Clinical trial results:
A multicenter study to evaluate safety and tolerability in patients with chronic heart failure and reduced ejection fraction from PARADIGM-HF receiving open label LCZ696

Summary

EudraCT number	2014-001971-30
Trial protocol	LV LT FI NL CZ SE SK HU PT DK EE ES IT DE BE BG FR PL
Global end of trial date	27 December 2017

Results information

Result version number	v1 (current)
This version publication date	04 January 2019
First version publication date	04 January 2019

Trial information

Trial identification

Sponsor protocol code	CLCZ696B2317

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02226120
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 December 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 December 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to continue to evaluate the safety and tolerability of LCZ696 in heart failure patients from PARADIGM-HF receiving open-label investigational drug.

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	29 October 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 71
Country: Number of subjects enrolled	Poland: 24
Country: Number of subjects enrolled	Portugal: 18
Country: Number of subjects enrolled	Romania: 32
Country: Number of subjects enrolled	Slovakia: 90
Country: Number of subjects enrolled	Spain: 97
Country: Number of subjects enrolled	Sweden: 11
Country: Number of subjects enrolled	United Kingdom: 87
Country: Number of subjects enrolled	Belgium: 30
Country: Number of subjects enrolled	Bulgaria: 86
Country: Number of subjects enrolled	Czech Republic: 70
Country: Number of subjects enrolled	Denmark: 46
Country: Number of subjects enrolled	Estonia: 10
Country: Number of subjects enrolled	Finland: 7
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Germany: 86
Country: Number of subjects enrolled	Hungary: 81
Country: Number of subjects enrolled	Italy: 47
Country: Number of subjects enrolled	Latvia: 3

Country: Number of subjects enrolled	Lithuania: 10
Country: Number of subjects enrolled	Argentina: 93
Country: Number of subjects enrolled	Brazil: 100
Country: Number of subjects enrolled	Canada: 43
Country: Number of subjects enrolled	Chile: 7
Country: Number of subjects enrolled	Guatemala: 44
Country: Number of subjects enrolled	Hong Kong: 8
Country: Number of subjects enrolled	India: 136
Country: Number of subjects enrolled	Israel: 50
Country: Number of subjects enrolled	Korea, Republic of: 36
Country: Number of subjects enrolled	Malaysia: 9
Country: Number of subjects enrolled	Mexico: 23
Country: Number of subjects enrolled	Panama: 3
Country: Number of subjects enrolled	Peru: 38
Country: Number of subjects enrolled	Philippines: 60
Country: Number of subjects enrolled	Russian Federation: 238
Country: Number of subjects enrolled	Singapore: 11
Country: Number of subjects enrolled	South Africa: 54
Country: Number of subjects enrolled	Taiwan: 27
Country: Number of subjects enrolled	Thailand: 11
Country: Number of subjects enrolled	Turkey: 19
Country: Number of subjects enrolled	United States: 62
Worldwide total number of subjects	1980
EEA total number of subjects	908

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)	729
From 65 to 84 years	1196
85 years and over	55

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 417 sites in 41 countries worldwide. 2060 patients were enrolled in the open-label extension (OLE), out of which 1979 completed the screening phase. The number of patients included in the safety set was 1980 instead of 1979 due to the study drug administration records in the database.

Pre-assignment

Screening details:

The enrollment number in the protocol section (2007) reflects the number of participants as per the Novartis Clinical Trial Management System (CTMS). The total number in the participant flow and baseline characteristics sections reflects the number of participants enrolled/treated (1980).

Period 1

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

Arms

Arm title	LCZ696

Arm description:

Angiotensin receptor antagonist neprilysin inhibitor (ARNI) with target dose of 200 mg bid

Arm type	Safety
Investigational medicinal product name	LCZ696
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

All patients previously treated with LCZ696 or enalapril in PARADIGM-HF were treated with LCZ696 at maximally tolerated doses with a target dose of 200 mg bid.

Number of subjects in period 1	LCZ696
Started	1980
Completed	1660
Not completed	320
Adverse event, serious fatal	172
Physician decision	21
Adverse event, non-fatal	60
Technical problems	4
Study terminated by sponsor	1
Non-compliance with study drug	10
Missing treatment disposition pages	2
Lost to follow-up	13

Withdrawal by parent/guardian	36
Protocol deviation	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study

Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	1980	1980	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	729	729	
From 65-84 years	1196	1196	
85 years and over	55	55	
Age continuous Units: years			
arithmetic mean	67.2		
standard deviation	± 10.56	-	
Gender categorical Units: Subjects			
Female	453	453	
Male	1527	1527	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	39	39	
Asian	305	305	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	80	80	
White	1450	1450	
More than one race	0	0	
Unknown or Not Reported	106	106	

End points

End points reporting groups

Reporting group title	LCZ696
Reporting group description:	
Angiotensin receptor antagonist neprilysin inhibitor (ARNI) with target dose of 200 mg bid	

Primary: Percentage of Participants with treatment emergent Adverse Events (AEs), Serious Adverse Events (SAEs) and Deaths as a measure of safety and tolerability of LCZ696

End point title	Percentage of Participants with treatment emergent Adverse Events (AEs), Serious Adverse Events (SAEs) and Deaths as a measure of safety and tolerability of LCZ696[1]
End point description:	
The primary assessments for safety were the reporting of angioedema, AEs suspected to be related to LCZ696, AEs leading to study drug discontinuation and serious adverse events (SAE) including death. The assessment of safety were based primarily on the frequency of adverse events of special interest, sitting systolic and diastolic blood pressure, heart rate, and serious adverse events suspected by the investigators to be related to LCZ696 for the Safety set. Only descriptive analysis done.	
End point type	Primary
End point timeframe:	
From first dose of study treatment to 30 days after last dose of study treatment	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis done

End point values	LCZ696			
Subject group type	Reporting group			
Number of subjects analysed	1980			
Units: Participants				
number (not applicable)				
AEs by Primary System Organ Class (SOC)	65.1			
SAEs by Primary System Organ Class (SOC)	28.03			
Deaths by Primary System Organ Class (SOC)	9.39			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Timeframe for AE	
Adverse event reporting additional description:	
AE additional description	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups	
Reporting group title	LCZ696
Reporting group description:	
LCZ696	

Serious adverse events	LCZ696		
Total subjects affected by serious adverse events			
subjects affected / exposed	555 / 1980 (28.03%)		
number of deaths (all causes)	186		
number of deaths resulting from adverse events	5		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	2 / 1980 (0.10%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
B-cell lymphoma			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Basal cell carcinoma			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bladder cancer recurrent			

subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bladder neoplasm			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bone cancer			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bone cancer metastatic			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Breast cancer			
subjects affected / exposed	3 / 1980 (0.15%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Cholangiocarcinoma			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Colon adenoma			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Colon cancer			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Laryngeal cancer			

subjects affected / exposed	2 / 1980 (0.10%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Lung adenocarcinoma			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Lung neoplasm			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung neoplasm malignant			
subjects affected / exposed	4 / 1980 (0.20%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 1		
Oesophageal squamous cell carcinoma			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Plasma cell myeloma			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Rectal cancer			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal cancer			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Squamous cell carcinoma			

subjects affected / exposed	2 / 1980 (0.10%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	1 / 1		
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	2 / 1980 (0.10%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Aortic embolus			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Circulatory collapse			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Deep vein thrombosis			
subjects affected / exposed	2 / 1980 (0.10%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Diabetic vascular disorder			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haematoma			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypertension			
subjects affected / exposed	2 / 1980 (0.10%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Hypotension			

