Clinical trial results:
A multicenter, prospective, randomized, open label study to assess the effect of serelaxin versus standard of care in acute heart failure (AHF) patients

Summary

EudraCT number	2013-002513-35
Trial protocol	GB AT HU IT CZ SK BE PT BG LT PL LV EE FI SI GR ES HR DK IS FR
Global end of trial date	25 April 2017

Results information

Result version number	v1 (current)
This version publication date	10 May 2018
First version publication date	10 May 2018

Trial information

Trial identification

Sponsor protocol code	CRLX030A3301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02064868
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, novartis.email@novartis.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	25 April 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 April 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

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 heart failure (WHF) requiring rescue therapy or all-cause death, from randomization through Day 5.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 January 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 56
Country: Number of subjects enrolled	Belgium: 87
Country: Number of subjects enrolled	Bulgaria: 74
Country: Number of subjects enrolled	Croatia: 11
Country: Number of subjects enrolled	Czech Republic: 78
Country: Number of subjects enrolled	Estonia: 26
Country: Number of subjects enrolled	Finland: 1
Country: Number of subjects enrolled	France: 239
Country: Number of subjects enrolled	Germany: 383
Country: Number of subjects enrolled	Greece: 49
Country: Number of subjects enrolled	Hungary: 149
Country: Number of subjects enrolled	Iceland: 8
Country: Number of subjects enrolled	Italy: 225
Country: Number of subjects enrolled	Latvia: 20
Country: Number of subjects enrolled	Lithuania: 40
Country: Number of subjects enrolled	Poland: 166
Country: Number of subjects enrolled	Portugal: 50
Country: Number of subjects enrolled	Romania: 95
Country: Number of subjects enrolled	Russian Federation: 382

Country: Number of subjects enrolled	Serbia: 176
Country: Number of subjects enrolled	Slovakia: 36
Country: Number of subjects enrolled	Slovenia: 17
Country: Number of subjects enrolled	Spain: 207
Country: Number of subjects enrolled	Switzerland: 34
Country: Number of subjects enrolled	United Kingdom: 41
Worldwide total number of subjects	2650
EEA total number of subjects	2058

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	402
From 65 to 84 years	1751
85 years and over	497

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The initial target was to randomize 3183 patients. This study was prematurely terminated (due to the neutral read-out of study RELAX-AHF-2) after 2666 patients were randomized. 16 patients had not qualified for randomization but were inadvertently randomized. These 16 patients did not enter the treatment phase and were not counted as started.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Serelaxin + Standard of Care

Arm description:

Serelaxin (30 µg/kg/day) as continuous 48 hour intravenous infusion plus standard of care.

Arm type	Experimental
Investigational medicinal product name	Serelaxin
Investigational medicinal product code	RLX030
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

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.

Arm title	Standard of Care (SOC)

Arm description:

All patients were required to receive standard of care background heart failure (HF) management during the study, according to local guidelines/international standards. This treatment can include but is not limited to intravenous and/or oral diuretics, angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor antagonists, beta blockers and aldosterone receptor antagonists, etc.

Arm type	Standard of Care

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Serelaxin + Standard of Care	Standard of Care (SOC)
Started	1756	894
Full Analysis Set	1756	894
Safety Set	1729	894
Completed	1722	881
Not completed	34	13
Consent withdrawn by subject	14	3

Physician decision	1	-
Technical Problems or Missing	5	2
Lost to follow-up	14	8

Baseline characteristics

Reporting groups	
Reporting group title	Serelaxin + Standard of Care
Reporting group description:	
Serelaxin (30 µg/kg/day) as continuous 48 hour intravenous infusion plus standard of care.	
Reporting group title	Standard of Care (SOC)
Reporting group description:	
All patients were required to receive standard of care background heart failure (HF) management during the study, according to local guidelines/international standards. This treatment can include but is not limited to intravenous and/or oral diuretics, angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor antagonists, beta blockers and aldosterone receptor antagonists, etc.	

Reporting group values	Serelaxin + Standard of Care	Standard of Care (SOC)	Total
Number of subjects	1756	894	2650
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	281	121	402
From 65-84 years	1151	600	1751
85 years and over	324	173	497
Age Continuous Units: Years			
arithmetic mean	75.24	75.95	
standard deviation	± 10.349	± 9.905	-
Sex: Female, Male Units: Subjects			
Female	760	383	1143
Male	996	511	1507
Race/Ethnicity, Customized Units: Subjects			
Caucasian|	1706	869	2575
Black|	4	4	8
Asian|	5	2	7
Unknown|	16	7	23
Other|	25	12	37

End points

End points reporting groups

Reporting group title	Serelaxin + Standard of Care
Reporting group description:	
Serelaxin (30 µg/kg/day) as continuous 48 hour intravenous infusion plus standard of care.	
Reporting group title	Standard of Care (SOC)
Reporting group description:	
All patients were required to receive standard of care background heart failure (HF) management during the study, according to local guidelines/international standards. This treatment can include but is not limited to intravenous and/or oral diuretics, angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor antagonists, beta blockers and aldosterone receptor antagonists, etc.	

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

End point title	Worsening heart failure (WHF) / all cause of deaths through day 5
End point description:	
In-hospital WHF through Day 5 post-randomization included worsening signs and/or symptoms of heart failure that required an intensification of intravenous therapy for heart failure or mechanical ventilation, renal or circulatory support. A central event adjudication committee was appointed to oversee the WHF primary endpoint adjudication.	
End point type	Primary
End point timeframe:	
5 days	

End point values	Serelaxin + Standard of Care	Standard of Care (SOC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1756	894		
Units: Percentage of Participants				
number (not applicable)	4.95	6.94		

Statistical analyses

Statistical analysis title	WHF / all cause of deaths
Comparison groups	Standard of Care (SOC) v Serelaxin + Standard of Care
Number of subjects included in analysis	2650
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0172 [1]
Method	Gehan’s generalized Wilcoxon test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.71

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	0.98

Notes:

[1] - One-sided p-value

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

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

End point description:

WHF/death/readmission for heart failure through Day 14. WHF/deaths through Day 5 were adjudicated and confirmed by the Clinical Endpoint Committee, WHF/deaths after Day 5 through Day 14 and readmission through Day 14 were as reported by the investigators.

End point type	Secondary

End point timeframe:

14 days

End point values	Serelaxin + Standard of Care	Standard of Care (SOC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1756	894		
Units: Percentage of Patients				
number (not applicable)	8.49	10.63		

Statistical analyses

Statistical analysis title	WHF/death/readmission for heart failure
Comparison groups	Serelaxin + Standard of Care v Standard of Care (SOC)
Number of subjects included in analysis	2650
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0634 [2]
Method	Gehan’s generalized Wilcoxon test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	1.02

Notes:

[2] - Two-sided p-value

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

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

End point description:

Persistent or non-improvement in any signs or symptoms of HF at any post baseline visit up to Day 5.

End point type	Secondary

End point timeframe:

5 days

End point values	Serelaxin + Standard of Care	Standard of Care (SOC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1744	894		
Units: Percentage of Participants				
number (confidence interval 95%)	86 (84 to 87)	91 (89 to 93)		

Statistical analyses

Statistical analysis title	Persistent or non-improvement in HF
Comparison groups	Serelaxin + Standard of Care v Standard of Care (SOC)
Number of subjects included in analysis	2638
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Chi-squared

Secondary: Renal deterioration at any post baseline visit through day 14

End point title	Renal deterioration at any post baseline visit through day 14

End point description:

Renal deterioration is defined as > or = 0.3 mg/dL increase from screening in serum creatinine.

End point type	Secondary

End point timeframe:

14 days

End point values	Serelaxin + Standard of Care	Standard of Care (SOC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1740	889		
Units: Percentage of Participants				
number (confidence interval 95%)	36 (34 to 38)	44 (40 to 47)		

Statistical analyses

Statistical analysis title	Renal Deterioration
Comparison groups	Serelaxin + Standard of Care v Standard of Care (SOC)
Number of subjects included in analysis	2629
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0002
Method	Chi-squared

Secondary: Length of index hospital stay

End point title	Length of index hospital stay

End point description:

Length of stay (in hours) is defined as the index hospitalization discharge date and time minus the index hospitalization start date and time.

End point type	Secondary

End point timeframe:

30 Days

End point values	Serelaxin + Standard of Care	Standard of Care (SOC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1756	894		
Units: hours				
arithmetic mean (standard deviation)	251.28 (± 162.368)	243.59 (± 160.270)		

Statistical analyses

Statistical analysis title	Length of Index Hospital Stay
Comparison groups	Serelaxin + Standard of Care v Standard of Care (SOC)

Number of subjects included in analysis	2650
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1392
Method	Wilcoxon (Mann-Whitney)

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

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

End point description:

End point type	Secondary

End point timeframe:

Adverse Events (AE): 5 Days / Serious Adverse Events (SAE): 14 days / All cause deaths 30 days

End point values	Serelaxin + Standard of Care	Standard of Care (SOC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1729	894		
Units: Percentage of participants				
number (not applicable)				
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		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

EQ-5D-5L is a questionnaire designed to assess health status in adults consisting of 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). The results were converted into a single index value using UK as the reference country for all countries. Range -0.3 (worst possible state) to 1 (best possible state).

End point type	Secondary

End point timeframe:

Baseline, Day 5, Day 14

End point values	Serelaxin + Standard of Care	Standard of Care (SOC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1545[3]	793[4]		
Units: Points				
arithmetic mean (standard deviation)				
Day 5|	0.28 (± 0.298)	0.27 (± 0.292)		
Day 14|	0.32 (± 0.328)	0.31 (± 0.317)		

Notes:

[3] - 1545 Subjects Analyzed at Day 5
1486 Subjects Analyzed at Day 14
[4] - 793 Subjects Analyzed at Day 5
756 Subjects Analyzed at Day 14

Statistical analyses

Statistical analysis title	Change in EQ-5D-5L
Statistical analysis description: Day 5	
Comparison groups	Serelaxin + Standard of Care v Standard of Care (SOC)
Number of subjects included in analysis	2338
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3115
Method	Mixed models analysis

Statistical analysis title	Change in EQ-5D-5L
Statistical analysis description: Day 14	
Comparison groups	Serelaxin + Standard of Care v Standard of Care (SOC)
Number of subjects included in analysis	2338
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1236
Method	Mixed models analysis

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs are collected from FPFV until LPLV. All AEs are reported in this record from First Patient First Treatment until LPLV.
For each patient AEs were collected to Day 5 and SAEs to Day 14. Deaths were reported only if an associated (S)AE was recorded.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the SAEs field "number of deaths resulting from adverse events" all those deaths, resulting from SAEs that are deemed to be causally related to treatment.
20 additional deaths in "Serelaxin + SOC" and 18 in "SOC" were recorded outside the reporting period of (S)AEs.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Serelaxin + SOC

Reporting group description:

Serelaxin + SOC

Reporting group title	Standard of Care

Reporting group description:

Standard of care (SOC)

Serious adverse events	Serelaxin + SOC	Standard of Care	
Total subjects affected by serious adverse events			
subjects affected / exposed	214 / 1729 (12.38%)	107 / 894 (11.97%)	
number of deaths (all causes)	43	25	
number of deaths resulting from adverse events	0	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder transitional cell carcinoma			
subjects affected / exposed	0 / 1729 (0.00%)	1 / 894 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastric cancer			

subjects affected / exposed	0 / 1729 (0.00%)	1 / 894 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leiomyoma			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plasma cell myeloma			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer metastatic			
subjects affected / exposed	0 / 1729 (0.00%)	1 / 894 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial disorder			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial stenosis			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis			

subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Arteriovenous fistula			
subjects affected / exposed	0 / 1729 (0.00%)	1 / 894 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Circulatory collapse			
subjects affected / exposed	0 / 1729 (0.00%)	1 / 894 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Femoral artery aneurysm			
subjects affected / exposed	0 / 1729 (0.00%)	1 / 894 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	2 / 1729 (0.12%)	1 / 894 (0.11%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypertensive crisis			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	7 / 1729 (0.40%)	2 / 894 (0.22%)	
occurrences causally related to treatment / all	3 / 7	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Peripheral artery thrombosis			

subjects affected / exposed	2 / 1729 (0.12%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	0 / 1729 (0.00%)	1 / 894 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock haemorrhagic			
subjects affected / exposed	0 / 1729 (0.00%)	1 / 894 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Left atrial appendage occlusion			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			
subjects affected / exposed	0 / 1729 (0.00%)	1 / 894 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Fatigue			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hyperthermia			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Organ failure			
subjects affected / exposed	0 / 1729 (0.00%)	1 / 894 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pyrexia			
subjects affected / exposed	4 / 1729 (0.23%)	2 / 894 (0.22%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden cardiac death			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sudden death			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Systemic inflammatory response syndrome			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	6 / 1729 (0.35%)	1 / 894 (0.11%)	
occurrences causally related to treatment / all	0 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 1729 (0.00%)	1 / 894 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	1 / 1729 (0.06%)	1 / 894 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 1729 (0.06%)	1 / 894 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 1729 (0.12%)	3 / 894 (0.34%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemothorax			
subjects affected / exposed	1 / 1729 (0.06%)	1 / 894 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercapnia			
subjects affected / exposed	1 / 1729 (0.06%)	2 / 894 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary mass			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	3 / 1729 (0.17%)	2 / 894 (0.22%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory disorder			

subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	0 / 1729 (0.00%)	1 / 894 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	6 / 1729 (0.35%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 0	
deaths causally related to treatment / all	0 / 4	0 / 0	
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Confusional state			
subjects affected / exposed	2 / 1729 (0.12%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	2 / 1729 (0.12%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Investigations			
Blood bilirubin increased			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	1 / 1729 (0.06%)	1 / 894 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram T wave inversion			

subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heart rate decreased			
subjects affected / exposed	0 / 1729 (0.00%)	1 / 894 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
International normalised ratio decreased			
subjects affected / exposed	0 / 1729 (0.00%)	1 / 894 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
International normalised ratio increased			
subjects affected / exposed	0 / 1729 (0.00%)	1 / 894 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test increased			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oxygen saturation decreased			
subjects affected / exposed	0 / 1729 (0.00%)	1 / 894 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Injury, poisoning and procedural complications			
Abdominal injury			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Ankle fracture			
subjects affected / exposed	0 / 1729 (0.00%)	1 / 894 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Craniocerebral injury			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Fall			
subjects affected / exposed	0 / 1729 (0.00%)	2 / 894 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria traumatic			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 1729 (0.00%)	1 / 894 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	2 / 1729 (0.12%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			

subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pneumothorax			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haemorrhage			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic haematoma			
subjects affected / exposed	0 / 1729 (0.00%)	1 / 894 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular pseudoaneurysm			
subjects affected / exposed	2 / 1729 (0.12%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute left ventricular failure			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			

subjects affected / exposed	6 / 1729 (0.35%)	4 / 894 (0.45%)	
occurrences causally related to treatment / all	0 / 6	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 2	
Angina pectoris			
subjects affected / exposed	0 / 1729 (0.00%)	2 / 894 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	1 / 1729 (0.06%)	4 / 894 (0.45%)	
occurrences causally related to treatment / all	1 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Aortic valve incompetence			
subjects affected / exposed	0 / 1729 (0.00%)	1 / 894 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve stenosis			
subjects affected / exposed	1 / 1729 (0.06%)	3 / 894 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	6 / 1729 (0.35%)	1 / 894 (0.11%)	
occurrences causally related to treatment / all	1 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	3 / 1729 (0.17%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Atrioventricular block second degree			
subjects affected / exposed	0 / 1729 (0.00%)	1 / 894 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradyarrhythmia			

subjects affected / exposed	2 / 1729 (0.12%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	7 / 1729 (0.40%)	2 / 894 (0.22%)	
occurrences causally related to treatment / all	0 / 7	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bundle branch block left			
subjects affected / exposed	0 / 1729 (0.00%)	1 / 894 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	6 / 1729 (0.35%)	2 / 894 (0.22%)	
occurrences causally related to treatment / all	1 / 6	0 / 2	
deaths causally related to treatment / all	0 / 4	0 / 2	
Cardiac failure			
subjects affected / exposed	38 / 1729 (2.20%)	26 / 894 (2.91%)	
occurrences causally related to treatment / all	1 / 39	0 / 26	
deaths causally related to treatment / all	0 / 7	0 / 8	
Cardiac failure acute			
subjects affected / exposed	6 / 1729 (0.35%)	2 / 894 (0.22%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 3	0 / 1	
Cardiac failure chronic			
subjects affected / exposed	2 / 1729 (0.12%)	1 / 894 (0.11%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	2 / 1729 (0.12%)	1 / 894 (0.11%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac hypertrophy			

subjects affected / exposed	0 / 1729 (0.00%)	1 / 894 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac ventricular thrombosis			
subjects affected / exposed	0 / 1729 (0.00%)	1 / 894 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiogenic shock			
subjects affected / exposed	3 / 1729 (0.17%)	2 / 894 (0.22%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiopulmonary failure			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiorenal syndrome			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiovascular insufficiency			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Congestive cardiomyopathy			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			

subjects affected / exposed	7 / 1729 (0.40%)	4 / 894 (0.45%)	
occurrences causally related to treatment / all	0 / 7	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	0 / 1729 (0.00%)	1 / 894 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diastolic dysfunction			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Left ventricular failure			
subjects affected / exposed	1 / 1729 (0.06%)	1 / 894 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Mitral valve incompetence			
subjects affected / exposed	5 / 1729 (0.29%)	1 / 894 (0.11%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	2 / 1729 (0.12%)	3 / 894 (0.34%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 2	0 / 2	
Myocardial ischaemia			
subjects affected / exposed	2 / 1729 (0.12%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocarditis			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right ventricular failure			

subjects affected / exposed	0 / 1729 (0.00%)	1 / 894 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sinus arrest			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stress cardiomyopathy			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	0 / 1729 (0.00%)	1 / 894 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	5 / 1729 (0.29%)	1 / 894 (0.11%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Ventricular tachycardia			
subjects affected / exposed	5 / 1729 (0.29%)	2 / 894 (0.22%)	
occurrences causally related to treatment / all	1 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Brain oedema			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Carotid artery stenosis			
subjects affected / exposed	0 / 1729 (0.00%)	1 / 894 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			

subjects affected / exposed	1 / 1729 (0.06%)	1 / 894 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Depressed level of consciousness			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	2 / 1729 (0.12%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercapnic coma			
subjects affected / exposed	0 / 1729 (0.00%)	1 / 894 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	3 / 1729 (0.17%)	4 / 894 (0.45%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 1	
Loss of consciousness			
subjects affected / exposed	0 / 1729 (0.00%)	1 / 894 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Status epilepticus			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	1 / 1729 (0.06%)	1 / 894 (0.11%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Microcytic anaemia			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Glaucoma			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain lower			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal strangulated hernia			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 1729 (0.00%)	1 / 894 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer haemorrhage			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal haemorrhage			

subjects affected / exposed	2 / 1729 (0.12%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal ischaemia			
subjects affected / exposed	3 / 1729 (0.17%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 3	0 / 0	
Melaena			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 1729 (0.12%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 1729 (0.00%)	1 / 894 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis toxic			
subjects affected / exposed	2 / 1729 (0.12%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			

Dermatitis exfoliative			
subjects affected / exposed	0 / 1729 (0.00%)	1 / 894 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	9 / 1729 (0.52%)	4 / 894 (0.45%)	
occurrences causally related to treatment / all	0 / 9	0 / 4	
deaths causally related to treatment / all	0 / 2	0 / 1	
Acute prerenal failure			
subjects affected / exposed	0 / 1729 (0.00%)	1 / 894 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anuria			
subjects affected / exposed	0 / 1729 (0.00%)	1 / 894 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	2 / 1729 (0.12%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephropathy			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephropathy toxic			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrotic syndrome			

subjects affected / exposed	1 / 1729 (0.06%)	1 / 894 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prerenal failure			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	6 / 1729 (0.35%)	3 / 894 (0.34%)	
occurrences causally related to treatment / all	1 / 6	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Renal impairment			
subjects affected / exposed	4 / 1729 (0.23%)	5 / 894 (0.56%)	
occurrences causally related to treatment / all	1 / 4	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal tubular necrosis			
subjects affected / exposed	1 / 1729 (0.06%)	1 / 894 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Chest wall haematoma			
subjects affected / exposed	0 / 1729 (0.00%)	1 / 894 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Joint swelling			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle haemorrhage			
subjects affected / exposed	0 / 1729 (0.00%)	1 / 894 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacteraemia			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	3 / 1729 (0.17%)	1 / 894 (0.11%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			

subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nosocomial infection			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oropharyngitis fungal			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parainfluenzae virus infection			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	11 / 1729 (0.64%)	6 / 894 (0.67%)	
occurrences causally related to treatment / all	1 / 11	0 / 6	
deaths causally related to treatment / all	0 / 2	0 / 1	
Pneumonia influenzal			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia klebsiella			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pneumococcal			
subjects affected / exposed	0 / 1729 (0.00%)	1 / 894 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory tract infection			

subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 1729 (0.12%)	2 / 894 (0.22%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 1	1 / 2	
Skin bacterial infection			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	0 / 1729 (0.00%)	1 / 894 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal infection			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheobronchitis			
subjects affected / exposed	2 / 1729 (0.12%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	3 / 1729 (0.17%)	4 / 894 (0.45%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			

subjects affected / exposed	2 / 1729 (0.12%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 1729 (0.12%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gout			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperammonaemia			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	1 / 1729 (0.06%)	0 / 894 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 1729 (0.06%)	2 / 894 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 1729 (0.00%)	2 / 894 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Type 2 diabetes mellitus			

subjects affected / exposed	0 / 1729 (0.00%)	1 / 894 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1.5 %

Non-serious adverse events	Serelaxin + SOC	Standard of Care	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	637 / 1729 (36.84%)	324 / 894 (36.24%)	
Investigations			
Blood pressure systolic decreased			
subjects affected / exposed	49 / 1729 (2.83%)	2 / 894 (0.22%)	
occurrences (all)	51	2	
Vascular disorders			
Hypotension			
subjects affected / exposed	48 / 1729 (2.78%)	18 / 894 (2.01%)	
occurrences (all)	49	18	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	34 / 1729 (1.97%)	23 / 894 (2.57%)	
occurrences (all)	34	23	
Cardiac failure			
subjects affected / exposed	81 / 1729 (4.68%)	56 / 894 (6.26%)	
occurrences (all)	85	58	
Mitral valve incompetence			
subjects affected / exposed	28 / 1729 (1.62%)	12 / 894 (1.34%)	
occurrences (all)	28	12	
Nervous system disorders			
Headache			
subjects affected / exposed	45 / 1729 (2.60%)	18 / 894 (2.01%)	
occurrences (all)	45	18	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	49 / 1729 (2.83%)	9 / 894 (1.01%)	
occurrences (all)	49	9	
General disorders and administration site conditions			

Pyrexia			
subjects affected / exposed	24 / 1729 (1.39%)	21 / 894 (2.35%)	
occurrences (all)	24	21	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	74 / 1729 (4.28%)	32 / 894 (3.58%)	
occurrences (all)	74	32	
Diarrhoea			
subjects affected / exposed	29 / 1729 (1.68%)	21 / 894 (2.35%)	
occurrences (all)	29	21	
Nausea			
subjects affected / exposed	40 / 1729 (2.31%)	17 / 894 (1.90%)	
occurrences (all)	40	17	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	27 / 1729 (1.56%)	16 / 894 (1.79%)	
occurrences (all)	28	16	
Insomnia			
subjects affected / exposed	58 / 1729 (3.35%)	21 / 894 (2.35%)	
occurrences (all)	58	21	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	18 / 1729 (1.04%)	18 / 894 (2.01%)	
occurrences (all)	18	18	
Renal impairment			
subjects affected / exposed	30 / 1729 (1.74%)	18 / 894 (2.01%)	
occurrences (all)	30	18	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	28 / 1729 (1.62%)	11 / 894 (1.23%)	
occurrences (all)	28	11	
Muscle spasms			
subjects affected / exposed	33 / 1729 (1.91%)	8 / 894 (0.89%)	
occurrences (all)	33	8	
Infections and infestations			

Bronchitis			
subjects affected / exposed	24 / 1729 (1.39%)	14 / 894 (1.57%)	
occurrences (all)	24	14	
Urinary tract infection			
subjects affected / exposed	56 / 1729 (3.24%)	26 / 894 (2.91%)	
occurrences (all)	56	26	
Metabolism and nutrition disorders			
Hyperuricaemia			
subjects affected / exposed	47 / 1729 (2.72%)	35 / 894 (3.91%)	
occurrences (all)	47	35	
Hypokalaemia			
subjects affected / exposed	119 / 1729 (6.88%)	73 / 894 (8.17%)	
occurrences (all)	120	74	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 February 2013	Amendment 1 was initiated at the request of German Health Authorities and was applicable only to German sites participating in this trial. As part of the review process, German health authorities requested to amend the protocol with inclusion of the following 2 requirements: 1. As part of additional safety measures and to avoid any potential risk of hypotension with the infusion of serelaxin, it was recommended to clarify the use of an infusion pump, a drip or any other controllable infusion systems to ensure a constant infusion rate of serelaxin at 10ml/hour. 2. To further clarify the informed consent procedure related to the nature of the witness, an "independent second physician or nurse" was added who will co-sign the ICF and thereby confirm that the patient provided informed consent according to his/her own will following receipt of all study related information based on his/her ability to understand the trial procedures.
19 June 2014	Amendment 2 was introduced based on the initial feedback gathered from the investigators already screening and recruiting patients, the request for clarification from some local health authorities, and further discussions with the Executive Committee Board. These changes aimed at further strengthening the protocol, facilitating recruitment and ensuring possible data merging with other serelaxin studies like RELAX-AHF-2.
24 June 2015	Amendment 3: AHF is a complex and subjective clinical diagnosis. Since the diagnosis of AHF is primarily based on clinical observations that are interpreted bedside, in an urgent care environment, based on the clinical judgment of the investigator, the diagnosis is sometimes difficult to qualify. Therefore, the study Executive Committee recommended changes to better specify the criteria defining AHF in the patient population under investigation, correct inconsistencies and improve the overall clarity of the study.
19 October 2016	Amendment 4 was introduced since the Executive Committee recommended during its meeting held on 15th of June 2016 to increase the number of randomized patients from 2,685 to 3,183. The rationale for the increase was that the number of events constitutive of the primary endpoint was lower than expected. This decision was endorsed by the Data Monitoring Committee (DMC).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

This study was terminated early following the neutral results from the Phase III RELAX-AHF-2 (CRLX030A2301) study which did not support further development of serelaxin in AHF.

Notes: