Clinical trial results:
A multicenter, randomized, open label, parallel group study comparing pre-discharge and posT-discharge tReatment initiation with LCZ696 in heArt failure patieNtS with reduced ejectIon-fracTion hospItalized for an acute decOmpensation eveNt (ADHF) (the TRANSITION study)

Summary

EudraCT number	2015-003266-87
Trial protocol	DE GB SK PT SE ES CZ FR BE PL HU IT
Global end of trial date	20 June 2018

Results information

Result version number	v2 (current)
This version publication date	19 July 2020
First version publication date	06 July 2019
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	CLCZ696B2401

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02661217
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	20 June 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 June 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to evaluate the proportion of subjects in the pre-discharge and post-discharge treatment initiation groups achieving the target dose of 200 mg LCZ696 bid at the end of the Week 10 after randomization (treatment epoch), regardless of previous temporary dose interruption or down-titration.

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	12 February 2016
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	Lebanon: 33
Country: Number of subjects enrolled	Saudi Arabia: 7
Country: Number of subjects enrolled	Turkey: 43
Country: Number of subjects enrolled	Belgium: 29
Country: Number of subjects enrolled	France: 20
Country: Number of subjects enrolled	Germany: 129
Country: Number of subjects enrolled	Italy: 30
Country: Number of subjects enrolled	Norway: 30
Country: Number of subjects enrolled	Portugal: 51
Country: Number of subjects enrolled	Spain: 147
Country: Number of subjects enrolled	Sweden: 5
Country: Number of subjects enrolled	Switzerland: 21
Country: Number of subjects enrolled	United Kingdom: 88
Country: Number of subjects enrolled	Czech Republic: 78
Country: Number of subjects enrolled	Poland: 104
Country: Number of subjects enrolled	Russian Federation: 74
Country: Number of subjects enrolled	Slovakia: 57
Country: Number of subjects enrolled	Argentina: 37

Country: Number of subjects enrolled	Canada: 19
Worldwide total number of subjects	1002
EEA total number of subjects	768

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)	392
From 65 to 84 years	570
85 years and over	40

Subject disposition

Recruitment

Recruitment details:

A total of 1002 patients were randomized, including 2 screen failure patients (1 in each group) and 2 patients who were randomized in error. A total of 998 patients entered the 10 week treatment epoch: 497 patients in pre-discharge group and 501 patients in post-discharged group.

Pre-assignment

Screening details:

The study consisted of 3 Epochs: the Screening Epoch (from signing of informed consent form to randomization), the treatment epoch (10 weeks following randomization), and a 16 weeks Follow-up Epoch following treatment epoch.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	LCZ696 Pre-discharge treatment initiation

Arm description:

Patients received first dose at any point after Randomization but no later than 12 h before discharge.

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

Dosage and administration details:

Subjects were required to take the study medication bid in addition to their daily therapies, possibly at 12 hour interval (i.e., at 7:00 am in the morning and 7:00 pm in the evening). Tablets were taken with a glass of water, and were administered with or without food.

Arm title	LCZ696 Post-discharge treatment initiation

Arm description:

Patients received first dose after discharge and up to 14 days thereafter.

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

Dosage and administration details:

Subjects were required to take the study medication bid in addition to their daily therapies, possibly at 12 hour interval (i.e., at 7:00 am in the morning and 7:00 pm in the evening). Tablets were taken with a glass of water, and were administered with or without food.

Number of subjects in period 1	LCZ696 Pre-discharge treatment initiation	LCZ696 Post-discharge treatment initiation
Started	500	502
10 weeks treatment epoch	460	455
Completed	425	419
Not completed	75	83
Adverse event, serious fatal	22	17
Physician decision	12	15
Consent withdrawn by subject	15	19
Adverse event, non-fatal	10	8
Protocol Deviation	-	4
Non-compliance with study treatment	5	5
Did not enter follow-up epoch	7	10
Mis-randomized and not treated	3	1
Lost to follow-up	1	4

Baseline characteristics

Reporting groups	
Reporting group title	LCZ696 Pre-discharge treatment initiation
Reporting group description:	
Patients received first dose at any point after Randomization but no later than 12 h before discharge.	
Reporting group title	LCZ696 Post-discharge treatment initiation
Reporting group description:	
Patients received first dose after discharge and up to 14 days thereafter.	