subjects affected / exposed	18 / 1980 (0.91%)			
occurrences causally related to treatment / all	14 / 18			
deaths causally related to treatment / all	0 / 0			
Leriche syndrome				
subjects affected / exposed	1 / 1980 (0.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Orthostatic hypotension				
subjects affected / exposed	1 / 1980 (0.05%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Peripheral arterial occlusive disease				
subjects affected / exposed	2 / 1980 (0.10%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Peripheral artery occlusion				
subjects affected / exposed	1 / 1980 (0.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peripheral artery stenosis				
subjects affected / exposed	1 / 1980 (0.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peripheral artery thrombosis				
subjects affected / exposed	1 / 1980 (0.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Shock				
subjects affected / exposed	1 / 1980 (0.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Asthenia				

subjects affected / exposed	3 / 1980 (0.15%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Cardiac death			
subjects affected / exposed	4 / 1980 (0.20%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 4		
Chest discomfort			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chest pain			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Death			
subjects affected / exposed	3 / 1980 (0.15%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 3		
General physical health deterioration			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Malaise			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Multiple organ dysfunction syndrome			
subjects affected / exposed	7 / 1980 (0.35%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 5		
Non-cardiac chest pain			

subjects affected / exposed	4 / 1980 (0.20%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Oedema peripheral				
subjects affected / exposed	3 / 1980 (0.15%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Sudden cardiac death				
subjects affected / exposed	15 / 1980 (0.76%)			
occurrences causally related to treatment / all	0 / 15			
deaths causally related to treatment / all	0 / 15			
Sudden death				
subjects affected / exposed	13 / 1980 (0.66%)			
occurrences causally related to treatment / all	1 / 13			
deaths causally related to treatment / all	1 / 13			
Social circumstances				
Treatment noncompliance				
subjects affected / exposed	1 / 1980 (0.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
Acquired hydrocele				
subjects affected / exposed	1 / 1980 (0.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Acquired phimosis				
subjects affected / exposed	1 / 1980 (0.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Genital ulceration				
subjects affected / exposed	1 / 1980 (0.05%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Vaginal haemorrhage				
subjects affected / exposed	1 / 1980 (0.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Acute pulmonary oedema				
subjects affected / exposed	5 / 1980 (0.25%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 0			
Acute respiratory failure				
subjects affected / exposed	3 / 1980 (0.15%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 1			
Asphyxia				
subjects affected / exposed	1 / 1980 (0.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Bronchial oedema				
subjects affected / exposed	1 / 1980 (0.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bronchitis chronic				
subjects affected / exposed	1 / 1980 (0.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bronchospasm				
subjects affected / exposed	1 / 1980 (0.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Chronic obstructive pulmonary disease				
subjects affected / exposed	10 / 1980 (0.51%)			
occurrences causally related to treatment / all	0 / 10			
deaths causally related to treatment / all	0 / 0			

Dyspnoea			
subjects affected / exposed	10 / 1980 (0.51%)		
occurrences causally related to treatment / all	0 / 13		
deaths causally related to treatment / all	0 / 1		
Dyspnoea exertional			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Epistaxis			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemoptysis			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hiccups			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hydrothorax			
subjects affected / exposed	2 / 1980 (0.10%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	3 / 1980 (0.15%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Pleurisy			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			

subjects affected / exposed	8 / 1980 (0.40%)			
occurrences causally related to treatment / all	0 / 9			
deaths causally related to treatment / all	0 / 6			
Pulmonary fibrosis				
subjects affected / exposed	1 / 1980 (0.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary hypertension				
subjects affected / exposed	1 / 1980 (0.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary oedema				
subjects affected / exposed	8 / 1980 (0.40%)			
occurrences causally related to treatment / all	0 / 8			
deaths causally related to treatment / all	0 / 1			
Respiratory acidosis				
subjects affected / exposed	1 / 1980 (0.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	2 / 1980 (0.10%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 2			
Psychiatric disorders				
Delirium				
subjects affected / exposed	1 / 1980 (0.05%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Depression				
subjects affected / exposed	2 / 1980 (0.10%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Disorientation				

subjects affected / exposed	1 / 1980 (0.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Mental disorder				
subjects affected / exposed	1 / 1980 (0.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Product issues				
Device battery issue				
subjects affected / exposed	3 / 1980 (0.15%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Device malfunction				
subjects affected / exposed	1 / 1980 (0.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lead dislodgement				
subjects affected / exposed	1 / 1980 (0.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				
Arteriogram coronary				
subjects affected / exposed	1 / 1980 (0.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood bilirubin increased				
subjects affected / exposed	1 / 1980 (0.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood creatinine increased				
subjects affected / exposed	1 / 1980 (0.05%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Blood potassium decreased				

subjects affected / exposed	1 / 1980 (0.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood potassium increased				
subjects affected / exposed	2 / 1980 (0.10%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Ejection fraction abnormal				
subjects affected / exposed	1 / 1980 (0.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Functional residual capacity decreased				
subjects affected / exposed	1 / 1980 (0.05%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Hepatic enzyme increased				
subjects affected / exposed	2 / 1980 (0.10%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
International normalised ratio increased				
subjects affected / exposed	1 / 1980 (0.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Liver function test increased				
subjects affected / exposed	1 / 1980 (0.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Weight decreased				
subjects affected / exposed	2 / 1980 (0.10%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				

Chest injury			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Craniocerebral injury			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Electric shock			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fall			
subjects affected / exposed	2 / 1980 (0.10%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Femur fracture			
subjects affected / exposed	5 / 1980 (0.25%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Fibula fracture			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Foot fracture			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fractured skull depressed			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Head injury			

subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hip fracture			
subjects affected / exposed	3 / 1980 (0.15%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Humerus fracture			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Incisional hernia, obstructive			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Laceration			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Limb injury			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lower limb fracture			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Multiple injuries			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Pelvic fracture			

subjects affected / exposed	1 / 1980 (0.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Procedural haemorrhage				
subjects affected / exposed	1 / 1980 (0.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Respiratory fume inhalation disorder				
subjects affected / exposed	1 / 1980 (0.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rib fracture				
subjects affected / exposed	3 / 1980 (0.15%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Road traffic accident				
subjects affected / exposed	2 / 1980 (0.10%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Subarachnoid haemorrhage				
subjects affected / exposed	3 / 1980 (0.15%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 1			
Subdural haematoma				
subjects affected / exposed	1 / 1980 (0.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Subdural haemorrhage				
subjects affected / exposed	1 / 1980 (0.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tendon rupture				

subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thoracic vertebral fracture			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tibia fracture			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Toxicity to various agents			
subjects affected / exposed	2 / 1980 (0.10%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Vascular graft occlusion			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular pseudoaneurysm			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Phimosis			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	3 / 1980 (0.15%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		

Acute left ventricular failure			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute myocardial infarction			
subjects affected / exposed	9 / 1980 (0.45%)		
occurrences causally related to treatment / all	0 / 10		
deaths causally related to treatment / all	0 / 3		
Adams-Stokes syndrome			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Angina pectoris			
subjects affected / exposed	14 / 1980 (0.71%)		
occurrences causally related to treatment / all	1 / 14		
deaths causally related to treatment / all	0 / 0		
Angina unstable			
subjects affected / exposed	10 / 1980 (0.51%)		
occurrences causally related to treatment / all	0 / 11		
deaths causally related to treatment / all	0 / 0		
Arrhythmia			
subjects affected / exposed	4 / 1980 (0.20%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 2		
Atrial fibrillation			
subjects affected / exposed	14 / 1980 (0.71%)		
occurrences causally related to treatment / all	1 / 17		
deaths causally related to treatment / all	0 / 0		
Atrioventricular block complete			
subjects affected / exposed	5 / 1980 (0.25%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Bradycardia			

subjects affected / exposed	3 / 1980 (0.15%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Cardiac arrest			
subjects affected / exposed	13 / 1980 (0.66%)		
occurrences causally related to treatment / all	1 / 13		
deaths causally related to treatment / all	1 / 9		
Cardiac failure			
subjects affected / exposed	144 / 1980 (7.27%)		
occurrences causally related to treatment / all	2 / 184		
deaths causally related to treatment / all	0 / 35		
Cardiac failure acute			
subjects affected / exposed	21 / 1980 (1.06%)		
occurrences causally related to treatment / all	1 / 26		
deaths causally related to treatment / all	1 / 9		
Cardiac failure chronic			
subjects affected / exposed	32 / 1980 (1.62%)		
occurrences causally related to treatment / all	0 / 41		
deaths causally related to treatment / all	0 / 5		
Cardiac failure congestive			
subjects affected / exposed	20 / 1980 (1.01%)		
occurrences causally related to treatment / all	2 / 26		
deaths causally related to treatment / all	1 / 3		
Cardio-respiratory arrest			
subjects affected / exposed	7 / 1980 (0.35%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 7		
Cardiogenic shock			
subjects affected / exposed	8 / 1980 (0.40%)		
occurrences causally related to treatment / all	0 / 8		
deaths causally related to treatment / all	0 / 5		
Cardiorenal syndrome			

subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiovascular disorder			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Congestive cardiomyopathy			
subjects affected / exposed	4 / 1980 (0.20%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 2		
Cor pulmonale			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Coronary artery disease			
subjects affected / exposed	2 / 1980 (0.10%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Left ventricular dysfunction			
subjects affected / exposed	2 / 1980 (0.10%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Left ventricular failure			
subjects affected / exposed	4 / 1980 (0.20%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 2		
Myocardial infarction			
subjects affected / exposed	16 / 1980 (0.81%)		
occurrences causally related to treatment / all	0 / 17		
deaths causally related to treatment / all	0 / 9		
Myocardial ischaemia			

subjects affected / exposed	2 / 1980 (0.10%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Nodal rhythm			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Palpitations			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sinus node dysfunction			
subjects affected / exposed	2 / 1980 (0.10%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Supraventricular tachycardia			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Systolic dysfunction			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ventricular arrhythmia			
subjects affected / exposed	5 / 1980 (0.25%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 1		
Ventricular fibrillation			
subjects affected / exposed	5 / 1980 (0.25%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Ventricular tachycardia			

subjects affected / exposed	31 / 1980 (1.57%)		
occurrences causally related to treatment / all	0 / 37		
deaths causally related to treatment / all	0 / 2		
Nervous system disorders			
Aphasia			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Brain injury			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Brain oedema			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cerebellar infarction			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cerebral haemorrhage			
subjects affected / exposed	2 / 1980 (0.10%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
Cerebral infarction			
subjects affected / exposed	6 / 1980 (0.30%)		
occurrences causally related to treatment / all	0 / 8		
deaths causally related to treatment / all	0 / 1		
Cerebral ischaemia			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cerebrovascular accident			

subjects affected / exposed	13 / 1980 (0.66%)		
occurrences causally related to treatment / all	0 / 13		
deaths causally related to treatment / all	0 / 4		
Cervicogenic vertigo			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Coma			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dementia			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dizziness			
subjects affected / exposed	4 / 1980 (0.20%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Dysarthria			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Epilepsy			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Facial paralysis			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemorrhagic stroke			

subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Hemianaesthesia			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hemiparesis			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoxic-ischaemic encephalopathy			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Ischaemic cerebral infarction			
subjects affected / exposed	2 / 1980 (0.10%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Ischaemic stroke			
subjects affected / exposed	7 / 1980 (0.35%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 1		
Loss of consciousness			
subjects affected / exposed	2 / 1980 (0.10%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Post stroke seizure			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Presyncope			

subjects affected / exposed	2 / 1980 (0.10%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Radiculopathy			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Seizure			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Syncope			
subjects affected / exposed	7 / 1980 (0.35%)		
occurrences causally related to treatment / all	3 / 7		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			
subjects affected / exposed	4 / 1980 (0.20%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Normocytic anaemia			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 1980 (0.10%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Eye disorders			

Cataract				
subjects affected / exposed	1 / 1980 (0.05%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Open angle glaucoma				
subjects affected / exposed	1 / 1980 (0.05%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Refraction disorder				
subjects affected / exposed	1 / 1980 (0.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal pain				
subjects affected / exposed	9 / 1980 (0.45%)			
occurrences causally related to treatment / all	0 / 10			
deaths causally related to treatment / all	0 / 0			
Abdominal pain upper				
subjects affected / exposed	3 / 1980 (0.15%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Ascites				
subjects affected / exposed	2 / 1980 (0.10%)			
occurrences causally related to treatment / all	0 / 7			
deaths causally related to treatment / all	0 / 0			
Constipation				
subjects affected / exposed	1 / 1980 (0.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	3 / 1980 (0.15%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Diverticulum intestinal				

subjects affected / exposed	1 / 1980 (0.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Duodenal ulcer				
subjects affected / exposed	1 / 1980 (0.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Duodenitis				
subjects affected / exposed	1 / 1980 (0.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dyspepsia				
subjects affected / exposed	1 / 1980 (0.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Enteritis				
subjects affected / exposed	1 / 1980 (0.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Enterocolitis				
subjects affected / exposed	1 / 1980 (0.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastric haemorrhage				
subjects affected / exposed	1 / 1980 (0.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastric ulcer				
subjects affected / exposed	1 / 1980 (0.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastritis				

subjects affected / exposed	2 / 1980 (0.10%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal angiodysplasia			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal haemorrhage			
subjects affected / exposed	2 / 1980 (0.10%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Ileus paralytic			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Incarcerated inguinal hernia			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Inguinal hernia			
subjects affected / exposed	2 / 1980 (0.10%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Intestinal pseudo-obstruction			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Large intestinal obstruction			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Large intestine polyp			

subjects affected / exposed	1 / 1980 (0.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Melaena				
subjects affected / exposed	1 / 1980 (0.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Mesenteric vein thrombosis				
subjects affected / exposed	1 / 1980 (0.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Mouth ulceration				
subjects affected / exposed	1 / 1980 (0.05%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatic mass				
subjects affected / exposed	1 / 1980 (0.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rectal haemorrhage				
subjects affected / exposed	1 / 1980 (0.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Umbilical hernia				
subjects affected / exposed	1 / 1980 (0.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	1 / 1980 (0.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Bile duct obstruction				

subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholangitis			
subjects affected / exposed	3 / 1980 (0.15%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Cholecystitis			
subjects affected / exposed	3 / 1980 (0.15%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Cholecystitis acute			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholecystitis chronic			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholelithiasis			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Hepatic cirrhosis			
subjects affected / exposed	2 / 1980 (0.10%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hepatic congestion			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatic failure			

subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diabetic foot			
subjects affected / exposed	2 / 1980 (0.10%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	18 / 1980 (0.91%)		
occurrences causally related to treatment / all	6 / 19		
deaths causally related to treatment / all	0 / 1		
Chronic kidney disease			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haematuria			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Leukocyturia			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nephrolithiasis			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal failure			

subjects affected / exposed	12 / 1980 (0.61%)		
occurrences causally related to treatment / all	1 / 13		
deaths causally related to treatment / all	0 / 1		
Renal impairment			
subjects affected / exposed	8 / 1980 (0.40%)		
occurrences causally related to treatment / all	1 / 8		
deaths causally related to treatment / all	0 / 1		
Urethral stenosis			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary retention			
subjects affected / exposed	2 / 1980 (0.10%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypothyroidism			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Back pain			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Joint effusion				
subjects affected / exposed	1 / 1980 (0.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Osteoarthritis				
subjects affected / exposed	3 / 1980 (0.15%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Rheumatic disorder				
subjects affected / exposed	1 / 1980 (0.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal osteoarthritis				
subjects affected / exposed	1 / 1980 (0.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Abdominal sepsis				
subjects affected / exposed	1 / 1980 (0.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Appendicitis				
subjects affected / exposed	3 / 1980 (0.15%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Arthritis bacterial				
subjects affected / exposed	1 / 1980 (0.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bacteraemia				
subjects affected / exposed	1 / 1980 (0.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bronchitis				

subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bursitis infective			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Campylobacter gastroenteritis			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	2 / 1980 (0.10%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cholecystitis infective			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cystitis			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diabetic foot infection			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea infectious			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diverticulitis			

subjects affected / exposed	3 / 1980 (0.15%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Ecthyma			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Erysipelas			
subjects affected / exposed	2 / 1980 (0.10%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gangrene			
subjects affected / exposed	3 / 1980 (0.15%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
Gastroenteritis			
subjects affected / exposed	5 / 1980 (0.25%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Hepatitis E			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatitis viral			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Implant site infection			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infection			

subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Infectious pleural effusion			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Influenza			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intervertebral discitis			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Localised infection			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection			
subjects affected / exposed	4 / 1980 (0.20%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 1		
Lung infection			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Orchitis			
subjects affected / exposed	2 / 1980 (0.10%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Otitis media chronic			

subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ovarian abscess			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peritonitis			
subjects affected / exposed	4 / 1980 (0.20%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 1		
Pneumococcal sepsis			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	47 / 1980 (2.37%)		
occurrences causally related to treatment / all	0 / 48		
deaths causally related to treatment / all	0 / 12		
Postoperative wound infection			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis acute			
subjects affected / exposed	2 / 1980 (0.10%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection			
subjects affected / exposed	3 / 1980 (0.15%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Sepsis			

subjects affected / exposed	12 / 1980 (0.61%)		
occurrences causally related to treatment / all	0 / 12		
deaths causally related to treatment / all	0 / 6		
Sepsis syndrome			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Septic shock			
subjects affected / exposed	10 / 1980 (0.51%)		
occurrences causally related to treatment / all	0 / 10		
deaths causally related to treatment / all	0 / 6		
Stoma site infection			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Streptococcal bacteraemia			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tooth infection			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tracheobronchitis			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection			
subjects affected / exposed	2 / 1980 (0.10%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			

subjects affected / exposed	10 / 1980 (0.51%)			
occurrences causally related to treatment / all	0 / 10			
deaths causally related to treatment / all	0 / 0			
Urosepsis				
subjects affected / exposed	3 / 1980 (0.15%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 1			
Viral diarrhoea				
subjects affected / exposed	1 / 1980 (0.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Viral infection				
subjects affected / exposed	2 / 1980 (0.10%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Wound sepsis				
subjects affected / exposed	1 / 1980 (0.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Dehydration				
subjects affected / exposed	4 / 1980 (0.20%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Diabetes mellitus				
subjects affected / exposed	4 / 1980 (0.20%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Diabetes mellitus inadequate control				
subjects affected / exposed	2 / 1980 (0.10%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Diabetic complication				

subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fluid overload			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperkalaemia			
subjects affected / exposed	2 / 1980 (0.10%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Hypoglycaemia			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	2 / 1980 (0.10%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Metabolic acidosis			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 1980 (0.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	LCZ696		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	352 / 1980 (17.78%)		
Vascular disorders			
Hypotension			
subjects affected / exposed	252 / 1980 (12.73%)		
occurrences (all)	279		
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	118 / 1980 (5.96%)		
occurrences (all)	140		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 March 2015	Amendment 1, issued 4 months after study start, introduced the following changes: • clarify the patient population from the CLCZ696B2314 (PARADIGM-HF) was eligible for enrolment in this study, as well as facilitate tracking of those patients.
28 April 2015	Amendment 2, issued 6 months after the study start, introduced a few administrative changes.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Two patients had missing treatment epoch disposition pages but were included in Safety Analysis Set (SAF)

Notes: