Clinical trial results:
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

Summary

EudraCT number	2013-001498-25
Trial protocol	SK BE SE IE BG HU PT LT IT CZ AT EE DK ES LV NL GR GB PL NO
Global end of trial date	01 February 2017

Results information

Result version number	v2 (current)
This version publication date	28 April 2018
First version publication date	07 February 2018
Version creation reason	• Correction of full data set The titles of end points 1, 2, 3 and 5 have been updated.

Trial information

Trial identification

Sponsor protocol code	CRLX030A2301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01870778
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,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,

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	01 February 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 February 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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.

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	02 October 2013
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	Australia: 45
Country: Number of subjects enrolled	Argentina: 493
Country: Number of subjects enrolled	Austria: 72
Country: Number of subjects enrolled	Belgium: 53
Country: Number of subjects enrolled	Brazil: 87
Country: Number of subjects enrolled	Bulgaria: 472
Country: Number of subjects enrolled	Canada: 9
Country: Number of subjects enrolled	Chile: 6
Country: Number of subjects enrolled	Colombia: 9
Country: Number of subjects enrolled	Czech Republic: 413
Country: Number of subjects enrolled	Denmark: 18
Country: Number of subjects enrolled	France: 138
Country: Number of subjects enrolled	Germany: 641
Country: Number of subjects enrolled	United Kingdom: 138
Country: Number of subjects enrolled	Greece: 97
Country: Number of subjects enrolled	Hungary: 351
Country: Number of subjects enrolled	Ireland: 18

Country: Number of subjects enrolled	Israel: 256
Country: Number of subjects enrolled	Italy: 266
Country: Number of subjects enrolled	Mexico: 46
Country: Number of subjects enrolled	Netherlands: 150
Country: Number of subjects enrolled	Peru: 1
Country: Number of subjects enrolled	Poland: 450
Country: Number of subjects enrolled	Portugal: 59
Country: Number of subjects enrolled	Romania: 466
Country: Number of subjects enrolled	Russian Federation: 420
Country: Number of subjects enrolled	Slovakia: 258
Country: Number of subjects enrolled	South Africa: 30
Country: Number of subjects enrolled	Spain: 239
Country: Number of subjects enrolled	Sweden: 27
Country: Number of subjects enrolled	Switzerland: 42
Country: Number of subjects enrolled	Turkey: 88
Country: Number of subjects enrolled	United States: 687
Worldwide total number of subjects	6545
EEA total number of subjects	4326

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)	1411
From 65 to 84 years	4210
85 years and over	924

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants were randomized in a 1:1 ratio to Serelaxin or matching placebo.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Serelaxin (RLX030)

Arm description:

Participants received continuous intravenous infusion of serelaxin 30 ug/kg/day for 48 hours.

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:

Participants received continuous intravenous infusion of serelaxin 30 ug/kg/day for 48 hours.

Arm title	Placebo

Arm description:

Participants received continuous intravenous infusion of matching placebo to serelaxin for 48 hours.

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

Dosage and administration details:

Participants received continuous intravenous infusion of matching placebo to serelaxin for 48 hours.

Number of subjects in period 1	Serelaxin (RLX030)	Placebo
Started	3274	3271
Safety set	3257 [1]	3248 [2]
Full analysis set	3274	3271
Biomarker analysis set	521 [3]	510 [4]

Completed	3266	3262
Not completed	8	9
Consent withdrawn by subject	8	7
Lost to follow-up	-	2

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: The numbers are correct.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: The numbers are correct.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: The numbers are correct.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: The numbers are correct.

Baseline characteristics

Reporting groups	
Reporting group title	Serelaxin (RLX030)
Reporting group description:	
Participants received continuous intravenous infusion of serelaxin 30 ug/kg/day for 48 hours.	
Reporting group title	Placebo
Reporting group description:	
Participants received continuous intravenous infusion of matching placebo to serelaxin for 48 hours.	

Reporting group values	Serelaxin (RLX030)	Placebo	Total
Number of subjects	3274	3271	6545
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)	686	725	1411
From 65-84 years	2106	2104	4210
85 years and over	482	442	924
Age Continuous Units: Years			
arithmetic mean	73.1	72.8	
standard deviation	± 11.24	± 11.17	-
Gender, Male/Female Units: Subjects			
Female	1296	1341	2637
Male	1978	1930	3908

End points

End points reporting groups	
Reporting group title	Serelaxin (RLX030)
Reporting group description:	
Participants received continuous intravenous infusion of serelaxin 30 ug/kg/day for 48 hours.	
Reporting group title	Placebo
Reporting group description:	
Participants received continuous intravenous infusion of matching placebo to serelaxin for 48 hours.	

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

End point title	Percentage of participants with confirmed cardiovascular (CV) death through day 180
End point description:	
The percentage of participants with an adjudicated CV death through day 180 was assessed.	
End point type	Primary
End point timeframe:	
180 days	

End point values	Serelaxin (RLX030)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3274	3271		
Units: Percentage of participants				
number (not applicable)	8.7	8.9		

Statistical analyses

Statistical analysis title	Time to confirmed CV death
Comparison groups	Placebo v Serelaxin (RLX030)
Number of subjects included in analysis	6545
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3857 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	1.15

Notes:

[1] - Adjusted alpha p-value based on multiple testing procedure.