Reporting group values	LCZ696 Pre-discharge treatment initiation	LCZ696 Post-discharge treatment initiation	Total
Number of subjects	500	502	1002
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)	206	186	392
From 65-84 years	275	295	570
85 years and over	19	21	40
Age Continuous Units: years			
arithmetic mean	66.7	67.0	
standard deviation	± 12.27	± 11.67	-
Sex: Female, Male Units: Subjects			
Female	126	125	251
Male	374	377	751
Race/Ethnicity, Customized Units: Subjects			
Caucasian	488	486	974
Black	5	8	13
Asian	7	3	10
Native American	0	1	1
Pacific Islander	0	1	1
Other	0	1	1
Unknown	0	2	2

End points

End points reporting groups

Reporting group title	LCZ696 Pre-discharge treatment initiation
Reporting group description:	
Patients received first dose at any point after Randomization but no later than 12 h before discharge.	
Reporting group title	LCZ696 Post-discharge treatment initiation
Reporting group description:	
Patients received first dose after discharge and up to 14 days thereafter.	

Primary: Percentage of patients achieving the target dose of LCZ696 200 mg bid at 10 weeks post randomization

End point title	Percentage of patients achieving the target dose of LCZ696 200 mg bid at 10 weeks post randomization
End point description:	
Percentage of patients achieving and maintaining LCZ696 200 mg bid for at least 2 weeks leading to Week 10	
End point type	Primary
End point timeframe:	
10 weeks after Randomization	

End point values	LCZ696 Pre-discharge treatment initiation	LCZ696 Post-discharge treatment initiation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	493	489		
Units: Percentage of patients				
number (not applicable)	45.44	50.72		

Statistical analyses

Statistical analysis title	Analysis of subjects achieving 200 mg at 10 weeks
Comparison groups	LCZ696 Pre-discharge treatment initiation v LCZ696 Post-discharge treatment initiation
Number of subjects included in analysis	982
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.099
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk ratio (RR)
Point estimate	0.896

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.786
upper limit	1.021

Secondary: Percentage of patients achieving and maintaining either LCZ696 100 mg and/or 200 mg bid

End point title	Percentage of patients achieving and maintaining either LCZ696 100 mg and/or 200 mg bid

End point description:

Percentage of patients achieving and maintaining either LCZ696 100 mg and/or 200 mg bid for at least 2 weeks leading to Week 10

End point type	Secondary

End point timeframe:

10 weeks after Randomization

End point values	LCZ696 Pre-discharge treatment initiation	LCZ696 Post-discharge treatment initiation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	493	489		
Units: Percentage of patients				
number (not applicable)	62.07	68.51		

Statistical analyses

Statistical analysis title	Subjects maintaining 100 and/or 200 mg
Comparison groups	LCZ696 Pre-discharge treatment initiation v LCZ696 Post-discharge treatment initiation
Number of subjects included in analysis	982
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.034
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk ratio (RR)
Point estimate	0.906
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.827
upper limit	0.993

Secondary: Percentage of patients achieving and maintaining any dose of LCZ696	
End point title	Percentage of patients achieving and maintaining any dose of LCZ696
End point description:	
Percentage of patients achieving any dose of LCZ696 for at least 2 weeks leading to 10 weeks of treatment	
End point type	Secondary
End point timeframe:	
10 weeks after Randomization	

End point values	LCZ696 Pre-discharge treatment initiation	LCZ696 Post-discharge treatment initiation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	493	489		
Units: Percentage of patients				
number (not applicable)	86.00	89.57		

Statistical analyses

Statistical analysis title	Subjects maintaining any dose
Comparison groups	LCZ696 Pre-discharge treatment initiation v LCZ696 Post-discharge treatment initiation
Number of subjects included in analysis	982
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.089
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk ratio (RR)
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.916
upper limit	1.006

Secondary: Percentage of patients permanently discontinued from treatment	
End point title	Percentage of patients permanently discontinued from treatment
End point description:	
Percentage of patients permanently discontinued from LCZ696 (1) up to week 10 due to AEs, and (2) up to week 26 due to any reasons	
End point type	Secondary
End point timeframe:	
10 weeks after Randomization AND 26 weeks after randomization	

End point values	LCZ696 Pre-discharge treatment initiation	LCZ696 Post-discharge treatment initiation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	493	489		
Units: Percentage of patients				
number (not applicable)				
up to week 10 due to AEs	7.3	4.91		
up to week 26 due to any reasons	16.84	15.95		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 26 weeks after randomization	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups	
Reporting group title	LCZ696 Pre-discharge treatment initiation
Reporting group description: Patients received first dose at any point after Randomization but no later than 12 h before discharge.	
Reporting group title	LCZ696 Post-discharge treatment
Reporting group description: Patients received first dose after discharge and up to 14 days thereafter.	
Reporting group title	All patients
Reporting group description: All patients	

Serious adverse events	LCZ696 Pre-discharge treatment initiation	LCZ696 Post-discharge treatment	All patients
Total subjects affected by serious adverse events			
subjects affected / exposed	159 / 493 (32.25%)	134 / 489 (27.40%)	293 / 982 (29.84%)
number of deaths (all causes)	23	13	36
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma gastric			
subjects affected / exposed	0 / 493 (0.00%)	1 / 489 (0.20%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain neoplasm			
subjects affected / exposed	1 / 493 (0.20%)	0 / 489 (0.00%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer			
subjects affected / exposed	2 / 493 (0.41%)	0 / 489 (0.00%)	2 / 982 (0.20%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Lung neoplasm malignant			
subjects affected / exposed	1 / 493 (0.20%)	0 / 489 (0.00%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant neoplasm of ampulla of Vater			
subjects affected / exposed	0 / 493 (0.00%)	1 / 489 (0.20%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant peritoneal neoplasm			
subjects affected / exposed	1 / 493 (0.20%)	0 / 489 (0.00%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to liver			
subjects affected / exposed	1 / 493 (0.20%)	0 / 489 (0.00%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to lung			
subjects affected / exposed	0 / 493 (0.00%)	1 / 489 (0.20%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal adenocarcinoma			
subjects affected / exposed	0 / 493 (0.00%)	1 / 489 (0.20%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transitional cell carcinoma			
subjects affected / exposed	0 / 493 (0.00%)	1 / 489 (0.20%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	0 / 493 (0.00%)	1 / 489 (0.20%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hypertension			
subjects affected / exposed	1 / 493 (0.20%)	0 / 489 (0.00%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	6 / 493 (1.22%)	2 / 489 (0.41%)	8 / 982 (0.81%)
occurrences causally related to treatment / all	2 / 5	2 / 2	4 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 493 (0.20%)	0 / 489 (0.00%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral vascular disorder			
subjects affected / exposed	2 / 493 (0.41%)	0 / 489 (0.00%)	2 / 982 (0.20%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 493 (0.20%)	0 / 489 (0.00%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Impaired healing			
subjects affected / exposed	1 / 493 (0.20%)	0 / 489 (0.00%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 493 (0.20%)	1 / 489 (0.20%)	2 / 982 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Non-cardiac chest pain			
subjects affected / exposed	2 / 493 (0.41%)	5 / 489 (1.02%)	7 / 982 (0.71%)
occurrences causally related to treatment / all	0 / 2	0 / 5	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Oedema peripheral			
subjects affected / exposed	1 / 493 (0.20%)	3 / 489 (0.61%)	4 / 982 (0.41%)
occurrences causally related to treatment / all	0 / 2	1 / 3	1 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 493 (0.00%)	1 / 489 (0.20%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden cardiac death			
subjects affected / exposed	1 / 493 (0.20%)	0 / 489 (0.00%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Sudden death			
subjects affected / exposed	2 / 493 (0.41%)	0 / 489 (0.00%)	2 / 982 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 2
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 493 (0.20%)	1 / 489 (0.20%)	2 / 982 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	1 / 493 (0.20%)	1 / 489 (0.20%)	2 / 982 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory failure			
subjects affected / exposed	1 / 493 (0.20%)	0 / 489 (0.00%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthma			

subjects affected / exposed	1 / 493 (0.20%)	0 / 489 (0.00%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	3 / 493 (0.61%)	4 / 489 (0.82%)	7 / 982 (0.71%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			
subjects affected / exposed	1 / 493 (0.20%)	1 / 489 (0.20%)	2 / 982 (0.20%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	6 / 493 (1.22%)	5 / 489 (1.02%)	11 / 982 (1.12%)
occurrences causally related to treatment / all	1 / 6	2 / 8	3 / 14
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	1 / 493 (0.20%)	0 / 489 (0.00%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mediastinal haematoma			
subjects affected / exposed	0 / 493 (0.00%)	1 / 489 (0.20%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthopnoea			
subjects affected / exposed	0 / 493 (0.00%)	1 / 489 (0.20%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 493 (0.00%)	1 / 489 (0.20%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary congestion			

subjects affected / exposed	0 / 493 (0.00%)	1 / 489 (0.20%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 493 (0.20%)	0 / 489 (0.00%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	3 / 493 (0.61%)	7 / 489 (1.43%)	10 / 982 (1.02%)
occurrences causally related to treatment / all	0 / 3	0 / 7	0 / 10
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Respiratory failure			
subjects affected / exposed	0 / 493 (0.00%)	1 / 489 (0.20%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 493 (0.00%)	1 / 489 (0.20%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device battery issue			
subjects affected / exposed	0 / 493 (0.00%)	1 / 489 (0.20%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device dislocation			
subjects affected / exposed	1 / 493 (0.20%)	0 / 489 (0.00%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood creatinine increased			
subjects affected / exposed	2 / 493 (0.41%)	0 / 489 (0.00%)	2 / 982 (0.20%)
occurrences causally related to treatment / all	2 / 2	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cardiac output decreased			
subjects affected / exposed	1 / 493 (0.20%)	0 / 489 (0.00%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ejection fraction abnormal			
subjects affected / exposed	1 / 493 (0.20%)	0 / 489 (0.00%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ejection fraction decreased			
subjects affected / exposed	0 / 493 (0.00%)	2 / 489 (0.41%)	2 / 982 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical condition abnormal			
subjects affected / exposed	1 / 493 (0.20%)	0 / 489 (0.00%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Heart rate abnormal			
subjects affected / exposed	1 / 493 (0.20%)	0 / 489 (0.00%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic enzyme abnormal			
subjects affected / exposed	1 / 493 (0.20%)	0 / 489 (0.00%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic enzyme increased			
subjects affected / exposed	0 / 493 (0.00%)	1 / 489 (0.20%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
International normalised ratio increased			
subjects affected / exposed	1 / 493 (0.20%)	0 / 489 (0.00%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight increased			

subjects affected / exposed	1 / 493 (0.20%)	0 / 489 (0.00%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	1 / 493 (0.20%)	0 / 489 (0.00%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Craniocerebral injury			
subjects affected / exposed	1 / 493 (0.20%)	0 / 489 (0.00%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	1 / 493 (0.20%)	1 / 489 (0.20%)	2 / 982 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	1 / 493 (0.20%)	1 / 489 (0.20%)	2 / 982 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	1 / 493 (0.20%)	0 / 489 (0.00%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple injuries			
subjects affected / exposed	0 / 493 (0.00%)	1 / 489 (0.20%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Patella fracture			
subjects affected / exposed	1 / 493 (0.20%)	0 / 489 (0.00%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haematoma			

subjects affected / exposed	1 / 493 (0.20%)	0 / 489 (0.00%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	0 / 493 (0.00%)	1 / 489 (0.20%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	1 / 493 (0.20%)	2 / 489 (0.41%)	3 / 982 (0.31%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal fracture			
subjects affected / exposed	0 / 493 (0.00%)	1 / 489 (0.20%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	0 / 493 (0.00%)	1 / 489 (0.20%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transplant failure			
subjects affected / exposed	0 / 493 (0.00%)	1 / 489 (0.20%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Tracheo-oesophageal fistula			
subjects affected / exposed	0 / 493 (0.00%)	1 / 489 (0.20%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 493 (0.20%)	2 / 489 (0.41%)	3 / 982 (0.31%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Acute myocardial infarction			
subjects affected / exposed	1 / 493 (0.20%)	3 / 489 (0.61%)	4 / 982 (0.41%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	2 / 493 (0.41%)	1 / 489 (0.20%)	3 / 982 (0.31%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Angina unstable			
subjects affected / exposed	3 / 493 (0.61%)	0 / 489 (0.00%)	3 / 982 (0.31%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia			
subjects affected / exposed	2 / 493 (0.41%)	1 / 489 (0.20%)	3 / 982 (0.31%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Arteriosclerosis coronary artery			
subjects affected / exposed	2 / 493 (0.41%)	0 / 489 (0.00%)	2 / 982 (0.20%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	4 / 493 (0.81%)	5 / 489 (1.02%)	9 / 982 (0.92%)
occurrences causally related to treatment / all	0 / 5	0 / 5	0 / 10
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	1 / 493 (0.20%)	1 / 489 (0.20%)	2 / 982 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial tachycardia			
subjects affected / exposed	1 / 493 (0.20%)	0 / 489 (0.00%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block complete			

subjects affected / exposed	2 / 493 (0.41%)	2 / 489 (0.41%)	4 / 982 (0.41%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	2 / 493 (0.41%)	1 / 489 (0.20%)	3 / 982 (0.31%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	4 / 493 (0.81%)	1 / 489 (0.20%)	5 / 982 (0.51%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 3	0 / 1	0 / 4
Cardiac failure			
subjects affected / exposed	46 / 493 (9.33%)	45 / 489 (9.20%)	91 / 982 (9.27%)
occurrences causally related to treatment / all	0 / 59	2 / 41	2 / 100
deaths causally related to treatment / all	0 / 4	0 / 2	0 / 6
Cardiac failure acute			
subjects affected / exposed	11 / 493 (2.23%)	9 / 489 (1.84%)	20 / 982 (2.04%)
occurrences causally related to treatment / all	0 / 13	1 / 7	1 / 20
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Cardiac failure chronic			
subjects affected / exposed	3 / 493 (0.61%)	2 / 489 (0.41%)	5 / 982 (0.51%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Cardiac failure congestive			
subjects affected / exposed	1 / 493 (0.20%)	4 / 489 (0.82%)	5 / 982 (0.51%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	1 / 493 (0.20%)	2 / 489 (0.41%)	3 / 982 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 2
Cardiogenic shock			

subjects affected / exposed	1 / 493 (0.20%)	5 / 489 (1.02%)	6 / 982 (0.61%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 5
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 2
Cardiomyopathy			
subjects affected / exposed	0 / 493 (0.00%)	1 / 489 (0.20%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congestive cardiomyopathy			
subjects affected / exposed	0 / 493 (0.00%)	2 / 489 (0.41%)	2 / 982 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	1 / 493 (0.20%)	0 / 489 (0.00%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic cardiomyopathy			
subjects affected / exposed	0 / 493 (0.00%)	1 / 489 (0.20%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left ventricular failure			
subjects affected / exposed	1 / 493 (0.20%)	1 / 489 (0.20%)	2 / 982 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Low cardiac output syndrome			
subjects affected / exposed	1 / 493 (0.20%)	0 / 489 (0.00%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Mitral valve incompetence			
subjects affected / exposed	0 / 493 (0.00%)	1 / 489 (0.20%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial fibrosis			

subjects affected / exposed	1 / 493 (0.20%)	0 / 489 (0.00%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	1 / 493 (0.20%)	1 / 489 (0.20%)	2 / 982 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Myocardial ischaemia			
subjects affected / exposed	2 / 493 (0.41%)	0 / 489 (0.00%)	2 / 982 (0.20%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Palpitations			
subjects affected / exposed	1 / 493 (0.20%)	0 / 489 (0.00%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus arrest			
subjects affected / exposed	1 / 493 (0.20%)	0 / 489 (0.00%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus node dysfunction			
subjects affected / exposed	1 / 493 (0.20%)	2 / 489 (0.41%)	3 / 982 (0.31%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	1 / 493 (0.20%)	0 / 489 (0.00%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular arrhythmia			
subjects affected / exposed	1 / 493 (0.20%)	2 / 489 (0.41%)	3 / 982 (0.31%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular extrasystoles			

subjects affected / exposed	0 / 493 (0.00%)	1 / 489 (0.20%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular fibrillation			
subjects affected / exposed	1 / 493 (0.20%)	1 / 489 (0.20%)	2 / 982 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular tachycardia			
subjects affected / exposed	3 / 493 (0.61%)	2 / 489 (0.41%)	5 / 982 (0.51%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Aphasia			
subjects affected / exposed	1 / 493 (0.20%)	0 / 489 (0.00%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Autonomic nervous system imbalance			
subjects affected / exposed	1 / 493 (0.20%)	0 / 489 (0.00%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain injury			
subjects affected / exposed	1 / 493 (0.20%)	0 / 489 (0.00%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral arteriosclerosis			
subjects affected / exposed	1 / 493 (0.20%)	0 / 489 (0.00%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral ischaemia			
subjects affected / exposed	1 / 493 (0.20%)	0 / 489 (0.00%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			

subjects affected / exposed	1 / 493 (0.20%)	2 / 489 (0.41%)	3 / 982 (0.31%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 2
Cognitive disorder			
subjects affected / exposed	1 / 493 (0.20%)	1 / 489 (0.20%)	2 / 982 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	1 / 493 (0.20%)	0 / 489 (0.00%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Extrapyramidal disorder			
subjects affected / exposed	1 / 493 (0.20%)	0 / 489 (0.00%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	1 / 493 (0.20%)	1 / 489 (0.20%)	2 / 982 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxic-ischaemic encephalopathy			
subjects affected / exposed	0 / 493 (0.00%)	1 / 489 (0.20%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	0 / 493 (0.00%)	2 / 489 (0.41%)	2 / 982 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			
subjects affected / exposed	0 / 493 (0.00%)	1 / 489 (0.20%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			

subjects affected / exposed	1 / 493 (0.20%)	0 / 489 (0.00%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sciatica			
subjects affected / exposed	1 / 493 (0.20%)	0 / 489 (0.00%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	3 / 493 (0.61%)	3 / 489 (0.61%)	6 / 982 (0.61%)
occurrences causally related to treatment / all	2 / 3	1 / 3	3 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 493 (0.00%)	1 / 489 (0.20%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 493 (0.61%)	2 / 489 (0.41%)	5 / 982 (0.51%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypocoagulable state			
subjects affected / exposed	1 / 493 (0.20%)	0 / 489 (0.00%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukocytosis			
subjects affected / exposed	0 / 493 (0.00%)	1 / 489 (0.20%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Splenic haemorrhage			
subjects affected / exposed	0 / 493 (0.00%)	1 / 489 (0.20%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			

Abdominal pain upper			
subjects affected / exposed	0 / 493 (0.00%)	1 / 489 (0.20%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 493 (0.00%)	3 / 489 (0.61%)	3 / 982 (0.31%)
occurrences causally related to treatment / all	0 / 0	1 / 3	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea haemorrhagic			
subjects affected / exposed	0 / 493 (0.00%)	1 / 489 (0.20%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	1 / 493 (0.20%)	0 / 489 (0.00%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 493 (0.20%)	1 / 489 (0.20%)	2 / 982 (0.20%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal inflammation			
subjects affected / exposed	0 / 493 (0.00%)	1 / 489 (0.20%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal haemorrhage			
subjects affected / exposed	0 / 493 (0.00%)	1 / 489 (0.20%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lip swelling			
subjects affected / exposed	1 / 493 (0.20%)	0 / 489 (0.00%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Melaena			

subjects affected / exposed	0 / 493 (0.00%)	1 / 489 (0.20%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	1 / 493 (0.20%)	1 / 489 (0.20%)	2 / 982 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subileus			
subjects affected / exposed	1 / 493 (0.20%)	0 / 489 (0.00%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Acute hepatic failure			
subjects affected / exposed	1 / 493 (0.20%)	0 / 489 (0.00%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Cholecystitis acute			
subjects affected / exposed	2 / 493 (0.41%)	0 / 489 (0.00%)	2 / 982 (0.20%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Hepatic function abnormal			
subjects affected / exposed	0 / 493 (0.00%)	1 / 489 (0.20%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis			
subjects affected / exposed	1 / 493 (0.20%)	0 / 489 (0.00%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperbilirubinaemia			
subjects affected / exposed	1 / 493 (0.20%)	0 / 489 (0.00%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice cholestatic			

subjects affected / exposed	0 / 493 (0.00%)	1 / 489 (0.20%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Diabetic foot			
subjects affected / exposed	1 / 493 (0.20%)	2 / 489 (0.41%)	3 / 982 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Skin ulcer			
subjects affected / exposed	0 / 493 (0.00%)	1 / 489 (0.20%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	12 / 493 (2.43%)	7 / 489 (1.43%)	19 / 982 (1.93%)
occurrences causally related to treatment / all	4 / 10	1 / 5	5 / 15
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Chronic kidney disease			
subjects affected / exposed	3 / 493 (0.61%)	2 / 489 (0.41%)	5 / 982 (0.51%)
occurrences causally related to treatment / all	0 / 2	1 / 2	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	0 / 493 (0.00%)	2 / 489 (0.41%)	2 / 982 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	3 / 493 (0.61%)	4 / 489 (0.82%)	7 / 982 (0.71%)
occurrences causally related to treatment / all	3 / 3	1 / 2	4 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal impairment			
subjects affected / exposed	0 / 493 (0.00%)	4 / 489 (0.82%)	4 / 982 (0.41%)
occurrences causally related to treatment / all	0 / 0	2 / 3	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			

Hypothyroidism			
subjects affected / exposed	0 / 493 (0.00%)	1 / 489 (0.20%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Bursitis			
subjects affected / exposed	1 / 493 (0.20%)	0 / 489 (0.00%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fistula			
subjects affected / exposed	1 / 493 (0.20%)	0 / 489 (0.00%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	0 / 493 (0.00%)	1 / 489 (0.20%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	0 / 493 (0.00%)	1 / 489 (0.20%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myalgia			
subjects affected / exposed	1 / 493 (0.20%)	0 / 489 (0.00%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 493 (0.00%)	1 / 489 (0.20%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	1 / 493 (0.20%)	0 / 489 (0.00%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infections and infestations			
Bacterial sepsis			
subjects affected / exposed	0 / 493 (0.00%)	1 / 489 (0.20%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Biliary sepsis			
subjects affected / exposed	0 / 493 (0.00%)	1 / 489 (0.20%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	1 / 493 (0.20%)	4 / 489 (0.82%)	5 / 982 (0.51%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Catheter site abscess			
subjects affected / exposed	0 / 493 (0.00%)	1 / 489 (0.20%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 493 (0.20%)	1 / 489 (0.20%)	2 / 982 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	1 / 493 (0.20%)	0 / 489 (0.00%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea infectious			
subjects affected / exposed	1 / 493 (0.20%)	0 / 489 (0.00%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocarditis			
subjects affected / exposed	0 / 493 (0.00%)	1 / 489 (0.20%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epididymitis			

subjects affected / exposed	0 / 493 (0.00%)	1 / 489 (0.20%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	1 / 493 (0.20%)	3 / 489 (0.61%)	4 / 982 (0.41%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gangrene			
subjects affected / exposed	1 / 493 (0.20%)	1 / 489 (0.20%)	2 / 982 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 493 (0.20%)	3 / 489 (0.61%)	4 / 982 (0.41%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	1 / 493 (0.20%)	0 / 489 (0.00%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Localised infection			
subjects affected / exposed	1 / 493 (0.20%)	0 / 489 (0.00%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	1 / 493 (0.20%)	0 / 489 (0.00%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection viral			
subjects affected / exposed	1 / 493 (0.20%)	0 / 489 (0.00%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			

subjects affected / exposed	0 / 493 (0.00%)	1 / 489 (0.20%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	7 / 493 (1.42%)	8 / 489 (1.64%)	15 / 982 (1.53%)
occurrences causally related to treatment / all	0 / 7	0 / 5	0 / 12
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative wound infection			
subjects affected / exposed	1 / 493 (0.20%)	0 / 489 (0.00%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Q fever			
subjects affected / exposed	1 / 493 (0.20%)	0 / 489 (0.00%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 493 (0.00%)	4 / 489 (0.82%)	4 / 982 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	2 / 493 (0.41%)	1 / 489 (0.20%)	3 / 982 (0.31%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Septic phlebitis			
subjects affected / exposed	1 / 493 (0.20%)	0 / 489 (0.00%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	1 / 493 (0.20%)	2 / 489 (0.41%)	3 / 982 (0.31%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Tuberculosis			

subjects affected / exposed	0 / 493 (0.00%)	1 / 489 (0.20%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	4 / 493 (0.81%)	2 / 489 (0.41%)	6 / 982 (0.61%)
occurrences causally related to treatment / all	0 / 5	0 / 1	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	1 / 493 (0.20%)	0 / 489 (0.00%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 493 (0.00%)	1 / 489 (0.20%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 493 (0.20%)	0 / 489 (0.00%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fluid overload			
subjects affected / exposed	0 / 493 (0.00%)	1 / 489 (0.20%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gout			
subjects affected / exposed	1 / 493 (0.20%)	0 / 489 (0.00%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 493 (0.00%)	1 / 489 (0.20%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			

subjects affected / exposed	3 / 493 (0.61%)	6 / 489 (1.23%)	9 / 982 (0.92%)
occurrences causally related to treatment / all	2 / 2	4 / 6	6 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	0 / 493 (0.00%)	1 / 489 (0.20%)	1 / 982 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	1 / 493 (0.20%)	2 / 489 (0.41%)	3 / 982 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	LCZ696 Pre-discharge treatment initiation	LCZ696 Post-discharge treatment	All patients
Total subjects affected by non-serious adverse events			
subjects affected / exposed	200 / 493 (40.57%)	201 / 489 (41.10%)	401 / 982 (40.84%)
Vascular disorders			
Hypotension			
subjects affected / exposed	71 / 493 (14.40%)	67 / 489 (13.70%)	138 / 982 (14.05%)
occurrences (all)	74	71	145
Nervous system disorders			
Dizziness			
subjects affected / exposed	32 / 493 (6.49%)	30 / 489 (6.13%)	62 / 982 (6.31%)
occurrences (all)	32	31	63
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	20 / 493 (4.06%)	26 / 489 (5.32%)	46 / 982 (4.68%)
occurrences (all)	19	29	48
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	17 / 493 (3.45%)	29 / 489 (5.93%)	46 / 982 (4.68%)
occurrences (all)	18	29	47
Renal and urinary disorders			

Renal impairment subjects affected / exposed occurrences (all)	36 / 493 (7.30%) 44	24 / 489 (4.91%) 24	60 / 982 (6.11%) 68
Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all)	29 / 493 (5.88%) 35	19 / 489 (3.89%) 14	48 / 982 (4.89%) 49
Metabolism and nutrition disorders Hyperkalaemia subjects affected / exposed occurrences (all)	67 / 493 (13.59%) 80	59 / 489 (12.07%) 73	126 / 982 (12.83%) 153

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 February 2016	The purpose of this amendment was to address the inquiry by the Health Authorities from Germany. This change applied to Germany only referring to the eligibility of subjects.
18 July 2016	Wording changes + clarifications

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported