (0.00%)	1 (0.11%)
Diastolic dysfunction	1 (0.06%)	0 (0.00%)
Left ventricular failure	1 (0.06%)	1 (0.11%)
Mitral valve incompetence	5 (0.29%)	1 (0.11%)
Myocardial infarction	2 (0.12%)	3 (0.34%)
Myocardial ischaemia	2 (0.12%)	0 (0.00%)
Myocarditis	1 (0.06%)	0 (0.00%)

Right ventricular failure	0 (0.00%)	1 (0.11%)
Sinus arrest	1 (0.06%)	0 (0.00%)
Stress cardiomyopathy	1 (0.06%)	0 (0.00%)
Tachycardia	0 (0.00%)	1 (0.11%)
Ventricular fibrillation	5 (0.29%)	1 (0.11%)
Ventricular tachycardia	5 (0.29%)	2 (0.22%)
Endocrine disorders		
Hypothyroidism	1 (0.06%)	0 (0.00%)
Eye disorders		
Glaucoma	1 (0.06%)	0 (0.00%)
Gastrointestinal disorders		
Abdominal pain lower	1 (0.06%)	0 (0.00%)
Abdominal strangulated hernia	1 (0.06%)	0 (0.00%)
Constipation	0 (0.00%)	1 (0.11%)
Duodenal ulcer haemorrhage	1 (0.06%)	0 (0.00%)
Dysphagia	1 (0.06%)	0 (0.00%)
Gastrointestinal haemorrhage	2 (0.12%)	0 (0.00%)
Intestinal ischaemia	3 (0.17%)	0 (0.00%)
Melaena	1 (0.06%)	0 (0.00%)
Nausea	1 (0.06%)	0 (0.00%)
Vomiting	2 (0.12%)	0 (0.00%)
General disorders and administration site		

conditions		
Death	0 (0.00%)	1 (0.11%)
Fatigue	1 (0.06%)	0 (0.00%)
Hyperthermia	1 (0.06%)	0 (0.00%)
Non-cardiac chest pain	1 (0.06%)	0 (0.00%)
Organ failure	0 (0.00%)	1 (0.11%)
Pyrexia	4 (0.23%)	2 (0.22%)
Sudden cardiac death	1 (0.06%)	0 (0.00%)
Sudden death	1 (0.06%)	0 (0.00%)
Systemic inflammatory response syndrome	1 (0.06%)	0 (0.00%)
Hepatobiliary disorders		
Cholecystitis	1 (0.06%)	0 (0.00%)
Cholelithiasis	0 (0.00%)	1 (0.11%)
Hepatitis toxic	2 (0.12%)	0 (0.00%)
Infections and infestations		
Bacteraemia	1 (0.06%)	0 (0.00%)
Bronchitis	3 (0.17%)	1 (0.11%)
Diverticulitis	1 (0.06%)	0 (0.00%)
Escherichia urinary tract infection	1 (0.06%)	0 (0.00%)
Infection	1 (0.06%)	0 (0.00%)
Lower respiratory tract infection	1 (0.06%)	0 (0.00%)
Nosocomial infection	1 (0.06%)	0 (0.00%)
Oropharyngitis fungal	1 (0.06%)	0 (0.00%)

Parainfluenzae virus infection	1 (0.06%)	0 (0.00%)
Pneumonia	11 (0.64%)	6 (0.67%)
Pneumonia influenzal	1 (0.06%)	0 (0.00%)
Pneumonia klebsiella	1 (0.06%)	0 (0.00%)
Pneumonia pneumococcal	0 (0.00%)	1 (0.11%)
Respiratory tract infection	1 (0.06%)	0 (0.00%)
Sepsis	2 (0.12%)	2 (0.22%)
Skin bacterial infection	1 (0.06%)	0 (0.00%)
Staphylococcal bacteraemia	1 (0.06%)	0 (0.00%)
Staphylococcal infection	0 (0.00%)	1 (0.11%)
Streptococcal infection	1 (0.06%)	0 (0.00%)
Tracheobronchitis	2 (0.12%)	0 (0.00%)
Urinary tract infection	3 (0.17%)	4 (0.45%)
Urosepsis	2 (0.12%)	0 (0.00%)
Injury, poisoning and procedural complications		
Abdominal injury	1 (0.06%)	0 (0.00%)
Ankle fracture	0 (0.00%)	1 (0.11%)
Craniocerebral injury	1 (0.06%)	0 (0.00%)
Fall	0 (0.00%)	2 (0.22%)
Femoral neck fracture	1 (0.06%)	0 (0.00%)
Haematuria traumatic	1 (0.06%)	0 (0.00%)
Head injury	1 (0.06%)	0 (0.00%)

Hip fracture	0 (0.00%)	1 (0.11%)
Lumbar vertebral fracture	2 (0.12%)	0 (0.00%)
Post procedural haemorrhage	1 (0.06%)	0 (0.00%)
Procedural pneumothorax	1 (0.06%)	0 (0.00%)
Subdural haemorrhage	1 (0.06%)	0 (0.00%)
Toxicity to various agents	1 (0.06%)	0 (0.00%)
Traumatic haematoma	0 (0.00%)	1 (0.11%)
Vascular pseudoaneurysm	2 (0.12%)	0 (0.00%)
Investigations		
Blood bilirubin increased	1 (0.06%)	0 (0.00%)
Blood creatinine increased	1 (0.06%)	1 (0.11%)
Electrocardiogram T wave inversion	1 (0.06%)	0 (0.00%)
Haemoglobin decreased	1 (0.06%)	0 (0.00%)
Heart rate decreased	0 (0.00%)	1 (0.11%)
International normalised ratio decreased	0 (0.00%)	1 (0.11%)
International normalised ratio increased	0 (0.00%)	1 (0.11%)
Liver function test increased	1 (0.06%)	0 (0.00%)
Oxygen saturation decreased	0 (0.00%)	1 (0.11%)

Metabolism and nutrition disorders		
Dehydration	2 (0.12%)	0 (0.00%)
Diabetic ketoacidosis	1 (0.06%)	0 (0.00%)
Gout	1 (0.06%)	0 (0.00%)
Hyperammonaemia	1 (0.06%)	0 (0.00%)
Hyperkalaemia	1 (0.06%)	0 (0.00%)
Hypoglycaemia	1 (0.06%)	2 (0.22%)
Hypokalaemia	0 (0.00%)	2 (0.22%)
Type 2 diabetes mellitus	0 (0.00%)	1 (0.11%)
Musculoskeletal and connective tissue disorders		
Chest wall haematoma	0 (0.00%)	1 (0.11%)
Joint swelling	1 (0.06%)	0 (0.00%)
Muscle haemorrhage	0 (0.00%)	1 (0.11%)
Rhabdomyolysis	1 (0.06%)	0 (0.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Bladder transitional cell carcinoma	0 (0.00%)	1 (0.11%)
Colon cancer	1 (0.06%)	0 (0.00%)
Gastric cancer	0 (0.00%)	1 (0.11%)
Leiomyoma	1 (0.06%)	0 (0.00%)
Lung neoplasm malignant	1 (0.06%)	0 (0.00%)
Plasma cell myeloma	1 (0.06%)	0 (0.00%)

Prostate cancer metastatic	0 (0.00%)	1 (0.11%)
Nervous system disorders		
Brain oedema	1 (0.06%)	0 (0.00%)
Carotid artery stenosis	0 (0.00%)	1 (0.11%)
Cerebrovascular accident	1 (0.06%)	1 (0.11%)
Depressed level of consciousness	1 (0.06%)	0 (0.00%)
Epilepsy	2 (0.12%)	0 (0.00%)
Hypercapnic coma	0 (0.00%)	1 (0.11%)
Ischaemic stroke	3 (0.17%)	4 (0.45%)
Loss of consciousness	0 (0.00%)	1 (0.11%)
Seizure	1 (0.06%)	0 (0.00%)
Status epilepticus	1 (0.06%)	0 (0.00%)
Psychiatric disorders		
Agitation	1 (0.06%)	0 (0.00%)
Confusional state	2 (0.12%)	0 (0.00%)
Delirium	2 (0.12%)	0 (0.00%)
Renal and urinary disorders		
Acute kidney injury	9 (0.52%)	4 (0.45%)
Acute prerenal failure	0 (0.00%)	1 (0.11%)
Anuria	0 (0.00%)	1 (0.11%)
Chronic kidney disease	2 (0.12%)	0 (0.00%)
Haematuria	1 (0.06%)	0 (0.00%)

Nephropathy	1 (0.06%)	0 (0.00%)
Nephropathy toxic	1 (0.06%)	0 (0.00%)
Nephrotic syndrome	1 (0.06%)	1 (0.11%)
Prerenal failure	1 (0.06%)	0 (0.00%)
Renal failure	6 (0.35%)	3 (0.34%)
Renal impairment	4 (0.23%)	5 (0.56%)
Renal tubular necrosis	1 (0.06%)	1 (0.11%)
Urinary retention	1 (0.06%)	0 (0.00%)
Respiratory, thoracic and mediastinal disorders		
Acute pulmonary oedema	6 (0.35%)	1 (0.11%)
Acute respiratory distress syndrome	0 (0.00%)	1 (0.11%)
Acute respiratory failure	1 (0.06%)	1 (0.11%)
Chronic obstructive pulmonary disease	1 (0.06%)	1 (0.11%)
Dyspnoea	2 (0.12%)	3 (0.34%)
Haemothorax	1 (0.06%)	1 (0.11%)
Hypercapnia	1 (0.06%)	2 (0.22%)
Pleural effusion	1 (0.06%)	0 (0.00%)
Pulmonary hypertension	1 (0.06%)	0 (0.00%)
Pulmonary mass	1 (0.06%)	0 (0.00%)
Pulmonary oedema	3 (0.17%)	2 (0.22%)
Respiratory disorder	1 (0.06%)	0 (0.00%)
Respiratory distress	0 (0.00%)	1 (0.11%)
Respiratory failure	6 (0.35%)	0 (0.00%)

Skin and subcutaneous tissue disorders		
Dermatitis exfoliative	0 (0.00%)	1 (0.11%)
Surgical and medical procedures		
Left atrial appendage occlusion	1 (0.06%)	0 (0.00%)
Vascular disorders		
Aortic stenosis	1 (0.06%)	0 (0.00%)
Arterial disorder	1 (0.06%)	0 (0.00%)
Arterial stenosis	1 (0.06%)	0 (0.00%)
Arteriosclerosis	1 (0.06%)	0 (0.00%)
Arteriovenous fistula	0 (0.00%)	1 (0.11%)
Circulatory collapse	0 (0.00%)	1 (0.11%)
Femoral artery aneurysm	0 (0.00%)	1 (0.11%)
Haematoma	1 (0.06%)	0 (0.00%)
Hypertension	2 (0.12%)	1 (0.11%)
Hypertensive crisis	1 (0.06%)	0 (0.00%)
Hypotension	7 (0.40%)	2 (0.22%)
Peripheral artery thrombosis	2 (0.12%)	0 (0.00%)
Peripheral ischaemia	0 (0.00%)	1 (0.11%)
Shock haemorrhagic	0 (0.00%)	1 (0.11%)

Other Adverse Events by System Organ Class

Time Frame	Serious Adverse Events: 14 days Other non-serious Adverse Events (AEs): 5 days
Additional Description	All AEs were collected through Day 5, and all serious adverse events were collected through Day 14. All cause mortality (43 in "Serelaxin + SOC" and 25 in "SOC") is presented in "total number affected" only if a corresponding (S)AE was recorded. 38 additional deaths (20 in "Serelaxin + SOC" and 18 in "SOC") were recorded outside the reporting period of (S)AE. So in total 106 deaths occurred in the study, 63 patients in the "Serelaxin + SOC" group and 43 patients in the "SOC" group.
Source Vocabulary for Table Default	MedDRA (20.0)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	1.5%

	Serelaxin + Standard of Care N = 1729	**Standard of Care (SOC) N = 894**
Total participants affected	637 (36.84%)	324 (36.24%)
Blood and lymphatic system disorders		
Anaemia	49 (2.83%)	9 (1.01%)
Cardiac disorders		
Atrial fibrillation	34 (1.97%)	23 (2.57%)
Cardiac failure	81 (4.68%)	56 (6.26%)
Mitral valve incompetence	28 (1.62%)	12 (1.34%)
Gastrointestinal disorders		
Constipation	74 (4.28%)	32 (3.58%)
Diarrhoea	29 (1.68%)	21 (2.35%)
Nausea	40 (2.31%)	17 (1.90%)

General disorders and administration site conditions		
Pyrexia	24 (1.39%)	21 (2.35%)
Infections and infestations		
Bronchitis	24 (1.39%)	14 (1.57%)
Urinary tract infection	56 (3.24%)	26 (2.91%)
Investigations		
Blood pressure systolic decreased	49 (2.83%)	2 (0.22%)
Metabolism and nutrition disorders		
Hyperuricaemia	47 (2.72%)	35 (3.91%)
Hypokalaemia	119 (6.88%)	73 (8.17%)
Musculoskeletal and connective tissue disorders		
Back pain	28 (1.62%)	11 (1.23%)
Muscle spasms	33 (1.91%)	8 (0.89%)
Nervous system disorders		
Headache	45 (2.60%)	18 (2.01%)
Psychiatric disorders		
Anxiety	27 (1.56%)	16 (1.79%)
Insomnia	58 (3.35%)	21 (2.35%)
Renal and urinary disorders		
Renal failure	18 (1.04%)	18 (2.01%)

Renal impairment	30 (1.74%)	18 (2.01%)
Vascular disorders		
Hypotension	48 (2.78%)	18 (2.01%)

Other Relevant Findings

None

Conclusion:

- This study was prematurely terminated, due to sponsor's decision to discontinue serelaxin development in AHF.
- Due to the reduced statistical power of the study as a consequence of its early termination, efficacy results should be interpreted with caution.
- No new or unexpected safety findings were reported in this study among AHF patients from European countries. Serelaxin infusion was well tolerated. The AE profile after study drug exposure was generally consistent with the previous knowledge of serelaxin.

Date of Clinical Trial Report

April 23, 2018