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

End point title	Percentage of participants with worsening of heart failure (WHF) through day 5

End point description:

The percentage of participants with WHF through day 5 was assessed.

End point type	Primary

End point timeframe:

Day 5

End point values	Serelaxin (RLX030)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3274	3271		
Units: Percentage of participants				
number (not applicable)	6.9	7.7		

Statistical analyses

Statistical analysis title	Time to WHF
Comparison groups	Serelaxin (RLX030) v Placebo
Number of subjects included in analysis	6545
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0968 [2]
Method	Gehan's generalized Wilcoxon test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	1.07

Notes:

[2] - Adjusted p-value based on multiple testing procedure

Secondary: Percentage of participants with all-cause death through day 180

End point title	Percentage of participants with all-cause death through day 180

End point description:

The percentage of participants with all-cause death through day 180 was assessed.

End point type	Secondary

End point timeframe:

180 days

End point values	Serelaxin (RLX030)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3274	3271		
Units: Percentage of participants				
number (not applicable)	11.2	11.9		

Statistical analyses

Statistical analysis title	Time to all cause death
Comparison groups	Serelaxin (RLX030) v Placebo
Number of subjects included in analysis	6545
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.389
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.81
upper limit	1.08

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

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

End point description:

Length of stay was defined as the index hospitalization discharge date and time minus the baseline date and time plus 1 day.

End point type	Secondary

End point timeframe:

180 days (Participants still in the hospital at Day 60 were censored at Day 60)

End point values	Serelaxin (RLX030)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3274	3271		
Units: days				
arithmetic mean (standard deviation)	9.362 (± 9.3581)	9.545 (± 9.6739)		

Statistical analyses

Statistical analysis title	LOS during the index AHF hospitalization
Comparison groups	Serelaxin (RLX030) v Placebo
Number of subjects included in analysis	6545
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2204 [3]
Method	Wilcoxon rank sum test

Notes:

[3] - Based on multiple testing procedure

Secondary: Percentage of participants with first occurrence of adjudicated CV death or adjudicated re-hospitalization

End point title	Percentage of participants with first occurrence of adjudicated CV death or adjudicated re-hospitalization

End point description:

The percentage of participants with adjudicated CV death or adjudicated re-hospitalization through day 180 was assessed.

End point type	Secondary

End point timeframe:

180 days

End point values	Serelaxin (RLX030)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3274	3271		
Units: Percentage of participants				
number (not applicable)	24.3	24.9		

Statistical analyses

Statistical analysis title	Time to 1st occ. of adj. CV death or adj. re-hosp.
Comparison groups	Serelaxin (RLX030) v Placebo

Number of subjects included in analysis	6545
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2744 [4]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.88
upper limit	1.07

Notes:

[4] - Adjusted p-value based on multiple testing procedure

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

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

End point description:

Length of stay was defined as the hospitalization discharge date and the time minus the baseline date and time plus 1 day.

End point type	Secondary

End point timeframe:

180 days (Patients still in the hospital at Day 60 were censored at Day 60)

End point values	Serelaxin (RLX030)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3274	3271		
Units: days				
arithmetic mean (standard deviation)	3.8 (± 8.29)	4.1 (± 8.77)		

Statistical analyses

Statistical analysis title	Length of ICU and/or CCU stay for index AHF hosp.
Comparison groups	Serelaxin (RLX030) v Placebo
Number of subjects included in analysis	6545
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2103
Method	Wilcoxon rank sum test

Secondary: Percentage of participants with first impovement since baseline in

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

End point description:

The percentage of participants with first improvement since baseline in congestive signs and symptoms of heart failure was assessed. The signs and symptoms included exertional dyspnea, orthopnea, rales, jugular venous pressure and peripheral edema/pre-sacral edema.

End point type	Secondary

End point timeframe:

From baseline to Day 5

End point values	Serelaxin (RLX030)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3044	3039		
Units: Percentage of participants				
number (not applicable)				
Exertinal 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/pre-sacral edema (n=2597,2622)	91.6	90.7		

Statistical analyses

Statistical analysis title	First improvement in exertional dyspnea
Comparison groups	Serelaxin (RLX030) v Placebo
Number of subjects included in analysis	6083
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.02
upper limit	1.14

Statistical analysis title	First improvement in orthopnea
Comparison groups	Serelaxin (RLX030) v Placebo

Number of subjects included in analysis	6083
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0051 [5]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.02
upper limit	1.14

Notes:

[5] - 2-sided p-value

Statistical analysis title	First improvement in rales
Comparison groups	Serelaxin (RLX030) v Placebo
Number of subjects included in analysis	6083
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9962 [6]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.95
upper limit	1.05

Notes:

[6] - 2-sided p-value

Statistical analysis title	First improvement in jugular venous pressure
Comparison groups	Serelaxin (RLX030) v Placebo
Number of subjects included in analysis	6083
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0196 [7]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.01
upper limit	1.15

Notes:

[7] - 2-sided p-value

Statistical analysis title	First improvement in peripheral/pre-sacral edema

Comparison groups	Serelaxin (RLX030) v Placebo
Number of subjects included in analysis	6083
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2158 [8]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.98
upper limit	1.1

Notes:

[8] - 2-sided p-value

Secondary: Change from baseline in hsTroponin T biomarker

End point title	Change from baseline in hsTroponin T biomarker

End point description:

Blood samples were collected to assess the change from baseline in hsTroponin T. The geometric least square mean (LSM) of the ratio of the post-baseline value to the baseline value is presented.

End point type	Secondary

End point timeframe:

Baseline, Day 2, Day 5 and Day 14

End point values	Serelaxin (RLX030)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	521	510		
Units: ug/L				
least squares mean (confidence interval 95%)				
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 analyses

Statistical analysis title	Change from baseline in hsTroponin T biomarker

Statistical analysis description:

Day 2

Comparison groups	Serelaxin (RLX030) v Placebo

Number of subjects included in analysis	1031
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0209
Method	Repeated measure model
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8921
upper limit	0.9907

Statistical analysis title	Change from baseline in hsTroponin T biomarker
Statistical analysis description: Day 5	
Comparison groups	Serelaxin (RLX030) v Placebo
Number of subjects included in analysis	1031
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0034
Method	Repeated measures model
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8358
upper limit	0.9649

Statistical analysis title	Change from baseline in hsTroponin T biomarker
Statistical analysis description: Day 14	
Comparison groups	Serelaxin (RLX030) v Placebo
Number of subjects included in analysis	1031
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0209
Method	Repeated measures model
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8355
upper limit	0.9854

Secondary: Change from baseline in NT-proBNP biomarker	
End point title	Change from baseline in NT-proBNP biomarker

End point description:

Blood samples were collected to assess the change from baseline in NT-proBNP. The ratio of the post-baseline value to the baseline value is presented.

End point type	Secondary

End point timeframe:

Baseline, Day 2, Day 5 and Day 14

End point values	Serelaxin (RLX030)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	521	510		
Units: pg/mL				
least squares mean (confidence interval 95%)				
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 analyses

Statistical analysis title	Change from baseline in NT-proBNP biomarker
Statistical analysis description:	
Day 2	
Comparison groups	Serelaxin (RLX030) v Placebo
Number of subjects included in analysis	1031
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0007
Method	Repeated measures model
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7876
upper limit	0.9385

Statistical analysis title	Change from baseline in NT-proBNP biomarker
Statistical analysis description:	
Day 5	
Comparison groups	Serelaxin (RLX030) v Placebo

Number of subjects included in analysis	1031
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3709
Method	Repeated measures model
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.86
upper limit	1.0579

Statistical analysis title	Change from baseline in NT-proBNP biomarker
Statistical analysis description:	
Day 14	
Comparison groups	Serelaxin (RLX030) v Placebo
Number of subjects included in analysis	1031
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3893
Method	Repeated measures model
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8578
upper limit	1.0617

Secondary: Change from baseline in Cystatin C biomarker

End point title	Change from baseline in Cystatin C biomarker
End point description:	
Blood samples were collected to assess the change from baseline in Cystatin C. The ratio of the post-baseline value to the baseline value is presented.	
End point type	Secondary
End point timeframe:	
Baseline, Day 2, Day 5 and Day 14	

End point values	Serelaxin (RLX030)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	521	510		
Units: mg/L				
least squares mean (confidence interval 95%)				
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 analyses

Statistical analysis title	Change from baseline in Cystatin C biomarker
Statistical analysis description: Day 2	
Comparison groups	Serelaxin (RLX030) v Placebo
Number of subjects included in analysis	1031
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0003
Method	Repeated measures model
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9447
upper limit	0.983

Statistical analysis title	Change from baseline in Cystatin C biomarker
Statistical analysis description: Day 5	
Comparison groups	Serelaxin (RLX030) v Placebo
Number of subjects included in analysis	1031
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5361
Method	Repeated measures model
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9677
upper limit	1.0172

Statistical analysis title	Change from baseline in Cystatin C biomarker
Statistical analysis description: Day 14	
Comparison groups	Serelaxin (RLX030) v Placebo

Number of subjects included in analysis	1031
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.375
Method	Repeated measures model
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9567
upper limit	1.0169

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	RLX030 30 ug/kg/day
Reporting group description:	
RLX030 30 ug/kg/day	
Reporting group title	Placebo
Reporting group description:	
Placebo	

Serious adverse events	RLX030 30 ug/kg/day	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	412 / 3257 (12.65%)	424 / 3248 (13.05%)	
number of deaths (all causes)	363	386	
number of deaths resulting from adverse events	6	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder transitional cell carcinoma			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon neoplasm			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			

subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric cancer			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colorectal adenocarcinoma			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (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 / 3257 (0.03%)	2 / 3248 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Lung adenocarcinoma metastatic			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Mesothelioma			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mediastinum neoplasm			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metastases to liver			

subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic gastric cancer			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to lung			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ovarian neoplasm			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelodysplastic syndrome			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal neoplasm			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Waldenstrom's macroglobulinaemia			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Small cell lung cancer			

subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic aneurysm rupture			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic aneurysm			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic dissection			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Arterial stenosis			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis			
subjects affected / exposed	0 / 3257 (0.00%)	2 / 3248 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Deep vein thrombosis			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			

subjects affected / exposed	1 / 3257 (0.03%)	3 / 3248 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypertensive crisis			
subjects affected / exposed	3 / 3257 (0.09%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	14 / 3257 (0.43%)	9 / 3248 (0.28%)	
occurrences causally related to treatment / all	5 / 14	3 / 9	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypovolaemic shock			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Iliac artery embolism			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral embolism			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phlebitis			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral vascular disorder			

subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Subclavian steal syndrome			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Cardioversion			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toe amputation			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery bypass			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (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			
Cardiac death			
subjects affected / exposed	0 / 3257 (0.00%)	2 / 3248 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	

Asthenia			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extravasation			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug effect increased			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion site phlebitis			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inflammation			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	4 / 3257 (0.12%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 3	0 / 1	
Non-cardiac chest pain			

subjects affected / exposed	2 / 3257 (0.06%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular stent occlusion			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sudden cardiac death			
subjects affected / exposed	3 / 3257 (0.09%)	6 / 3248 (0.18%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 3	0 / 6	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Acquired phimosis			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	5 / 3257 (0.15%)	5 / 3248 (0.15%)	
occurrences causally related to treatment / all	0 / 5	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 1	
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 3257 (0.03%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute respiratory failure			
subjects affected / exposed	3 / 3257 (0.09%)	3 / 3248 (0.09%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Bronchitis chronic			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	5 / 3257 (0.15%)	7 / 3248 (0.22%)	
occurrences causally related to treatment / all	0 / 5	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bronchospasm			
subjects affected / exposed	1 / 3257 (0.03%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	6 / 3257 (0.18%)	5 / 3248 (0.15%)	
occurrences causally related to treatment / all	0 / 6	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea exertional			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Epistaxis			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemothorax			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercapnia			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 3257 (0.03%)	2 / 3248 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Interstitial lung disease			
subjects affected / exposed	1 / 3257 (0.03%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infiltration			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 3257 (0.00%)	2 / 3248 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	5 / 3257 (0.15%)	2 / 3248 (0.06%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary cavitation			

subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	5 / 3257 (0.15%)	7 / 3248 (0.22%)	
occurrences causally related to treatment / all	1 / 5	0 / 7	
deaths causally related to treatment / all	1 / 5	0 / 2	
Pulmonary fibrosis			
subjects affected / exposed	1 / 3257 (0.03%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Pulmonary hypertension			
subjects affected / exposed	1 / 3257 (0.03%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	3 / 3257 (0.09%)	2 / 3248 (0.06%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary mass			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory acidosis			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory arrest			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory depression			

subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory failure			
subjects affected / exposed	7 / 3257 (0.21%)	10 / 3248 (0.31%)	
occurrences causally related to treatment / all	0 / 7	0 / 11	
deaths causally related to treatment / all	0 / 3	0 / 4	
Psychiatric disorders			
Acute psychosis			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	2 / 3257 (0.06%)	2 / 3248 (0.06%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	2 / 3257 (0.06%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium tremens			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			

Device battery issue			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device malfunction			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device leakage			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	2 / 3257 (0.06%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood pressure decreased			
subjects affected / exposed	0 / 3257 (0.00%)	2 / 3248 (0.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	1 / 3257 (0.03%)	2 / 3248 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-reactive protein increased			
subjects affected / exposed	1 / 3257 (0.03%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac output decreased			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ejection fraction decreased			
subjects affected / exposed	2 / 3257 (0.06%)	2 / 3248 (0.06%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram T wave inversion			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	3 / 3257 (0.09%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oxygen saturation decreased			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Troponin increased			
subjects affected / exposed	1 / 3257 (0.03%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test increased			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular resistance pulmonary increased			

subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Aortic restenosis			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac valve replacement complication			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial bones fracture			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery restenosis			
subjects affected / exposed	2 / 3257 (0.06%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural myocardial infarction			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural complication			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lumbar vertebral fracture			

subjects affected / exposed	2 / 3257 (0.06%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	2 / 3257 (0.06%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural hypotension			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (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	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	0 / 3257 (0.00%)	2 / 3248 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Rib fracture			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (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 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular pseudoaneurysm			
subjects affected / exposed	0 / 3257 (0.00%)	2 / 3248 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute left ventricular failure			

subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	1 / 3257 (0.03%)	3 / 3248 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 3257 (0.03%)	7 / 3248 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute myocardial infarction			
subjects affected / exposed	14 / 3257 (0.43%)	12 / 3248 (0.37%)	
occurrences causally related to treatment / all	1 / 14	1 / 12	
deaths causally related to treatment / all	1 / 2	0 / 0	
Aortic valve incompetence			
subjects affected / exposed	1 / 3257 (0.03%)	2 / 3248 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	2 / 3257 (0.06%)	2 / 3248 (0.06%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve stenosis			
subjects affected / exposed	4 / 3257 (0.12%)	9 / 3248 (0.28%)	
occurrences causally related to treatment / all	0 / 4	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	0 / 3257 (0.00%)	2 / 3248 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Atrial fibrillation			

subjects affected / exposed	10 / 3257 (0.31%)	13 / 3248 (0.40%)	
occurrences causally related to treatment / all	0 / 10	1 / 13	
deaths causally related to treatment / all	0 / 1	0 / 1	
Arteriosclerosis coronary artery			
subjects affected / exposed	2 / 3257 (0.06%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	2 / 3257 (0.06%)	2 / 3248 (0.06%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial thrombosis			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	5 / 3257 (0.15%)	2 / 3248 (0.06%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block second degree			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular dissociation			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradyarrhythmia			

subjects affected / exposed	1 / 3257 (0.03%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	4 / 3257 (0.12%)	4 / 3248 (0.12%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	4 / 3257 (0.12%)	9 / 3248 (0.28%)	
occurrences causally related to treatment / all	0 / 4	0 / 9	
deaths causally related to treatment / all	0 / 4	0 / 7	
Cardiac failure			
subjects affected / exposed	62 / 3257 (1.90%)	68 / 3248 (2.09%)	
occurrences causally related to treatment / all	5 / 62	2 / 69	
deaths causally related to treatment / all	2 / 20	0 / 22	
Cardiac failure acute			
subjects affected / exposed	14 / 3257 (0.43%)	8 / 3248 (0.25%)	
occurrences causally related to treatment / all	0 / 14	0 / 9	
deaths causally related to treatment / all	0 / 3	0 / 2	
Cardiac failure chronic			
subjects affected / exposed	2 / 3257 (0.06%)	3 / 3248 (0.09%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 2	
Cardiac failure congestive			
subjects affected / exposed	12 / 3257 (0.37%)	9 / 3248 (0.28%)	
occurrences causally related to treatment / all	1 / 12	0 / 9	
deaths causally related to treatment / all	1 / 2	0 / 1	
Cardio-respiratory arrest			
subjects affected / exposed	2 / 3257 (0.06%)	2 / 3248 (0.06%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 2	
Cardiogenic shock			

subjects affected / exposed	5 / 3257 (0.15%)	6 / 3248 (0.18%)	
occurrences causally related to treatment / all	2 / 5	0 / 6	
deaths causally related to treatment / all	1 / 3	0 / 6	
Cardiopulmonary failure			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (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 / 3257 (0.03%)	2 / 3248 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Chordae tendinae rupture			
subjects affected / exposed	2 / 3257 (0.06%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congestive cardiomyopathy			
subjects affected / exposed	0 / 3257 (0.00%)	2 / 3248 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	17 / 3257 (0.52%)	12 / 3248 (0.37%)	
occurrences causally related to treatment / all	0 / 18	0 / 12	
deaths causally related to treatment / all	0 / 1	0 / 0	
Coronary artery perforation			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	5 / 3257 (0.15%)	2 / 3248 (0.06%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery occlusion			

subjects affected / exposed	1 / 3257 (0.03%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Defect conduction intraventricular			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic cardiomyopathy			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction			
subjects affected / exposed	2 / 3257 (0.06%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Mitral valve incompetence			
subjects affected / exposed	5 / 3257 (0.15%)	5 / 3248 (0.15%)	
occurrences causally related to treatment / all	0 / 5	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	2 / 3257 (0.06%)	3 / 3248 (0.09%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve stenosis			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	3 / 3257 (0.09%)	4 / 3248 (0.12%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 2	
Sinus node dysfunction			

subjects affected / exposed	1 / 3257 (0.03%)	2 / 3248 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus bradycardia			
subjects affected / exposed	1 / 3257 (0.03%)	2 / 3248 (0.06%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Pericarditis			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 3257 (0.03%)	2 / 3248 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachyarrhythmia			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Torsade de pointes			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular arrhythmia			
subjects affected / exposed	1 / 3257 (0.03%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			

subjects affected / exposed	4 / 3257 (0.12%)	6 / 3248 (0.18%)	
occurrences causally related to treatment / all	0 / 4	0 / 6	
deaths causally related to treatment / all	0 / 1	0 / 5	
Ventricular tachycardia			
subjects affected / exposed	14 / 3257 (0.43%)	11 / 3248 (0.34%)	
occurrences causally related to treatment / all	1 / 14	2 / 12	
deaths causally related to treatment / all	0 / 2	0 / 1	
Nervous system disorders			
Altered state of consciousness			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aphasia			
subjects affected / exposed	1 / 3257 (0.03%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain stem stroke			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Carotid artery stenosis			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid sinus syndrome			
subjects affected / exposed	1 / 3257 (0.03%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral artery embolism			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			

subjects affected / exposed	1 / 3257 (0.03%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	2 / 3257 (0.06%)	3 / 3248 (0.09%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cognitive disorder			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dementia			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 3257 (0.03%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolic stroke			
subjects affected / exposed	1 / 3257 (0.03%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hemiparesis			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Epilepsy			

subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic cerebral infarction			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercapnic coma			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
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	11 / 3257 (0.34%)	16 / 3248 (0.49%)	
occurrences causally related to treatment / all	1 / 11	0 / 16	
deaths causally related to treatment / all	0 / 2	0 / 6	
Muscle contractions involuntary			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	2 / 3257 (0.06%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiculopathy			

subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	2 / 3257 (0.06%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Somnolence			
subjects affected / exposed	1 / 3257 (0.03%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	5 / 3257 (0.15%)	3 / 3248 (0.09%)	
occurrences causally related to treatment / all	1 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	6 / 3257 (0.18%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular encephalopathy			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	7 / 3257 (0.21%)	7 / 3248 (0.22%)	
occurrences causally related to treatment / all	0 / 7	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haemorrhagic anaemia			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia macrocytic			

subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heparin-induced thrombocytopenia			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 3257 (0.06%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Diarrhoea			

subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer haemorrhage			
subjects affected / exposed	1 / 3257 (0.03%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis erosive			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroduodenal ulcer			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (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 / 3257 (0.06%)	2 / 3248 (0.06%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haematochezia			

subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	2 / 3257 (0.06%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	1 / 3257 (0.03%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus paralytic			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal stenosis			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Melaena			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal haemorrhage			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine polyp			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritoneal haemorrhage			

subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Rectal haemorrhage			
subjects affected / exposed	1 / 3257 (0.03%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroperitoneal haemorrhage			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Subileus			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Alcoholic liver disease			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic congestion			

subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	2 / 3257 (0.06%)	3 / 3248 (0.09%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Hepatic function abnormal			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Drug-induced liver injury			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular injury			
subjects affected / exposed	2 / 3257 (0.06%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver injury			
subjects affected / exposed	1 / 3257 (0.03%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Drug eruption			

subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic foot			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Panniculitis			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	0 / 3257 (0.00%)	2 / 3248 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	20 / 3257 (0.61%)	25 / 3248 (0.77%)	
occurrences causally related to treatment / all	4 / 20	3 / 28	
deaths causally related to treatment / all	0 / 1	1 / 5	
Anuria			
subjects affected / exposed	2 / 3257 (0.06%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Azotaemia			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			

subjects affected / exposed	4 / 3257 (0.12%)	3 / 3248 (0.09%)	
occurrences causally related to treatment / all	0 / 4	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	1 / 3257 (0.03%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrotic syndrome			
subjects affected / exposed	1 / 3257 (0.03%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oliguria			
subjects affected / exposed	1 / 3257 (0.03%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephropathy toxic			
subjects affected / exposed	0 / 3257 (0.00%)	6 / 3248 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal artery stenosis			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prerenal failure			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	13 / 3257 (0.40%)	9 / 3248 (0.28%)	
occurrences causally related to treatment / all	1 / 13	1 / 9	
deaths causally related to treatment / all	0 / 2	0 / 3	
Renal failure			

subjects affected / exposed	10 / 3257 (0.31%)	16 / 3248 (0.49%)	
occurrences causally related to treatment / all	1 / 10	2 / 16	
deaths causally related to treatment / all	0 / 1	0 / 0	
Renal mass			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Facial asymmetry			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint effusion			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (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	2 / 3257 (0.06%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myositis			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Muscle spasms			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Arthritis bacterial			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspergilloma			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			

subjects affected / exposed	9 / 3257 (0.28%)	4 / 3248 (0.12%)	
occurrences causally related to treatment / all	0 / 9	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cholecystitis infective			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic hepatitis B			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis bacterial			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	1 / 3257 (0.03%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	3 / 3257 (0.09%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis bacterial			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			

subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis clostridial			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	2 / 3257 (0.06%)	2 / 3248 (0.06%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral discitis			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	2 / 3257 (0.06%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasopharyngitis			

subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nosocomial infection			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orchitis			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (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	34 / 3257 (1.04%)	32 / 3248 (0.99%)	
occurrences causally related to treatment / all	1 / 34	0 / 32	
deaths causally related to treatment / all	0 / 6	0 / 4	
Pneumococcal sepsis			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia streptococcal			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sepsis			
subjects affected / exposed	1 / 3257 (0.03%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			

subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	6 / 3257 (0.18%)	8 / 3248 (0.25%)	
occurrences causally related to treatment / all	0 / 6	0 / 8	
deaths causally related to treatment / all	0 / 1	0 / 4	
Septic shock			
subjects affected / exposed	4 / 3257 (0.12%)	2 / 3248 (0.06%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Staphylococcal bacteraemia			
subjects affected / exposed	2 / 3257 (0.06%)	3 / 3248 (0.09%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal bacteraemia			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal sepsis			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection pseudomonal			

subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	13 / 3257 (0.40%)	5 / 3248 (0.15%)	
occurrences causally related to treatment / all	0 / 14	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 3257 (0.03%)	3 / 3248 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	3 / 3257 (0.09%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gout			
subjects affected / exposed	1 / 3257 (0.03%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	3 / 3257 (0.09%)	2 / 3248 (0.06%)	
occurrences causally related to treatment / all	1 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 3257 (0.03%)	2 / 3248 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			

subjects affected / exposed	1 / 3257 (0.03%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemia			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			
subjects affected / exposed	1 / 3257 (0.03%)	0 / 3248 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lactic acidosis			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic alkalosis			
subjects affected / exposed	0 / 3257 (0.00%)	1 / 3248 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0.5 %

Non-serious adverse events	RLX030 30 ug/kg/day	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1336 / 3257 (41.02%)	1277 / 3248 (39.32%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	23 / 3257 (0.71%)	37 / 3248 (1.14%)	
occurrences (all)	24	37	
Hypotension			
subjects affected / exposed	69 / 3257 (2.12%)	58 / 3248 (1.79%)	
occurrences (all)	69	58	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	31 / 3257 (0.95%)	41 / 3248 (1.26%)	
occurrences (all)	31	41	
Non-cardiac chest pain			
subjects affected / exposed	12 / 3257 (0.37%)	20 / 3248 (0.62%)	
occurrences (all)	13	20	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	6 / 3257 (0.18%)	17 / 3248 (0.52%)	
occurrences (all)	8	17	
Epistaxis			
subjects affected / exposed	19 / 3257 (0.58%)	14 / 3248 (0.43%)	
occurrences (all)	19	14	
Dyspnoea			
subjects affected / exposed	17 / 3257 (0.52%)	15 / 3248 (0.46%)	
occurrences (all)	17	15	
Cough			
subjects affected / exposed	41 / 3257 (1.26%)	36 / 3248 (1.11%)	
occurrences (all)	41	36	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	16 / 3257 (0.49%)	30 / 3248 (0.92%)	
occurrences (all)	17	31	
Insomnia			

subjects affected / exposed	42 / 3257 (1.29%)	48 / 3248 (1.48%)	
occurrences (all)	42	48	
Confusional state			
subjects affected / exposed	25 / 3257 (0.77%)	28 / 3248 (0.86%)	
occurrences (all)	25	28	
Investigations			
Blood creatinine increased			
subjects affected / exposed	36 / 3257 (1.11%)	49 / 3248 (1.51%)	
occurrences (all)	36	49	
Blood potassium decreased			
subjects affected / exposed	15 / 3257 (0.46%)	20 / 3248 (0.62%)	
occurrences (all)	15	21	
Blood pressure decreased			
subjects affected / exposed	36 / 3257 (1.11%)	23 / 3248 (0.71%)	
occurrences (all)	37	23	
Blood urea increased			
subjects affected / exposed	24 / 3257 (0.74%)	25 / 3248 (0.77%)	
occurrences (all)	24	25	
Blood pressure systolic decreased			
subjects affected / exposed	29 / 3257 (0.89%)	24 / 3248 (0.74%)	
occurrences (all)	29	24	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	17 / 3257 (0.52%)	15 / 3248 (0.46%)	
occurrences (all)	17	15	
Aortic valve stenosis			
subjects affected / exposed	23 / 3257 (0.71%)	13 / 3248 (0.40%)	
occurrences (all)	23	13	
Aortic valve incompetence			
subjects affected / exposed	21 / 3257 (0.64%)	25 / 3248 (0.77%)	
occurrences (all)	21	25	
Cardiac failure			
subjects affected / exposed	162 / 3257 (4.97%)	185 / 3248 (5.70%)	
occurrences (all)	164	191	
Bradycardia			

subjects affected / exposed	23 / 3257 (0.71%)	22 / 3248 (0.68%)	
occurrences (all)	23	22	
Atrial fibrillation			
subjects affected / exposed	46 / 3257 (1.41%)	45 / 3248 (1.39%)	
occurrences (all)	47	47	
Mitral valve incompetence			
subjects affected / exposed	52 / 3257 (1.60%)	47 / 3248 (1.45%)	
occurrences (all)	52	47	
Ventricular tachycardia			
subjects affected / exposed	37 / 3257 (1.14%)	24 / 3248 (0.74%)	
occurrences (all)	38	25	
Tricuspid valve incompetence			
subjects affected / exposed	30 / 3257 (0.92%)	21 / 3248 (0.65%)	
occurrences (all)	30	21	
Nervous system disorders			
Dizziness			
subjects affected / exposed	27 / 3257 (0.83%)	17 / 3248 (0.52%)	
occurrences (all)	27	17	
Headache			
subjects affected / exposed	74 / 3257 (2.27%)	92 / 3248 (2.83%)	
occurrences (all)	76	95	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	48 / 3257 (1.47%)	47 / 3248 (1.45%)	
occurrences (all)	48	47	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	18 / 3257 (0.55%)	19 / 3248 (0.58%)	
occurrences (all)	18	19	
Constipation			
subjects affected / exposed	70 / 3257 (2.15%)	57 / 3248 (1.75%)	
occurrences (all)	70	57	
Diarrhoea			
subjects affected / exposed	44 / 3257 (1.35%)	52 / 3248 (1.60%)	
occurrences (all)	44	52	
Nausea			

subjects affected / exposed	59 / 3257 (1.81%)	51 / 3248 (1.57%)	
occurrences (all)	59	51	
Vomiting			
subjects affected / exposed	30 / 3257 (0.92%)	24 / 3248 (0.74%)	
occurrences (all)	31	24	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	20 / 3257 (0.61%)	20 / 3248 (0.62%)	
occurrences (all)	20	20	
Renal failure			
subjects affected / exposed	42 / 3257 (1.29%)	46 / 3248 (1.42%)	
occurrences (all)	42	46	
Acute kidney injury			
subjects affected / exposed	35 / 3257 (1.07%)	34 / 3248 (1.05%)	
occurrences (all)	35	34	
Renal impairment			
subjects affected / exposed	48 / 3257 (1.47%)	55 / 3248 (1.69%)	
occurrences (all)	49	55	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	22 / 3257 (0.68%)	26 / 3248 (0.80%)	
occurrences (all)	22	26	
Muscle spasms			
subjects affected / exposed	79 / 3257 (2.43%)	49 / 3248 (1.51%)	
occurrences (all)	82	50	
Arthralgia			
subjects affected / exposed	25 / 3257 (0.77%)	21 / 3248 (0.65%)	
occurrences (all)	25	22	
Pain in extremity			
subjects affected / exposed	27 / 3257 (0.83%)	32 / 3248 (0.99%)	
occurrences (all)	27	33	
Infections and infestations			
Pneumonia			
subjects affected / exposed	17 / 3257 (0.52%)	22 / 3248 (0.68%)	
occurrences (all)	17	22	
Cystitis			

subjects affected / exposed	18 / 3257 (0.55%)	7 / 3248 (0.22%)	
occurrences (all)	18	7	
Bronchitis			
subjects affected / exposed	30 / 3257 (0.92%)	47 / 3248 (1.45%)	
occurrences (all)	30	47	
Urinary tract infection			
subjects affected / exposed	58 / 3257 (1.78%)	68 / 3248 (2.09%)	
occurrences (all)	58	68	
Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	16 / 3257 (0.49%)	28 / 3248 (0.86%)	
occurrences (all)	16	28	
Hyperkalaemia			
subjects affected / exposed	40 / 3257 (1.23%)	36 / 3248 (1.11%)	
occurrences (all)	40	36	
Hyperglycaemia			
subjects affected / exposed	25 / 3257 (0.77%)	17 / 3248 (0.52%)	
occurrences (all)	25	17	
Hyperuricaemia			
subjects affected / exposed	25 / 3257 (0.77%)	21 / 3248 (0.65%)	
occurrences (all)	25	21	
Hypoglycaemia			
subjects affected / exposed	29 / 3257 (0.89%)	22 / 3248 (0.68%)	
occurrences (all)	29	24	
Hypokalaemia			
subjects affected / exposed	263 / 3257 (8.07%)	241 / 3248 (7.42%)	
occurrences (all)	268	250	
Hyponatraemia			
subjects affected / exposed	19 / 3257 (0.58%)	13 / 3248 (0.40%)	
occurrences (all)	19	13	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 August 2013	Amendment 1 introduced the following changes in order to comply with Health Authority requests stemming from the Volunteer Harmonization Procedure: • A criterion was added excluding patients with hematocrit < 25%, or a history of blood transfusion within the 14 days prior to Screening, or active life-threatening gastrointestinal bleeding. • ECG assessments were included at Screening and at Day 5 or Discharge, whichever occurred first. • An echocardiogram was included. The echocardiogram had to be performed during the index hospitalization, to determine a patient's ejection fraction which was used to classify the type of HF for subgroup analysis. The echocardiogram was to be performed as soon as possible post randomization, and prior to Discharge. • The follow up period was changed from a minimum of 14 days to 180 days for the case the study was concluded early for efficacy following the interim analysis. • A minor clarification was made to the timing of the ECG sub-study: the first sub-study ECG was to be performed at Baseline, not at Screening. • A minor clarification was made to the Laboratory sub-study urine assessment: the data was to be maintained in the source documents only and not in the database.
23 September 2013	Amendment 2 introduced the following changes: • In the original protocol, all-cause death through Day 180 was not included in the multiple testing procedure of the key secondary efficacy variables, i.e., only the other 3 key secondary efficacy variables were included. As per feedback from FDA, all 4 key secondary efficacy variables were included in the multiple testing procedure, so the overall type I error including all-cause death and other 3 key efficacy variables was controlled at 5% alpha level. • In addition, a minor change was made to the Physician assessment of signs and symptoms criteria. NA, not evaluable, was removed from the assessments for exertional dyspnea and orthopnea. This was done to avoid confusion during data collection between when the evaluation was not evaluable (patient was immobile) and when the evaluation was simply not done.
06 January 2014	Amendment 3 introduced the following changes: • Exclusion criterion #8 was amended criteria to exclude current treatment within 2 hours prior to randomization (and not at Screening) in order to improve patient recruitment. • Additional information about 5% dextrose infusion bags and materials which can be used during preparation of study treatment was included. • Filter name was updated based on the availability of a new brand name. • The timing of the physical examination was clarified due to inconsistency with the assessment schedule. • The summary of Amendment 2 was updated to remove the requirement for IRB/EC protocol approval prior to implementation since this was not valid in select countries. • Schedule of assessments table was updated to clarify the intervals for collection of WHF assessment (at hours 24, 48, 72, 96 and 120) as part of the physician assessment of HF signs and symptoms. • The safety set definition was updated to clarify a statement that any patient who has received serelaxin was included as part of the serelaxin treatment group. • Time-to-event was changed to be defined as randomization to the event. • Length of stay definition was changed to index hospitalization discharge date and time minus the randomization date and time.

09 September 2014	Amendment 4 introduced the changes to improve the overall clarity of the study inclusion and exclusion criteria: Some of the changes included: Inclusion criteria: • The criteria for hospitalization due to AHF were enhanced to read: hospitalized for AHF with the anticipated requirement of i.v. therapy (including i.v. diuretics) for at least 48 hours. • The dyspnea at rest criteria was enhanced to read: persistent dyspnea at rest or with minimal exertion at screening and at the time of randomization, despite standard background therapy for AHF including the protocol required i.v. furosemide of at least 40 mg total (or equivalent). • The BNP and NT proBNP criteria were increased to BNP ≥ 500 pg/mL or NT-proBNP ≥ 2,000 pg/mL. The following BNP and NT proBNP criteria were also added: 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. • The inclusion criteria for i.v. furosemide were updated to add the following criteria: Time from presentation to start of furosemide administration was to be less than 6 hours.
18 February 2015	Amendment 5 introduced the following changes: • The reduction of WHF events through Day 5 was added as an additional primary endpoint. • The target number of CV deaths and the sample size was increased to adjust for the alpha-split required to accommodate the additional primary objective. • Minor changes to provide some clarity and flexibility around the conduct and timing of the study visits and visit procedures.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported