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Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Serelaxin

Trial Indication(s)

Acute heart failure

Protocol Number

CRLX030A2301

Protocol Title

A multicenter, randomized, double-blind, placebo-controlled phase III study to evaluate the efficacy, safety and tolerability of Serelaxin when added to standard therapy in acute heart failure patients

Clinical Trial Phase

Phase 3

Phase of Drug Development

Phase 3

Study Start/End Dates

Study Start Date: August 2013 (Actual)
Primary Completion Date: January 2017 (Actual)
Study Completion Date: February 2017 (Actual)

Reason for Termination (If applicable)

Study Design/Methodology

This was a multicenter, randomized, double-blind, placebo-controlled, event-driven Phase III study designed to evaluate the efficacy and safety of an i.v. infusion of serelaxin when added to standard therapy in AHF patients. Eligible patients were randomized 1:1 to receive an i.v. infusion of either serelaxin or matching placebo in a double-blind manner for up to 48 hours according to a weight-range adjusted dosing regimen at the nominal dose of 30 µg/kg/day.

Centers

682 centers in 34 countries: Sweden(5), United States(156), Switzerland(4), Spain(25), Hungary(18), United Kingdom(26), Slovakia (Slovak Republic)(15), Bulgaria(14), South Africa(12), Germany(83), Poland(22), Denmark(5), Czech Republic(20), Netherlands(15), Norway(3), Israel(12), Greece(7), Romania(22), Austria(9), Italy(32), Australia(14), Ireland(7), Portugal(12), France(22), Belgium(10), Turkey(7), Argentina(37), Brazil(12), Russia(30), Mexico(8), Canada(6), Colombia(5), Peru(4), Chile(3)

Objectives:

The primary objectives of this study were:

- To demonstrate that serelaxin was superior to placebo in reducing cardiovascular (CV) death in acute heart failure (AHF) patients during a follow-up period of 180 days.
- To demonstrate that serelaxin was superior to placebo in reducing worsening heart failure (WHF) through Day 5.

Key secondary objectives were:

- To demonstrate that serelaxin was superior to placebo in reducing all-cause mortality during a follow-up period of 180 days.
- To demonstrate that serelaxin was superior to placebo in reducing the length of total hospital stay (LOS) during the index AHF hospitalization.

- To demonstrate that serelaxin was superior to placebo in reducing the composite endpoint of CV death or re-hospitalization due to heart failure (HF)/renal failure (RF) during a follow-up period of 180 days.

Other secondary objectives were:

- To demonstrate that serelaxin was superior to placebo in reducing the length of intensive care unit (ICU) and/or coronary care unit (CCU) stay during the index AHF hospitalization.
- To demonstrate that serelaxin was superior to placebo in relieving signs and symptoms of congestion through Day 5.
- To compare serelaxin to placebo in the changes of selected biomarkers in a subset of randomized patients.
- To evaluate the safety and tolerability of intravenous (i.v.) serelaxin in AHF patients.

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

Serelaxin (and/or matching placebo) was administered according to a weight-range adjusted dosing regimen at a nominal dose of 30 µg/kg/day as a continuous i.v. infusion for 48 hours. The study drug was provided as a 1 mg/mL solution in 6 mL vials (with 3.5 mL fill). For the randomized patients to receive the study drug infusion, it could be withdrawn from the vials contained in the blinded kits, injected into a 250 mL i.v. bag of 5% dextrose solution, and then infused through a dedicated i.v. line or port, using compatible tubing, infusion filters, and i.v. bags according to instructions in the Pharmacy Manual.

Statistical Methods

The SAS procedures PHREG and LIFETEST were used to conduct the analyses.

Primary endpoint: time to confirmed CV death

The statistical hypothesis was:

H_0: $\lambda_2/\lambda_1 \geq 1$, i.e., the rate of primary event of CV death is greater or equal in the serelaxin group relative to the placebo group *versus the one-sided alternative* H_A: $\lambda_2/\lambda_1 < 1$, i.e., the rate of CV death is smaller in the serelaxin group relative to the placebo group, where λ_1 and λ_2 are the hazard rates for CV death in the placebo group and serelaxin group, respectively. The ratio λ_2/λ_1 is also called the hazard ratio of serelaxin to placebo.

The hypothesis was tested based on the full analysis set (FAS) with a log rank test at an initial significance level of (4/5)α within a sequentially rejective multiple testing procedure.

Number and percentage of patients who died from CV reasons based on the number of patients in the population as denominator were provided by treatment group. The hazard ratio (HR) (relative risk) and its associated two-sided 95% confidence interval (CI) were estimated based on a Cox proportional hazards model with treatment assignment as a factor.

The Kaplan-Meier estimates of the survival functions for each treatment group were plotted. The Kaplan-Meier estimates of the cumulative event rate were also presented in tables by treatment group for each day and also by time interval.

Primary endpoint: time to WHF

Time to WHF through Day 5 was analyzed using Gehan's generalized Wilcoxon test at an initial significance level of (1/5)α within a sequentially rejective multiple testing procedure.

Number and percentage of patients who experienced WHF based on the number of patients in the population as denominator were provided by treatment group. The HR (relative risk) and its associated two-sided 95% CI were estimated based on a Cox proportional hazards model with treatment as a factor.

Kaplan-Meier curves were presented graphically by treatment group and Kaplan-Meier estimates for selected time points with 95% CIs were tabulated.

Key secondary endpoint: time to all-cause death

The time-to-event (from baseline to the event) analysis similar to the primary analysis on CV death was used for the analyses of all-cause death at Day 180.

For patients without events, the censoring date was the earliest in the following dates:

- 180 days.
- Date patient withdrew consent to all follow-up (if no subsequent vital status documented).
- Date of patient's last visit or contact or vital status.

A covariate-adjusted Cox-regression model similar to the sensitivity analysis of primary efficacy variable was also performed as sensitivity analysis.

Key secondary endpoint: LOS during the index AHF hospitalization

LOS was defined as the index hospitalization discharge date and time minus the randomization date and time, whereas time was used for better precision and converted to days.

Patients still in the hospital at Day 60 were censored at Day 60. Patients who died during the initial hospitalization were assigned the maximum LOS (including those censored at Day 60) plus 1 day.

Patients missing the discharge date, such that a determination of the LOS could not be calculated, were assigned the mean LOS over all patients with not missing discharge date.

Treatment groups were compared using a Wilcoxon rank sum test.

For subgroup analysis, a p-value for the test of the treatment by subgroup interaction term was based on a two-way model with treatment, subgroup and treatment-by-subgroup interaction using rank-transformed data.

The van Elteren extension to the Wilcoxon rank sum test was be carried out stratifying by region.

Key secondary endpoint: time to first occurrence of the composite endpoint of CV death or re-hospitalization due to HF/RF through Day 180

Time to event was calculated as date of first event of adjudicated CV death or adjudicated re-hospitalization due to HF/RF minus randomization date in days. If the reason for adjudicated re-hospitalization was unknown, it was considered as HF or RF.

The analysis was performed similarly to primary endpoint.

For patients without events, the censoring date was the earliest in the following dates:

- 180 days.
- Date patient withdrew consent to all follow-up.
- Date of patient's last visit or contact.
- Date of non-CV death.

In addition, the estimates with 95% CI at 30, 60, and 90 days from the Kaplan-Meier method were provided. Of note, estimates at 60 and 90 days were considered as exploratory analyses.

The analysis for one of components of the composite endpoint, time to re-hospitalization due to HF/RF through Day 180, was also performed. The estimates with 95% CI and p-value at Day 180 from the Kaplan-Meier method were also provided.

Study Population: Key Inclusion/Exclusion Criteria

Key Inclusion Criteria:
-Male or female 18 years of age, with body weight ≤160 kg
-Hospitalized for AHF with anticipated requirment of IV therapy for at least 48 hours; AHF is defined as including all of the following measured at any time between presentation (including the emergency department) and the end of screening:
• Persistent dyspnea at rest or with minimal exertion
• Pulmonary congestion on chest radiograph
• BNP ≥500 pg/mL or NT-proBNP ≥2000 pg/mL; for patients ≥ 75 years of age or with current atrial fibrillation (at the time of randomization), BNP ≥ 750 pg/mL or NT-proBNP ≥ 3,000 pg/mL
-Systolic BP ≥125 mmHg at the start and at the end of screening
-Able to be randomized within 16 hours from presentation to the hospital, including the emergency department
-Received intravenous furosemide of at least 40 mg total (or equivalent) at any time between presentation (this includes outpatient clinic, ambulance, or hospital including emergency department) and the start of screening for the study for the treatment of the current acute HF episode.

Key Exclusion Criteria:
-Dyspnea primarily due to non-cardiac causes
-Known history of respiratory disorders requiring the daily use of IV or oral steroids (does not include inhaled steroids); need for intubation or the current use of IV or oral steroids for COPD
-Temperature >38.5°C (oral or equivalent) or sepsis or active infection requiring IV anti-microbial treatment
-Clinical evidence of acute coronary syndrome currently or within 30 days prior to enrollment.
-AHF due to significant arrhythmias, which include any of the following: sustained ventricular tachycardia, bradycardia with sustained ventricular rate <45 beats per minute, or atrial fibrillation/flutter with sustained ventricular response of >130 beats per minute
-Patients with severe renal impairment defined as pre-randomization eGFR < 25 mL/min/1.73m2 calculated using the sMDRD equation, and/or those receiving current or planned dialysis or ultrafiltration
-Patients with hematocrit <25%, or a history of blood transfusion within the 14 days prior to screening, or active life-threatening GI bleeding.
-Known hepatic impairment (as evidenced by total bilirubin > 3 mg/dL, or increased ammonia levels, if performed) or history of cirrhosis with evidence of portal hypertension such as varices.
-Significant, uncorrected, left ventricular outflow obstruction, such as obstructive hypertrophic cardiomyopathy or severe aortic stenosis (i.e., aortic valve area <1.0 cm2 or mean gradient >40 mmHg on prior or current echocardiogram), and severe mitral stenosis

-Severe aortic insufficiency or severe mitral regurgitation for which surgical or percutaneous intervention is indicated.
-Documented, prior to or at the time of randomization, restrictive amyloid myocardiopathy, OR 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 (RLX030)	Placebo
Started	3274	3271
Safety set	3257	3248
Full analysis set	3274	3271
Biomarker analysis set	521	510
Completed	3266	3262
Not Completed	8	9
Withdrawal by Subject	8	7
Lost to Follow-up	0	2

Baseline Characteristics

	Serelaxin (RLX030)	Placebo	Total
Number of Participants [units: participants]	3274	3271	6545

Age Continuous (units: Years) Mean ± Standard Deviation			
	73.1±11.24	72.8±11.17	73.0±11.20
Gender, Male/Female (units:) Count of Participants (Not Applicable)			
Female	1296	1341	2637
Male	1978	1930	3908
Race (NIH/OMB) (units:) Count of Participants (Not Applicable)			
American Indian or Alaska Native	13	18	31
Asian	14	16	30
Native Hawaiian or Other Pacific Islander	4	4	8
Black or African American	163	171	334
White	3017	2999	6016
More than one race	46	46	92
Unknown or Not Reported	17	17	34

Summary of Efficacy

Primary Outcome Result(s)

Percentage of participants with confirmed cardiovascular (CV) death through day 180

	Serelaxin (RLX030)	Placebo
Number of Participants Analyzed [units: participants]	3274	3271
Percentage of participants with confirmed cardiovascular (CV) death through day 180 (units: Percentage of participants)		
	8.7	8.9

Statistical Analysis

Groups	Serelaxin (RLX030), Placebo	
P Value	0.3857	Adjusted alpha p-value based on multiple testing procedure.
Method	Log Rank	One-sided p-value
Hazard Ratio (HR)	0.98	
95 % Confidence Interval 2-Sided	0.83 to 1.15	

Percentage of participants with heart failure (WHF) through day 5

	Serelaxin (RLX030)	Placebo
Number of Participants Analyzed [units:	3274	3271

participants]		
Percentage of participants with heart failure (WHF) through day 5 (units: Percentage of participants)		
	6.9	7.7

Statistical Analysis

Groups	Serelaxin (RLX030), Placebo	
P Value	0.0968	Adjusted p-value based on multiple testing procedure
Method	Other Gehan's generalized Wilcoxon test	One-sided p-value
Hazard Ratio (HR)	0.89	
95 % Confidence Interval 2-Sided	0.75 to 1.07	

Secondary Outcome Result(s)

Percentage of participants with all-cause death through day 180

	Serelaxin (RLX030)	**Placebo**
Number of Participants Analyzed [units: participants]	3274	3271
Percentage of		

participants with all-cause death through day 180 (units: Percentage of participants)		
	11.2	11.9

Statistical Analysis

Groups	Serelaxin (RLX030), Placebo	
P Value	0.3890	
Method	Log Rank	2-sided p-value
Hazard Ratio (HR)	0.94	
95 % Confidence Interval 2-Sided	0.81 to 1.08	

Length of total hospital stay (LOS) during the index acute heart failure (AHF) hospitalization

	Serelaxin (RLX030)	**Placebo**
Number of Participants Analyzed [units: participants]	3274	3271
Length of total hospital stay (LOS) during the index acute heart failure (AHF) hospitalization (units: days) Mean ± Standard Deviation		
	9.362 ±	9.545 ±

	9.3581	9.6739

Statistical Analysis

Groups	Serelaxin (RLX030), Placebo	
P Value	0.2204	Based on multiple testing procedure
Method	Other Wilcoxon rank sum test	One-sided p-value

Percentage of participants with adjudicated CV death or adjudicated re-hospitalization

	Serelaxin (RLX030)	**Placebo**
Number of Participants Analyzed [units: participants]	3274	3271
Percentage of participants with adjudicated CV death or adjudicated re-hospitalization (units: Percentage of participants)		
	24.3	24.9

Statistical Analysis

Groups	Serelaxin (RLX030), Placebo	
P Value	0.2744	Adjusted p-value based on multiple testing procedure
Method	Log Rank One-sided p-value	

Hazard Ratio (HR)	0.97
95 % Confidence Interval 2-Sided	0.88 to 1.07

Length of Intensive Care Unit (ICU) and/or Coronary care unit (CCU) stay for the index AHF hospitalization

	Serelaxin (RLX030)	Placebo
Number of Participants Analyzed [units: participants]	3274	3271
Length of Intensive Care Unit (ICU) and/or Coronary care unit (CCU) stay for the index AHF hospitalization (units: days) Mean ± Standard Deviation	3.8 ± 8.29	4.1 ± 8.77

Statistical Analysis

Groups	Serelaxin (RLX030), Placebo	
P Value	0.2103	
Method	Other Wilcoxon rank sum test	2-sided p-value

Percentage of participants with first impovement since baseline in congestive signs and symptoms of heart failure

	Serelaxin (RLX030)	Placebo
Number of Participants Analyzed [units:	3044	3039

participants]

Percentage of participants with first impovement since baseline in congestive signs and symptoms of heart failure
(units: Percentage of participants)

Exertional dyspnea (n=3044,3039)	94.1	92.6
Orthopnea (n=2937,2967)	92.9	91.2
Rales (n=2888,2877)	94.1	93.7
Jugular venous pressure (n=2054,2034)	90.4	88.0
Peripheral edema, pre-sacral edema (n=2597,2622)	91.6	90.7

Statistical Analysis

Groups	Serelaxin (RLX030), Placebo	Exertional dyspnea
P Value	0.0050	
Method	Log Rank	2-sided p-value
Hazard Ratio (HR)	1.08	
95 % Confidence Interval 2-Sided	1.02 to 1.14	

Statistical Analysis

Groups	Serelaxin (RLX030), Placebo	Orthopnea
P Value	0.0051	

Method	Log Rank	2-sided p-value
Hazard Ratio (HR)	1.08	
95 % Confidence Interval 2-Sided	1.02 to 1.14	

Statistical Analysis

Groups	Serelaxin (RLX030), Placebo	Rales
P Value	0.9962	
Method	Log Rank	2-sided p-value
Hazard Ratio (HR)	1.00	
95 % Confidence Interval 2-Sided	0.95 to 1.05	

Statistical Analysis

Groups	Serelaxin (RLX030), Placebo	Jugular venous pressure
P Value	0.0196	
Method	Log Rank	2-sided p-value
Hazard Ratio (HR)	1.08	
95 % Confidence Interval 2-Sided	1.01 to 1.15	

Statistical Analysis

Groups	Serelaxin (RLX030), Placebo	Peripheral edema, pre-sacral edema
P Value	0.2158	
Method	Log Rank	2-sided p-value
Hazard Ratio (HR)	1.04	
95 % Confidence Interval 2-Sided	0.98 to 1.10	

Change from baseline in hsTroponin T biomarker

	Serelaxin (RLX030)	Placebo
Number of Participants Analyzed [units: participants]	521	510
Change from baseline in hsTroponin T biomarker (units: ug/L) Geometric Least Squares Mean (95% Confidence Interval)		
Day 2 (n=464,459)	0.9808 (0.9452 to 1.0177)	1.0432 (1.0052 to 1.0827)
Day 5 (n=458,449)	0.9589 (0.9116 to 1.0087)	1.0678 (1.0148 to 1.1237)
Day 14 (n=436,418)	0.7813 (0.7374 to 0.8278)	0.8611 (0.8119 to 0.9132)

Statistical Analysis

Groups	Serelaxin (RLX030), Placebo	Day 2

P Value	0.0209
Method	Other Repeated measures model
Other Ratio of RLX030 to placebo	0.9401
95 % Confidence Interval 2-Sided	0.8921 to 0.9907

Statistical Analysis

Groups	Serelaxin (RLX030), Placebo	Day 5
P Value	0.0034	
Method	Other Repeated measures model	
Other Ratio of RLX030 to placebo	0.8980	
95 % Confidence Interval 2-Sided	0.8358 to 0.9649	

Statistical Analysis

Groups	Serelaxin (RLX030), Placebo	Day 14
P Value	0.0209	
Method	Other Repeated measures model	
Other Ratio of RLX030 to placebo	0.9074	
95 % Confidence Interval	0.8355 to 0.9854	

2-Sided

Change from baseline in NT-proBNP biomarker

	Serelaxin (RLX030)	Placebo
Number of Participants Analyzed [units: participants]	521	510
Change from baseline in NT-proBNP biomarker (units: pg/mL) Geometric Least Squares Mean (95% Confidence Interval)		
Day 2 (n=472,465)	0.4902 (0.4609 to 0.5214)	0.5702 (0.5358 to 0.6068)
Day 5 (n=465,455)	0.4249 (0.3950 to 0.4570)	0.4454 (0.4138 to 0.4794)
Day 14 (n=446,429)	0.4265 (0.3957 to 0.4596)	0.4469 (0.4143 to 0.4822)

Statistical Analysis

Groups	Serelaxin (RLX030), Placebo	Day 2
P Value	0.0007	
Method	Other Repeated measures model	
Other Ratio of RLX030 to placebo	0.8597	
95 % Confidence Interval 2-Sided	0.7876 to 0.9385	

Statistical Analysis

Groups	Serelaxin (RLX030), Placebo	Day 5
P Value	0.3709	
Method	Other Repeated measures model	
Other Ratio of RLX030 to placebo	0.9539	
95 % Confidence Interval 2-Sided	0.8600 to 1.0579	

Statistical Analysis

Groups	Serelaxin (RLX030), Placebo	Day 14
P Value	0.3893	
Method	Other Repeated measures model	
Other Ratio of RLX030 to placebo	0.9543	
95 % Confidence Interval 2-Sided	0.8578 to 1.0617	

Change from baseline in Cystatin C biomarker

	Serelaxin (RLX030)	Placebo
Number of Participants Analyzed [units: participants]	521	510

Change from baseline in Cystatin C biomarker
(units: mg/L)
Least Squares Mean (95% Confidence Interval)

Day 2 (n=474,465)	1.0261 (1.0119 to 1.0406)	1.0648 (1.0499 to 1.0799)
Day 5 (n=467,456)	1.1171 (1.0976 to 1.1369)	1.1259 (1.1061 to 1.1461)
Day 14 (n=445,432)	1.1186 (1.0949 to 1.1429)	1.1342 (1.1098 to 1.1591)

Statistical Analysis

Groups	Serelaxin (RLX030), Placebo	Day 2
P Value	0.0003	
Method	Other Repeated measures model	
Other Ratio of RLX030 to placebo	0.9637	
95 % Confidence Interval 2-Sided	0.9447 to 0.9830	

Statistical Analysis

Groups	Serelaxin (RLX030), Placebo	Day 5
P Value	0.5361	
Method	Other Repeated measures model	
Other Ratio of RLX030 to placebo	0.9922	
95	0.9677 to 1.0172	

% Confidence Interval
2-Sided

Statistical Analysis

Groups	Serelaxin (RLX030), Placebo	Day 14
P Value	0.3750	
Method	Other Repeated measures model	
Other Ratio of RLX030 to placebo	0.9863	
95 % Confidence Interval 2-Sided	0.9567 to 1.0169	

Summary of Safety

Safety Results

All-Cause Mortality

	Serelaxin (RLX030) N = 3257	**Placebo N = 3248**
Total participants affected	363 (11.15%)	386 (11.88%)

Serious Adverse Events by System Organ Class

Time Frame	up to 180 days
Source Vocabulary for Table Default	MedDRA (19.1)
Assessment Type for Table Default	Systematic Assessment

	Serelaxin (RLX030) N = 3257	Placebo N = 3248
Total participants affected	412 (12.65%)	424 (13.05%)
Blood and lymphatic system disorders		
Anaemia	7 (0.21%)	7 (0.22%)
Anaemia macrocytic	1 (0.03%)	0 (0.00%)
Haemorrhagic anaemia	0 (0.00%)	1 (0.03%)
Heparin-induced thrombocytopenia	0 (0.00%)	1 (0.03%)
Leukocytosis	0 (0.00%)	1 (0.03%)
Leukopenia	1 (0.03%)	0 (0.00%)
Lymphadenopathy	0 (0.00%)	1 (0.03%)
Cardiac disorders		
Acute coronary syndrome	1 (0.03%)	3 (0.09%)
Acute left ventricular failure	1 (0.03%)	0 (0.00%)
Acute myocardial infarction	14 (0.43%)	12 (0.37%)

Angina pectoris	1 (0.03%)	7 (0.22%)
Angina unstable	2 (0.06%)	2 (0.06%)
Aortic valve incompetence	1 (0.03%)	2 (0.06%)
Aortic valve stenosis	4 (0.12%)	9 (0.28%)
Arrhythmia	0 (0.00%)	2 (0.06%)
Arteriosclerosis coronary artery	2 (0.06%)	0 (0.00%)
Atrial fibrillation	10 (0.31%)	13 (0.40%)
Atrial flutter	2 (0.06%)	2 (0.06%)
Atrial thrombosis	0 (0.00%)	1 (0.03%)
Atrioventricular block	1 (0.03%)	0 (0.00%)
Atrioventricular block complete	5 (0.15%)	2 (0.06%)
Atrioventricular block second degree	0 (0.00%)	1 (0.03%)
Atrioventricular dissociation	1 (0.03%)	0 (0.00%)
Bradyarrhythmia	1 (0.03%)	1 (0.03%)
Bradycardia	4 (0.12%)	4 (0.12%)
Cardiac arrest	4 (0.12%)	9 (0.28%)
Cardiac failure	62 (1.90%)	68 (2.09%)
Cardiac failure acute	14 (0.43%)	8 (0.25%)
Cardiac failure chronic	2 (0.06%)	3 (0.09%)
Cardiac failure congestive	12 (0.37%)	9 (0.28%)
Cardiogenic shock	5 (0.15%)	6 (0.18%)
Cardiopulmonary failure	1 (0.03%)	0 (0.00%)

Cardiorenal syndrome	1 (0.03%)	2 (0.06%)
Cardio-respiratory arrest	2 (0.06%)	2 (0.06%)
Chordae tendinae rupture	2 (0.06%)	1 (0.03%)
Congestive cardiomyopathy	0 (0.00%)	2 (0.06%)
Coronary artery disease	17 (0.52%)	12 (0.37%)
Coronary artery occlusion	1 (0.03%)	1 (0.03%)
Coronary artery perforation	1 (0.03%)	0 (0.00%)
Coronary artery stenosis	5 (0.15%)	2 (0.06%)
Defect conduction intraventricular	0 (0.00%)	1 (0.03%)
Ischaemic cardiomyopathy	1 (0.03%)	0 (0.00%)
Left ventricular dysfunction	2 (0.06%)	0 (0.00%)
Mitral valve incompetence	5 (0.15%)	5 (0.15%)
Mitral valve stenosis	0 (0.00%)	1 (0.03%)
Myocardial infarction	3 (0.09%)	4 (0.12%)
Myocardial ischaemia	2 (0.06%)	3 (0.09%)
Pericarditis	0 (0.00%)	1 (0.03%)
Sinus bradycardia	1 (0.03%)	2 (0.06%)
Sinus node dysfunction	1 (0.03%)	2 (0.06%)
Supraventricular tachycardia	1 (0.03%)	2 (0.06%)
Tachyarrhythmia	0 (0.00%)	1 (0.03%)
Tachycardia	1 (0.03%)	0 (0.00%)

Torsade de pointes	1 (0.03%)	0 (0.00%)
Ventricular arrhythmia	1 (0.03%)	1 (0.03%)
Ventricular fibrillation	4 (0.12%)	6 (0.18%)
Ventricular tachycardia	14 (0.43%)	11 (0.34%)
Endocrine disorders		
Hyperthyroidism	0 (0.00%)	1 (0.03%)
Gastrointestinal disorders		
Abdominal pain	2 (0.06%)	0 (0.00%)
Ascites	1 (0.03%)	0 (0.00%)
Colitis	0 (0.00%)	1 (0.03%)
Diarrhoea	1 (0.03%)	0 (0.00%)
Duodenal ulcer haemorrhage	1 (0.03%)	1 (0.03%)
Dyspepsia	0 (0.00%)	1 (0.03%)
Enterocolitis	0 (0.00%)	1 (0.03%)
Gastritis	1 (0.03%)	0 (0.00%)
Gastritis erosive	1 (0.03%)	0 (0.00%)
Gastroduodenal ulcer	1 (0.03%)	0 (0.00%)
Gastrointestinal haemorrhage	2 (0.06%)	2 (0.06%)
Haematochezia	1 (0.03%)	0 (0.00%)
Ileus	2 (0.06%)	0 (0.00%)
Ileus paralytic	0 (0.00%)	1 (0.03%)
Inguinal hernia	1 (0.03%)	1 (0.03%)
Intestinal stenosis	0 (0.00%)	1 (0.03%)
Large intestinal	0 (0.00%)	1 (0.03%)

haemorrhage		
Large intestine polyp	1 (0.03%)	0 (0.00%)
Melaena	1 (0.03%)	0 (0.00%)
Pancreatitis	0 (0.00%)	1 (0.03%)
Peritoneal haemorrhage	0 (0.00%)	1 (0.03%)
Rectal haemorrhage	1 (0.03%)	1 (0.03%)
Retroperitoneal haemorrhage	1 (0.03%)	0 (0.00%)
Small intestinal obstruction	0 (0.00%)	1 (0.03%)
Subileus	0 (0.00%)	1 (0.03%)
Vomiting	1 (0.03%)	0 (0.00%)
General disorders and administration site conditions		
Asthenia	0 (0.00%)	1 (0.03%)
Cardiac death	0 (0.00%)	2 (0.06%)
Drug effect increased	1 (0.03%)	0 (0.00%)
Extravasation	0 (0.00%)	1 (0.03%)
Fatigue	0 (0.00%)	1 (0.03%)
General physical health deterioration	1 (0.03%)	0 (0.00%)
Inflammation	1 (0.03%)	0 (0.00%)
Infusion site phlebitis	0 (0.00%)	1 (0.03%)
Multiple organ dysfunction syndrome	4 (0.12%)	1 (0.03%)
Non-cardiac chest pain	2 (0.06%)	0 (0.00%)
Pyrexia	0 (0.00%)	1 (0.03%)
Sudden cardiac death	3 (0.09%)	6 (0.18%)

Sudden death	0 (0.00%)	1 (0.03%)
Vascular stent occlusion	0 (0.00%)	1 (0.03%)
Hepatobiliary disorders		
Alcoholic liver disease	0 (0.00%)	1 (0.03%)
Drug-induced liver injury	0 (0.00%)	1 (0.03%)
Hepatic congestion	1 (0.03%)	0 (0.00%)
Hepatic failure	2 (0.06%)	3 (0.09%)
Hepatic function abnormal	1 (0.03%)	0 (0.00%)
Hepatocellular injury	2 (0.06%)	1 (0.03%)
Hyperbilirubinaemia	0 (0.00%)	1 (0.03%)
Jaundice	1 (0.03%)	0 (0.00%)
Liver injury	1 (0.03%)	1 (0.03%)
Immune system disorders		
Hypersensitivity	1 (0.03%)	0 (0.00%)
Infections and infestations		
Abdominal abscess	1 (0.03%)	0 (0.00%)
Appendicitis	0 (0.00%)	1 (0.03%)
Arthritis bacterial	1 (0.03%)	0 (0.00%)
Aspergilloma	0 (0.00%)	1 (0.03%)
Bacteraemia	0 (0.00%)	1 (0.03%)
Bronchitis	9 (0.28%)	4 (0.12%)
Cellulitis	0 (0.00%)	1 (0.03%)
Cholecystitis infective	1 (0.03%)	0 (0.00%)
Chronic hepatitis B	1 (0.03%)	0 (0.00%)

Clostridium difficile infection	1 (0.03%)	1 (0.03%)
Cystitis	3 (0.09%)	1 (0.03%)
Cystitis bacterial	0 (0.00%)	1 (0.03%)
Device related infection	0 (0.00%)	1 (0.03%)
Diverticulitis	0 (0.00%)	1 (0.03%)
Enterocolitis bacterial	0 (0.00%)	1 (0.03%)
Erysipelas	1 (0.03%)	0 (0.00%)
Gastroenteritis	2 (0.06%)	2 (0.06%)
Gastroenteritis clostridial	0 (0.00%)	1 (0.03%)
Influenza	1 (0.03%)	0 (0.00%)
Intervertebral discitis	0 (0.00%)	1 (0.03%)
Lower respiratory tract infection	2 (0.06%)	0 (0.00%)
Nasopharyngitis	0 (0.00%)	1 (0.03%)
Nosocomial infection	1 (0.03%)	0 (0.00%)
Orchitis	0 (0.00%)	1 (0.03%)
Pharyngitis	1 (0.03%)	0 (0.00%)
Pneumococcal sepsis	1 (0.03%)	0 (0.00%)
Pneumonia	34 (1.04%)	32 (0.99%)
Pneumonia streptococcal	1 (0.03%)	0 (0.00%)
Pulmonary sepsis	1 (0.03%)	1 (0.03%)
Pyelonephritis	0 (0.00%)	1 (0.03%)
Respiratory tract infection	0 (0.00%)	1 (0.03%)
Sepsis	6 (0.18%)	8 (0.25%)
Septic shock	4 (0.12%)	2 (0.06%)

Staphylococcal bacteraemia	2 (0.06%)	3 (0.09%)
Staphylococcal infection	0 (0.00%)	1 (0.03%)
Streptococcal bacteraemia	1 (0.03%)	0 (0.00%)
Streptococcal sepsis	1 (0.03%)	0 (0.00%)
Urinary tract infection	13 (0.40%)	5 (0.15%)
Urinary tract infection pseudomonal	0 (0.00%)	1 (0.03%)
Urosepsis	1 (0.03%)	3 (0.09%)
Injury, poisoning and procedural complications		
Aortic restenosis	1 (0.03%)	0 (0.00%)
Cardiac valve replacement complication	0 (0.00%)	1 (0.03%)
Coronary artery restenosis	2 (0.06%)	1 (0.03%)
Facial bones fracture	0 (0.00%)	1 (0.03%)
Fall	1 (0.03%)	0 (0.00%)
Femoral neck fracture	2 (0.06%)	0 (0.00%)
Lumbar vertebral fracture	2 (0.06%)	0 (0.00%)
Post procedural myocardial infarction	1 (0.03%)	0 (0.00%)
Procedural complication	1 (0.03%)	0 (0.00%)
Procedural hypotension	1 (0.03%)	0 (0.00%)
Procedural pneumothorax	0 (0.00%)	1 (0.03%)

Rib fracture	1 (0.03%)	0 (0.00%)
Subdural haematoma	0 (0.00%)	2 (0.06%)
Toxicity to various agents	1 (0.03%)	0 (0.00%)
Vascular pseudoaneurysm	0 (0.00%)	2 (0.06%)
Investigations		
Aspartate aminotransferase increased	1 (0.03%)	0 (0.00%)
Blood bilirubin increased	2 (0.06%)	0 (0.00%)
Blood creatinine increased	1 (0.03%)	2 (0.06%)
Blood pressure decreased	0 (0.00%)	2 (0.06%)
Cardiac output decreased	1 (0.03%)	0 (0.00%)
C-reactive protein increased	1 (0.03%)	1 (0.03%)
Ejection fraction decreased	2 (0.06%)	2 (0.06%)
Electrocardiogram T wave inversion	0 (0.00%)	1 (0.03%)
Haemoglobin decreased	0 (0.00%)	1 (0.03%)
Hepatic enzyme increased	3 (0.09%)	1 (0.03%)
Liver function test increased	0 (0.00%)	1 (0.03%)
Oxygen saturation decreased	1 (0.03%)	0 (0.00%)
Troponin increased	1 (0.03%)	1 (0.03%)

Vascular resistance pulmonary increased	1 (0.03%)	0 (0.00%)
Metabolism and nutrition disorders		
Dehydration	3 (0.09%)	1 (0.03%)
Diabetes mellitus	0 (0.00%)	1 (0.03%)
Gout	1 (0.03%)	1 (0.03%)
Hyperkalaemia	3 (0.09%)	2 (0.06%)
Hypoglycaemia	1 (0.03%)	2 (0.06%)
Hypokalaemia	1 (0.03%)	1 (0.03%)
Hyponatraemia	1 (0.03%)	0 (0.00%)
Hypovolaemia	1 (0.03%)	0 (0.00%)
Lactic acidosis	0 (0.00%)	1 (0.03%)
Metabolic acidosis	1 (0.03%)	0 (0.00%)
Metabolic alkalosis	0 (0.00%)	1 (0.03%)
Type 2 diabetes mellitus	0 (0.00%)	1 (0.03%)
Musculoskeletal and connective tissue disorders		
Facial asymmetry	0 (0.00%)	1 (0.03%)
Joint effusion	1 (0.03%)	0 (0.00%)
Muscle haemorrhage	2 (0.06%)	0 (0.00%)
Muscle spasms	1 (0.03%)	0 (0.00%)
Musculoskeletal chest pain	1 (0.03%)	0 (0.00%)
Myositis	1 (0.03%)	0 (0.00%)
Pain in extremity	0 (0.00%)	1 (0.03%)

Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Bladder transitional cell carcinoma	1 (0.03%)	0 (0.00%)
Breast cancer	0 (0.00%)	1 (0.03%)
Colon neoplasm	1 (0.03%)	0 (0.00%)
Colorectal adenocarcinoma	0 (0.00%)	1 (0.03%)
Gastric cancer	0 (0.00%)	1 (0.03%)
Lung adenocarcinoma	1 (0.03%)	0 (0.00%)
Lung adenocarcinoma metastatic	0 (0.00%)	1 (0.03%)
Lung neoplasm malignant	1 (0.03%)	2 (0.06%)
Mediastinum neoplasm	0 (0.00%)	1 (0.03%)
Mesothelioma	0 (0.00%)	1 (0.03%)
Metastases to liver	0 (0.00%)	1 (0.03%)
Metastases to lung	0 (0.00%)	1 (0.03%)
Metastatic gastric cancer	0 (0.00%)	1 (0.03%)
Myelodysplastic syndrome	1 (0.03%)	0 (0.00%)
Ovarian neoplasm	0 (0.00%)	1 (0.03%)
Prostate cancer	1 (0.03%)	0 (0.00%)
Renal neoplasm	0 (0.00%)	1 (0.03%)
Small cell lung cancer	0 (0.00%)	1 (0.03%)
Waldenstrom's macroglobulinaemia	1 (0.03%)	0 (0.00%)

Nervous system disorders		
Altered state of consciousness	1 (0.03%)	0 (0.00%)
Aphasia	1 (0.03%)	1 (0.03%)
Brain stem stroke	0 (0.00%)	1 (0.03%)
Carotid artery stenosis	0 (0.00%)	1 (0.03%)
Carotid sinus syndrome	1 (0.03%)	1 (0.03%)
Cerebral artery embolism	0 (0.00%)	1 (0.03%)
Cerebral infarction	1 (0.03%)	1 (0.03%)
Cerebrovascular accident	2 (0.06%)	3 (0.09%)
Cognitive disorder	0 (0.00%)	1 (0.03%)
Dementia	0 (0.00%)	1 (0.03%)
Dizziness	1 (0.03%)	1 (0.03%)
Embolic stroke	1 (0.03%)	1 (0.03%)
Epilepsy	1 (0.03%)	0 (0.00%)
Haemorrhage intracranial	0 (0.00%)	1 (0.03%)
Hemiparesis	0 (0.00%)	1 (0.03%)
Hypercapnic coma	0 (0.00%)	1 (0.03%)
Ischaemic cerebral infarction	1 (0.03%)	0 (0.00%)
Ischaemic stroke	11 (0.34%)	16 (0.49%)
Loss of consciousness	1 (0.03%)	0 (0.00%)
Muscle contractions involuntary	1 (0.03%)	0 (0.00%)
Neuropathy peripheral	1 (0.03%)	0 (0.00%)

Presyncope	2 (0.06%)	0 (0.00%)
Radiculopathy	1 (0.03%)	0 (0.00%)
Seizure	2 (0.06%)	0 (0.00%)
Somnolence	1 (0.03%)	1 (0.03%)
Syncope	5 (0.15%)	3 (0.09%)
Transient ischaemic attack	6 (0.18%)	1 (0.03%)
Vascular encephalopathy	1 (0.03%)	0 (0.00%)
Product issues		
Device battery issue	1 (0.03%)	0 (0.00%)
Device leakage	1 (0.03%)	0 (0.00%)
Device malfunction	0 (0.00%)	1 (0.03%)
Psychiatric disorders		
Acute psychosis	0 (0.00%)	1 (0.03%)
Confusional state	2 (0.06%)	1 (0.03%)
Delirium	2 (0.06%)	2 (0.06%)
Delirium tremens	1 (0.03%)	0 (0.00%)
Suicidal ideation	0 (0.00%)	1 (0.03%)
Renal and urinary disorders		
Acute kidney injury	20 (0.61%)	25 (0.77%)
Anuria	2 (0.06%)	0 (0.00%)
Azotaemia	1 (0.03%)	0 (0.00%)
Chronic kidney disease	4 (0.12%)	3 (0.09%)
Haematuria	1 (0.03%)	1 (0.03%)

Nephropathy toxic	0 (0.00%)	6 (0.18%)
Nephrotic syndrome	1 (0.03%)	1 (0.03%)
Oliguria	1 (0.03%)	1 (0.03%)
Prerenal failure	1 (0.03%)	0 (0.00%)
Renal artery stenosis	0 (0.00%)	1 (0.03%)
Renal failure	10 (0.31%)	16 (0.49%)
Renal impairment	13 (0.40%)	9 (0.28%)
Renal mass	0 (0.00%)	1 (0.03%)
Urinary retention	1 (0.03%)	0 (0.00%)
Reproductive system and breast disorders		
Acquired phimosis	0 (0.00%)	1 (0.03%)
Benign prostatic hyperplasia	0 (0.00%)	1 (0.03%)
Respiratory, thoracic and mediastinal disorders		
Acute pulmonary oedema	5 (0.15%)	5 (0.15%)
Acute respiratory distress syndrome	1 (0.03%)	1 (0.03%)
Acute respiratory failure	3 (0.09%)	3 (0.09%)
Bronchitis chronic	0 (0.00%)	1 (0.03%)
Bronchospasm	1 (0.03%)	1 (0.03%)
Chronic obstructive pulmonary disease	5 (0.15%)	7 (0.22%)
Dyspnoea	6 (0.18%)	5 (0.15%)
Dyspnoea exertional	0 (0.00%)	1 (0.03%)
Epistaxis	0 (0.00%)	1 (0.03%)

Haemothorax	1 (0.03%)	0 (0.00%)
Hypercapnia	0 (0.00%)	1 (0.03%)
Hypoxia	1 (0.03%)	2 (0.06%)
Interstitial lung disease	1 (0.03%)	1 (0.03%)
Lung infiltration	0 (0.00%)	1 (0.03%)
Pleural effusion	5 (0.15%)	2 (0.06%)
Pneumothorax	0 (0.00%)	2 (0.06%)
Pulmonary cavitation	0 (0.00%)	1 (0.03%)
Pulmonary embolism	5 (0.15%)	7 (0.22%)
Pulmonary fibrosis	1 (0.03%)	1 (0.03%)
Pulmonary hypertension	1 (0.03%)	1 (0.03%)
Pulmonary mass	0 (0.00%)	1 (0.03%)
Pulmonary oedema	3 (0.09%)	2 (0.06%)
Respiratory acidosis	0 (0.00%)	1 (0.03%)
Respiratory arrest	0 (0.00%)	1 (0.03%)
Respiratory depression	0 (0.00%)	1 (0.03%)
Respiratory distress	1 (0.03%)	0 (0.00%)
Respiratory failure	7 (0.21%)	10 (0.31%)
Skin and subcutaneous tissue disorders		
Diabetic foot	0 (0.00%)	1 (0.03%)
Drug eruption	1 (0.03%)	0 (0.00%)
Panniculitis	1 (0.03%)	0 (0.00%)
Rash maculo-papular	0 (0.00%)	1 (0.03%)
Skin ulcer	0 (0.00%)	2 (0.06%)
Surgical and medical procedures		

Cardioversion	1 (0.03%)	0 (0.00%)
Coronary artery bypass	1 (0.03%)	0 (0.00%)
Toe amputation	0 (0.00%)	1 (0.03%)
Vascular disorders		
Aortic aneurysm	0 (0.00%)	1 (0.03%)
Aortic aneurysm rupture	1 (0.03%)	0 (0.00%)
Aortic dissection	1 (0.03%)	0 (0.00%)
Arterial stenosis	0 (0.00%)	1 (0.03%)
Arteriosclerosis	0 (0.00%)	2 (0.06%)
Arteriovenous fistula	0 (0.00%)	1 (0.03%)
Deep vein thrombosis	0 (0.00%)	1 (0.03%)
Hypertension	1 (0.03%)	3 (0.09%)
Hypertensive crisis	3 (0.09%)	1 (0.03%)
Hypotension	14 (0.43%)	9 (0.28%)
Hypovolaemic shock	0 (0.00%)	1 (0.03%)
Iliac artery embolism	1 (0.03%)	0 (0.00%)
Orthostatic hypotension	0 (0.00%)	1 (0.03%)
Peripheral embolism	1 (0.03%)	0 (0.00%)
Peripheral vascular disorder	0 (0.00%)	1 (0.03%)
Phlebitis	0 (0.00%)	1 (0.03%)
Shock	1 (0.03%)	0 (0.00%)
Subclavian steal syndrome	1 (0.03%)	0 (0.00%)
Thrombophlebitis	0 (0.00%)	1 (0.03%)

Other Adverse Events by System Organ Class

Time Frame	up to 180 days
Source Vocabulary for Table Default	MedDRA (19.1)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	0.5%

	Serelaxin (RLX030) N = 3257	**Placebo N = 3248**
Total participants affected	1336 (41.02%)	1277 (39.32%)
Blood and lymphatic system disorders		
Anaemia	48 (1.47%)	47 (1.45%)
Cardiac disorders		
Angina pectoris	17 (0.52%)	15 (0.46%)
Aortic valve incompetence	21 (0.64%)	25 (0.77%)
Aortic valve stenosis	23 (0.71%)	13 (0.40%)
Atrial fibrillation	46 (1.41%)	45 (1.39%)
Bradycardia	23 (0.71%)	22 (0.68%)
Cardiac failure	162 (4.97%)	185 (5.70%)
Mitral valve incompetence	52 (1.60%)	47 (1.45%)
Tricuspid valve incompetence	30 (0.92%)	21 (0.65%)

Ventricular tachycardia	37 (1.14%)	24 (0.74%)
Gastrointestinal disorders		
Abdominal pain	18 (0.55%)	19 (0.58%)
Constipation	70 (2.15%)	57 (1.75%)
Diarrhoea	44 (1.35%)	52 (1.60%)
Nausea	59 (1.81%)	51 (1.57%)
Vomiting	30 (0.92%)	24 (0.74%)
General disorders and administration site conditions		
Non-cardiac chest pain	12 (0.37%)	20 (0.62%)
Pyrexia	31 (0.95%)	41 (1.26%)
Infections and infestations		
Bronchitis	30 (0.92%)	47 (1.45%)
Cystitis	18 (0.55%)	7 (0.22%)
Pneumonia	17 (0.52%)	22 (0.68%)
Urinary tract infection	58 (1.78%)	68 (2.09%)
Investigations		
Blood creatinine increased	36 (1.11%)	49 (1.51%)
Blood potassium decreased	15 (0.46%)	20 (0.62%)
Blood pressure decreased	36 (1.11%)	23 (0.71%)
Blood pressure systolic decreased	29 (0.89%)	24 (0.74%)
Blood urea increased	24 (0.74%)	25 (0.77%)

Metabolism and nutrition disorders		
Gout	16 (0.49%)	28 (0.86%)
Hyperglycaemia	25 (0.77%)	17 (0.52%)
Hyperkalaemia	40 (1.23%)	36 (1.11%)
Hyperuricaemia	25 (0.77%)	21 (0.65%)
Hypoglycaemia	29 (0.89%)	22 (0.68%)
Hypokalaemia	263 (8.07%)	241 (7.42%)
Hyponatraemia	19 (0.58%)	13 (0.40%)
Musculoskeletal and connective tissue disorders		
Arthralgia	25 (0.77%)	21 (0.65%)
Back pain	22 (0.68%)	26 (0.80%)
Muscle spasms	79 (2.43%)	49 (1.51%)
Pain in extremity	27 (0.83%)	32 (0.99%)
Nervous system disorders		
Dizziness	27 (0.83%)	17 (0.52%)
Headache	74 (2.27%)	92 (2.83%)
Psychiatric disorders		
Anxiety	16 (0.49%)	30 (0.92%)
Confusional state	25 (0.77%)	28 (0.86%)
Insomnia	42 (1.29%)	48 (1.48%)
Renal and urinary disorders		
Acute kidney injury	35 (1.07%)	34 (1.05%)

Haematuria	20 (0.61%)	20 (0.62%)
Renal failure	42 (1.29%)	46 (1.42%)
Renal impairment	48 (1.47%)	55 (1.69%)
Respiratory, thoracic and mediastinal disorders		
Chronic obstructive pulmonary disease	6 (0.18%)	17 (0.52%)
Cough	41 (1.26%)	36 (1.11%)
Dyspnoea	17 (0.52%)	15 (0.46%)
Epistaxis	19 (0.58%)	14 (0.43%)
Vascular disorders		
Hypertension	23 (0.71%)	37 (1.14%)
Hypotension	69 (2.12%)	58 (1.79%)

Other Relevant Findings

None

Conclusion:

- The RELAX-AHF-2 study did not provide the expected evidence for serelaxin to support serelaxin to become a potential treatment for AHF patients on top of standard of care and hence this molecule will not be contributing to address the remaining high unmet medical needs in AHF.
- The study did not meet any of its primary and key secondary endpoints.
- Slight numerical differences in favor of serelaxin for time to WHF through Day 5 and the component “re-hospitalization due to HF or RF” of the composite endpoint time to first occurrence of CV death or re-hospitalization due to HF or RF were not statistically significant.

- Serelaxin showed statistically noteworthy improvements in the assessment of signs and symptoms (e.g. exertional dyspnea, orthopnea and JVP) at certain time points up to Day 5.
- A hemodynamic effect of serelaxin was shown by a more pronounced BP reduction observed during the drug administration and up to Day 5 as compared to placebo.
- Serelaxin treatment showed favorable effect in some key renal, myocardial and liver biomarkers (e.g. creatinine, urea and eGFR, Cystatin C, hsTroponin T and NT-proBNP).
- The observed hemodynamic and biological effects were not translated into a CV mortality benefit.
- Biochemistry parameters suggested a biological effect of serelaxin in terms of potentially limiting organ dysfunction and injury during AHF.
- Serelaxin infusion was well tolerated. The AE profile after study drug exposure was generally benign and similar as for patients treated with placebo.
- As expected, serelaxin treatment was associated with a higher incidence of CBPDE and hypotension, although these events were transitory, mild or moderate in intensity, and/or mostly asymptomatic.
- The observed higher risk of hypotension with serelaxin treatment was consistent with prior experience.

Date of Clinical Trial Report

November 28, 2017