Clinical trial results:
A 24-week, randomized, double-blind, multi-center, parallel group, active controlled study to evaluate the effect of LCZ696 on NT-proBNP, exercise capacity, symptoms and safety compared to individualized medical management of comorbidities in patients with heart failure and preserved ejection fraction

Summary

EudraCT number	2016-003410-28
Trial protocol	PT HU LV ES FR SK CZ GB LT AT DK BG BE NL IT
Global end of trial date	28 October 2019

Results information

Result version number	v1 (current)
This version publication date	11 November 2020
First version publication date	11 November 2020

Trial information

Trial identification

Sponsor protocol code	CLCZ696D2302

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03066804
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	28 October 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 October 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The Primary Objectives were to demonstrate that sacubitril/valsartan is superior to individualized medical therapy for comorbidities in reducing N-terminal pro-brain natriuretic peptide (NT-proBNP) from baseline after 12 weeks of treatment, and to demonstrate that sacubitril/valsartan is superior to individualized medical therapy for comorbidities in improving exercise capacity as assessed by the six-minute walk test (6MWT) at Week 24 in a subset of patients

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	22 August 2017
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	Argentina: 105
Country: Number of subjects enrolled	Austria: 31
Country: Number of subjects enrolled	Belgium: 23
Country: Number of subjects enrolled	Brazil: 77
Country: Number of subjects enrolled	Bulgaria: 178
Country: Number of subjects enrolled	Canada: 14
Country: Number of subjects enrolled	Colombia: 44
Country: Number of subjects enrolled	Czech Republic: 149
Country: Number of subjects enrolled	Denmark: 12
Country: Number of subjects enrolled	Estonia: 51
Country: Number of subjects enrolled	France: 32
Country: Number of subjects enrolled	Germany: 417
Country: Number of subjects enrolled	Guatemala: 60
Country: Number of subjects enrolled	Hungary: 134
Country: Number of subjects enrolled	India: 97
Country: Number of subjects enrolled	Israel: 30
Country: Number of subjects enrolled	Italy: 48

Country: Number of subjects enrolled	Latvia: 18
Country: Number of subjects enrolled	Lithuania: 29
Country: Number of subjects enrolled	Mexico: 14
Country: Number of subjects enrolled	Netherlands: 52
Country: Number of subjects enrolled	Peru: 58
Country: Number of subjects enrolled	Portugal: 33
Country: Number of subjects enrolled	Romania: 93
Country: Number of subjects enrolled	Russian Federation: 139
Country: Number of subjects enrolled	Serbia: 26
Country: Number of subjects enrolled	Slovakia: 243
Country: Number of subjects enrolled	Spain: 127
Country: Number of subjects enrolled	Thailand: 12
Country: Number of subjects enrolled	Turkey: 74
Country: Number of subjects enrolled	United Kingdom: 33
Country: Number of subjects enrolled	United States: 119
Worldwide total number of subjects	2572
EEA total number of subjects	1703

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)	418
From 65 to 84 years	2154
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 2572 participants were randomized in a 1:1 ratio to receive either sacubitril/valsartan or Individualized Medical Therapy (IMT).

Pre-assignment

Screening details:

A total of 2572 participants were randomized in a 1:1 ratio to receive either sacubitril/valsartan or Individualized Medical Therapy (IMT).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Sacubitril/Valsartan (LCZ696)

Arm description:

All patients who fulfilled the inclusion/exclusion criteria were stratified before randomization based upon prior therapy for comorbidities to one of 3 strata: ACEi, ARB or no RASi. Patients in the ACEi strata received LCZ696 or enalapril. Patients in the ARB strata received LCZ696 or valsartan. Patients in the no RASi strata received LCZ696 or matching placebo. Patients in the ACEi and ARB strata took two pills twice daily for each dose: one tablet from the LCZ696 pack and one tablet from the comparator pack. Patients in the no RASi strata took only one tablet twice daily (LCZ696 or matching placebo). In the LCZ696 arm, patients received active LCZ696 in titrated doses from level 1 up to level 3 (50 mg, 100 mg and 200 mg twice daily orally).

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

Dosage and administration details:

LCZ696 50 mg (24mg/26mg), 100 mg (49mg/51mg) and 200 mg (97 mg/103mg)

Investigational medicinal product name	Enalapril
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Enalapril 2.5 mg, 5 mg, and 10 mg

Investigational medicinal product name	Valsartan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Valsartan 40 g, 80 mg, 160 mg

Investigational medicinal product name	Sacubitril/Valsartan
Investigational medicinal product code	LCZ696
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo to match LCZ696 50 mg, 100 mg, 200 mg

Arm title	Individualized Medical Therapy (IMT) Comparator

Arm description:

Patients randomized to the comparator arm received either enalapril (ACE stratum) valsartan (ARB stratum) or LCZ696 matching placebo (no RASi stratum). Patients in the ACE stratum randomized to comparator, received enalapril in titrated doses from level 1 up to level 3 (2.5 mg, 5 mg and 10 mg twice daily). Patients in the ARB stratum randomized to comparator received valsartan in titrated doses from level 1 up to level 3 (40 mg , 80 mg and 160 mg twice daily). Patients in the no RASi stratum randomized to comparator received LCZ696 matching placebo.

Arm type	Active comparator
Investigational medicinal product name	Enalapril
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Enalapril 2.5 mg, 5 mg, 10 mg

Investigational medicinal product name	Valsartan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Valsartan 40 mg, 80 mg, 160 mg

Investigational medicinal product name	Sacubitril/Valsartan
Investigational medicinal product code	LCZ696
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo to match LCZ696 50 mg, 100 mg, and 200 mg

Investigational medicinal product name	Valsartan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo to match Valsartan 40 mg, 80 mg 160 mg

Number of subjects in period 1	Sacubitril/Valsartan (LCZ696)	Individualized Medical Therapy (IMT) Comparator
Started	1286	1286
Completed	1235	1236
Not completed	51	50
Adverse event, serious fatal	23	17
Consent withdrawn by subject	19	25
Physician decision	-	4
Adverse event, non-fatal	2	3
Technical problems	5	1
Lost to follow-up	2	-

Baseline characteristics

Reporting groups

Reporting group title	Sacubitril/Valsartan (LCZ696)

Reporting group description:

All patients who fulfilled the inclusion/exclusion criteria were stratified before randomization based upon prior therapy for comorbidities to one of 3 strata: ACEi, ARB or no RASi. Patients in the ACEi strata received LCZ696 or enalapril. Patients in the ARB strata received LCZ696 or valsartan. Patients in the no RASi strata received LCZ696 or matching placebo. Patients in the ACEi and ARB strata took two pills twice daily for each dose: one tablet from the LCZ696 pack and one tablet from the comparator pack. Patients in the no RASi strata took only one tablet twice daily (LCZ696 or matching placebo). In the LCZ696 arm, patients received active LCZ696 in titrated doses from level 1 up to level 3 (50 mg, 100 mg and 200 mg twice daily orally).

Reporting group title	Individualized Medical Therapy (IMT) Comparator

Reporting group description:

Patients randomized to the comparator arm received either enalapril (ACE stratum) valsartan (ARB stratum) or LCZ696 matching placebo (no RASi stratum). Patients in the ACE stratum randomized to comparator, received enalapril in titrated doses from level 1 up to level 3 (2.5 mg, 5 mg and 10 mg twice daily). Patients in the ARB stratum randomized to comparator received valsartan in titrated doses from level 1 up to level 3 (40 mg , 80 mg and 160 mg twice daily). Patients in the no RASi stratum randomized to comparator received LCZ696 matching placebo.

Reporting group values	Sacubitril/Valsartan (LCZ696)	Individualized Medical Therapy (IMT) Comparator	Total
Number of subjects	1286	1286	2572
Age Categorical Units: Participants			
<65 years	197	221	418
>=65 years	1089	1065	2154
Sex: Female, Male Units:			
Female	646	658	1304
Male	640	628	1268
Race/Ethnicity, Customized Units: Subjects			
Caucasian	1117	1118	2235
Black	11	16	27
Asian	56	59	115
Native American	39	33	72
Pacific Islander	0	1	1
Unknown	4	3	7
Other	59	56	115

End points

End points reporting groups

Reporting group title	Sacubitril/Valsartan (LCZ696)

Reporting group description:

All patients who fulfilled the inclusion/exclusion criteria were stratified before randomization based upon prior therapy for comorbidities to one of 3 strata: ACEi, ARB or no RASi. Patients in the ACEi strata received LCZ696 or enalapril. Patients in the ARB strata received LCZ696 or valsartan. Patients in the no RASi strata received LCZ696 or matching placebo. Patients in the ACEi and ARB strata took two pills twice daily for each dose: one tablet from the LCZ696 pack and one tablet from the comparator pack. Patients in the no RASi strata took only one tablet twice daily (LCZ696 or matching placebo). In the LCZ696 arm, patients received active LCZ696 in titrated doses from level 1 up to level 3 (50 mg, 100 mg and 200 mg twice daily orally).

Reporting group title	Individualized Medical Therapy (IMT) Comparator

Reporting group description:

Patients randomized to the comparator arm received either enalapril (ACE stratum) valsartan (ARB stratum) or LCZ696 matching placebo (no RASi stratum). Patients in the ACE stratum randomized to comparator, received enalapril in titrated doses from level 1 up to level 3 (2.5 mg, 5 mg and 10 mg twice daily). Patients in the ARB stratum randomized to comparator received valsartan in titrated doses from level 1 up to level 3 (40 mg , 80 mg and 160 mg twice daily). Patients in the no RASi stratum randomized to comparator received LCZ696 matching placebo.

Primary: Change from baseline in N-terminal pro-brain natriuretic peptide (NT-proBNP) at Week 12

End point title	Change from baseline in N-terminal pro-brain natriuretic peptide (NT-proBNP) at Week 12

End point description:

To demonstrate that LCZ696 is superior to individualized medical therapy for comorbidities in reducing NT-proBNP from baseline at Week 12 in patients with HFpEF

End point type	Primary

End point timeframe:

Baseline, week 12

End point values	Sacubitril/Valsartan (LCZ696)	Individualized Medical Therapy (IMT) Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1281	1285		
Units: Percentage				
geometric mean (confidence interval 95%)	0.8218 (0.7955 to 0.8489)	0.9828 (0.9515 to 1.0151)		

Statistical analyses

Statistical analysis title	Primary Endpoint

Statistical analysis description:

Week 12

Comparison groups	Sacubitril/Valsartan (LCZ696) v Individualized Medical Therapy (IMT) Comparator
Number of subjects included in analysis	2566
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Geometric Mean Ratio
Point estimate	0.8362
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7987
upper limit	0.8754

Primary: Change from baseline in 6 minute walk distance (6MWD) at Week 24

End point title	Change from baseline in 6 minute walk distance (6MWD) at Week 24

End point description:

Change from baseline in 6-minute walk distance (6MWD) will be reported at Week 24. The 6 MWT will be performed in accordance with the guidelines of the American Thoracic Society 2002.

End point type	Primary

End point timeframe:

Baseline, week 24

End point values	Sacubitril/Valsartan (LCZ696)	Individualized Medical Therapy (IMT) Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1154	1159		
Units: Meter				
arithmetic mean (confidence interval 95%)	9.6935 (5.4310 to 13.9559)	12.1920 (7.9202 to 16.4638)		

Statistical analyses

Statistical analysis title	Primary Endpoint
Comparison groups	Sacubitril/Valsartan (LCZ696) v Individualized Medical Therapy (IMT) Comparator

Number of subjects included in analysis	2313
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4164
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-2.4985
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.5267
upper limit	3.52297

Secondary: Mean change from baseline in Kansas City Cardiomyopathy Questionnaire (KCCQ) Clinical Summary Score (CSS) at Week 24

End point title	Mean change from baseline in Kansas City Cardiomyopathy Questionnaire (KCCQ) Clinical Summary Score (CSS) at Week 24

End point description:

The KCCQ is a self-administered questionnaire that requires 4 to 6 minutes to complete. It contains 23 items, covering physical function, clinical symptoms, social function, self-efficacy and knowledge, and Quality of Life (QoL). The CSS is a combined score based upon the clinical symptoms and physical function domains of the questionnaire. Scores are transformed to a range of 0 - 100, in which higher scores reflect better health status.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Sacubitril/Valsartan (LCZ696)	Individualized Medical Therapy (IMT) Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1281	1285		
Units: Scores on a scale				
arithmetic mean (confidence interval 95%)	12.3399 (11.3151 to 13.3647)	11.8168 (10.7922 to 12.8415)		

Statistical analyses

Statistical analysis title	Secondary Enpoint
Comparison groups	Sacubitril/Valsartan (LCZ696) v Individualized Medical Therapy (IMT) Comparator

Number of subjects included in analysis	2566
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4791
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.5231
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9258
upper limit	1.972

Secondary: Percentage of patients with ≥ 5-points deterioration in KCCQ CSS at Week 24

End point title	Percentage of patients with ≥ 5-points deterioration in KCCQ CSS at Week 24

End point description:

Percentage of patients with KCCQ CSS deterioration ≥ 5-points will be reported at Week 24. The KCCQ is a self-administered questionnaire that requires 4 to 6 minutes to complete. It contains 23 items, covering physical function, clinical symptoms, social function, self-efficacy and knowledge, and Quality of Life (QoL). The CSS is a combined score based upon the clinical symptoms and physical function domains of the questionnaire. Scores are transformed to a range of 0 - 100, in which higher scores reflect better health status.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Sacubitril/Valsartan (LCZ696)	Individualized Medical Therapy (IMT) Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1281	1285		
Units: Percentage of participants				
number (not applicable)	15.49	16.69		

Statistical analyses

Statistical analysis title	Secondary Endpoint
Comparison groups	Sacubitril/Valsartan (LCZ696) v Individualized Medical Therapy (IMT) Comparator

Number of subjects included in analysis	2566
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5294
Method	longitudinal binary logistic regression
Parameter estimate	Odds ratio (OR)
Point estimate	0.8993
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6461
upper limit	1.2518

Secondary: Percentage of patients with ≥ 5-points improvement in KCCQ CSS at Week 24

End point title	Percentage of patients with ≥ 5-points improvement in KCCQ CSS at Week 24

End point description:

Percentage of patients with KCCQ CSS improvement ≥ 5-points will be reported at Week 24. The KCCQ is a self-administered questionnaire that requires 4 to 6 minutes to complete. It contains 23 items, covering physical function, clinical symptoms, social function, self-efficacy and knowledge, and Quality of Life (QoL). The CSS is a combined score based upon the clinical symptoms and physical function domains of the questionnaire. Scores are transformed to a range of 0 - 100, in which higher scores reflect better health status.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Sacubitril/Valsartan (LCZ696)	Individualized Medical Therapy (IMT) Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1281	1285		
Units: Percentage of participants				
number (not applicable)	67.94	65.70		

Statistical analyses

Statistical analysis title	Secondary Endpoint
Comparison groups	Sacubitril/Valsartan (LCZ696) v Individualized Medical Therapy (IMT) Comparator

Number of subjects included in analysis	2566
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4938
Method	longitudinal binary logistic regression
Parameter estimate	Odds ratio (OR)
Point estimate	1.106
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8287
upper limit	1.476

Secondary: Change from baseline in NYHA functional class at Week 24

End point title	Change from baseline in NYHA functional class at Week 24

End point description:

NYHA classification is a subjective physician's assessment of patient's functional capacity and symptomatic status and can change frequently over time. Class I - No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF Class II - Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of HF Class III - Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of HF Class IV - Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest The NYHA class change will be analyzed as a three category ordinal variable with levels: "improved", "unchanged", and "worsened", defined by at least one class improvement, no change, at least one class worsening, in NYHA class, respectively.

End point type	Secondary

End point timeframe:

Baseline, week 24

End point values	Sacubitril/Valsartan (LCZ696)	Individualized Medical Therapy (IMT) Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1281	1285		
Units: Percentage of Participants				
number (not applicable)				
Improved	23.62	24.00		
Unchanged	72.23	71.68		
Worsened	4.15	4.31		

Statistical analyses

Statistical analysis title	Secondary Endpoint
Comparison groups	Sacubitril/Valsartan (LCZ696) v Individualized Medical Therapy (IMT) Comparator

Number of subjects included in analysis	2566
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.8314
Method	Proportional cumulative odds model
Parameter estimate	Odds ratio (OR)
Point estimate	0.9798
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8122
upper limit	1.182

Secondary: Change from baseline in The Short Form 36 Health Survey (SF-36) physical component summary (PCS) score at week 24

End point title	Change from baseline in The Short Form 36 Health Survey (SF-36) physical component summary (PCS) score at week 24

End point description:

The Short Form Health Survey (SF-36) is a widely used and extensively studied instrument to measure health-related quality of life among healthy patients and patients with acute and chronic conditions. It consists of eight subscales that can be scored individually: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. This analysis will report change in symptoms as measured by the physical component summary (PCS) score at Week 24.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Sacubitril/Valsartan (LCZ696)	Individualized Medical Therapy (IMT) Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1281	1285		
Units: Scores on a scale				
arithmetic mean (confidence interval 95%)	2.5405 (2.0787 to 3.0023)	2.6975 (2.2360 to 3.1590)		

Statistical analyses

Statistical analysis title	Secondary Endpoint
Comparison groups	Sacubitril/Valsartan (LCZ696) v Individualized Medical Therapy (IMT) Comparator

Number of subjects included in analysis	2566
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.637
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.157
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8093
upper limit	0.4953

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events were collected from first dose of study treatment until end of study treatment plus 30 days post treatment, up to maximum duration of approx. 2 years.	
Adverse event reporting additional description:	
Any sign or symptom that occurs during the study treatment plus the 30 days post treatment.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups	
Reporting group title	LCZ696
Reporting group description:	
LCZ696	
Reporting group title	Total
Reporting group description:	
Total	
Reporting group title	Individualized Medical Therapy Comparator
Reporting group description:	
IMT	

Serious adverse events	LCZ696	Total	Individualized Medical Therapy Comparator
Total subjects affected by serious adverse events			
subjects affected / exposed	186 / 1280 (14.53%)	377 / 2564 (14.70%)	191 / 1284 (14.88%)
number of deaths (all causes)	23	40	17
number of deaths resulting from adverse events	1	1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 1280 (0.08%)	3 / 2564 (0.12%)	2 / 1284 (0.16%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder neoplasm			
subjects affected / exposed	2 / 1280 (0.16%)	2 / 2564 (0.08%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer			

subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervix carcinoma			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon adenoma			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon cancer			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric cancer			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
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 carcinoma			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngeal cancer			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung cancer metastatic			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Lung neoplasm malignant			

subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphoma			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Malignant melanoma			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to liver			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Metastases to spine			
subjects affected / exposed	2 / 1280 (0.16%)	2 / 2564 (0.08%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Metastatic neoplasm			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Nasal cavity cancer			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuroendocrine tumour			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal squamous cell carcinoma			

subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Plasma cell myeloma			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	2 / 1280 (0.16%)	2 / 2564 (0.08%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer metastatic			
subjects affected / exposed	1 / 1280 (0.08%)	2 / 2564 (0.08%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal adenocarcinoma			
subjects affected / exposed	1 / 1280 (0.08%)	2 / 2564 (0.08%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal cell carcinoma			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal neoplasm			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal meningioma benign			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma			

subjects affected / exposed	0 / 1280 (0.00%)	2 / 2564 (0.08%)	2 / 1284 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract neoplasm			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
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			
Accelerated hypertension			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic dissection			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Aortic stenosis			
subjects affected / exposed	1 / 1280 (0.08%)	2 / 2564 (0.08%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arterial rupture			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma			
subjects affected / exposed	1 / 1280 (0.08%)	3 / 2564 (0.12%)	2 / 1284 (0.16%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			

subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	2 / 1280 (0.16%)	3 / 2564 (0.12%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive urgency			
subjects affected / exposed	0 / 1280 (0.00%)	2 / 2564 (0.08%)	2 / 1284 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	6 / 1280 (0.47%)	8 / 2564 (0.31%)	2 / 1284 (0.16%)
occurrences causally related to treatment / all	7 / 8	9 / 10	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Iliac artery stenosis			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthostatic hypotension			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery occlusion			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral vascular disorder			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock			

subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Thrombophlebitis			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosis			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vasculitis			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Cardiac death			
subjects affected / exposed	2 / 1280 (0.16%)	2 / 2564 (0.08%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 2	0 / 0
Chest pain			
subjects affected / exposed	1 / 1280 (0.08%)	2 / 2564 (0.08%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	1 / 1	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	0 / 1280 (0.00%)	2 / 2564 (0.08%)	2 / 1284 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 2
Fatigue			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gait disturbance			

subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalised oedema			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	0 / 1280 (0.00%)	2 / 2564 (0.08%)	2 / 1284 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	1 / 1280 (0.08%)	3 / 2564 (0.12%)	2 / 1284 (0.16%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			

subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
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	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthma			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	3 / 1280 (0.23%)	7 / 2564 (0.27%)	4 / 1284 (0.31%)
occurrences causally related to treatment / all	0 / 3	0 / 9	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic respiratory failure			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	1 / 1280 (0.08%)	7 / 2564 (0.27%)	6 / 1284 (0.47%)
occurrences causally related to treatment / all	0 / 1	0 / 7	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	0 / 1280 (0.00%)	3 / 2564 (0.12%)	3 / 1284 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			

subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary hypertension			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 1280 (0.08%)	2 / 2564 (0.08%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 2	0 / 1
Psychiatric disorders			
Alcohol abuse			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
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 breakage			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood urine present			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoglobin decreased			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
International normalised ratio increased			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver function test abnormal			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Agitation postoperative			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Animal bite			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Contusion			

subjects affected / exposed	2 / 1280 (0.16%)	2 / 2564 (0.08%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Facial bones fracture			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 1280 (0.00%)	4 / 2564 (0.16%)	4 / 1284 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fractured ischium			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fractured sacrum			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Limb injury			

subjects affected / exposed	0 / 1280 (0.00%)	2 / 2564 (0.08%)	2 / 1284 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meniscus injury			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple injuries			
subjects affected / exposed	1 / 1280 (0.08%)	2 / 2564 (0.08%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural complication			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haemorrhage			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pubis fracture			
subjects affected / exposed	1 / 1280 (0.08%)	2 / 2564 (0.08%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seroma			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal fracture			
subjects affected / exposed	1 / 1280 (0.08%)	3 / 2564 (0.12%)	2 / 1284 (0.16%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			

subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Thoracic vertebral fracture			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper limb fracture			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Mitochondrial myopathy			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	4 / 1280 (0.31%)	5 / 2564 (0.20%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 4	0 / 5	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	2 / 1280 (0.16%)	6 / 2564 (0.23%)	4 / 1284 (0.31%)
occurrences causally related to treatment / all	0 / 3	0 / 8	0 / 5
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Angina pectoris			
subjects affected / exposed	8 / 1280 (0.63%)	16 / 2564 (0.62%)	8 / 1284 (0.62%)
occurrences causally related to treatment / all	0 / 8	2 / 16	2 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	6 / 1280 (0.47%)	13 / 2564 (0.51%)	7 / 1284 (0.55%)
occurrences causally related to treatment / all	0 / 6	0 / 14	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Aortic valve disease			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic valve incompetence			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	13 / 1280 (1.02%)	30 / 2564 (1.17%)	17 / 1284 (1.32%)
occurrences causally related to treatment / all	0 / 13	0 / 34	0 / 21
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	4 / 1280 (0.31%)	6 / 2564 (0.23%)	2 / 1284 (0.16%)
occurrences causally related to treatment / all	0 / 4	0 / 6	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Atrial tachycardia			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block complete			
subjects affected / exposed	2 / 1280 (0.16%)	5 / 2564 (0.20%)	3 / 1284 (0.23%)
occurrences causally related to treatment / all	0 / 2	0 / 5	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block second degree			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	1 / 1280 (0.08%)	3 / 2564 (0.12%)	2 / 1284 (0.16%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			

subjects affected / exposed	1 / 1280 (0.08%)	2 / 2564 (0.08%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	21 / 1280 (1.64%)	52 / 2564 (2.03%)	31 / 1284 (2.41%)
occurrences causally related to treatment / all	1 / 26	1 / 62	0 / 36
deaths causally related to treatment / all	0 / 5	0 / 8	0 / 3
Cardiac failure acute			
subjects affected / exposed	3 / 1280 (0.23%)	12 / 2564 (0.47%)	9 / 1284 (0.70%)
occurrences causally related to treatment / all	0 / 5	0 / 15	0 / 10
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 2
Cardiac failure chronic			
subjects affected / exposed	2 / 1280 (0.16%)	3 / 2564 (0.12%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Cardiac failure congestive			
subjects affected / exposed	2 / 1280 (0.16%)	9 / 2564 (0.35%)	7 / 1284 (0.55%)
occurrences causally related to treatment / all	1 / 2	1 / 11	0 / 9
deaths causally related to treatment / all	1 / 1	1 / 2	0 / 1
Cardiac perforation			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Cardiogenic shock			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Cor pulmonale acute			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			

subjects affected / exposed	4 / 1280 (0.31%)	5 / 2564 (0.20%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 4	0 / 5	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dressler's syndrome			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left ventricular failure			
subjects affected / exposed	1 / 1280 (0.08%)	2 / 2564 (0.08%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mitral valve incompetence			
subjects affected / exposed	1 / 1280 (0.08%)	2 / 2564 (0.08%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	1 / 1280 (0.08%)	5 / 2564 (0.20%)	4 / 1284 (0.31%)
occurrences causally related to treatment / all	0 / 1	0 / 5	0 / 4
deaths causally related to treatment / all	0 / 1	0 / 3	0 / 2
Myocardial ischaemia			
subjects affected / exposed	1 / 1280 (0.08%)	2 / 2564 (0.08%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 2	0 / 1
Pericardial effusion			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus arrest			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus node dysfunction			

subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Carotid artery aneurysm			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haemorrhage			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Cerebrovascular accident			
subjects affected / exposed	2 / 1280 (0.16%)	2 / 2564 (0.08%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Dementia			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic neuropathy			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			

subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalopathy			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic transformation stroke			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic encephalopathy			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxic-ischaemic encephalopathy			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Ischaemic stroke			
subjects affected / exposed	0 / 1280 (0.00%)	6 / 2564 (0.23%)	6 / 1284 (0.47%)
occurrences causally related to treatment / all	0 / 0	0 / 6	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parkinson's disease			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sciatica			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sensory disturbance			

subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Syncope			
subjects affected / exposed	2 / 1280 (0.16%)	4 / 2564 (0.16%)	2 / 1284 (0.16%)
occurrences causally related to treatment / all	1 / 2	1 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	4 / 1280 (0.31%)	4 / 2564 (0.16%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 1280 (0.16%)	5 / 2564 (0.20%)	3 / 1284 (0.23%)
occurrences causally related to treatment / all	0 / 2	0 / 5	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphadenopathy			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertigo positional			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vestibular ataxia			

subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Cataract			
subjects affected / exposed	1 / 1280 (0.08%)	3 / 2564 (0.12%)	2 / 1284 (0.16%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye haemorrhage			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Iris neovascularisation			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Macular hole			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal artery occlusion			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Visual acuity reduced			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
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 hernia			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			

subjects affected / exposed	0 / 1280 (0.00%)	2 / 2564 (0.08%)	2 / 1284 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer perforation			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric haemorrhage			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis erosive			
subjects affected / exposed	0 / 1280 (0.00%)	2 / 2564 (0.08%)	2 / 1284 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal ulcer haemorrhage			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Haemorrhagic erosive gastritis			

subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	2 / 1280 (0.16%)	3 / 2564 (0.12%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Incarcerated inguinal hernia			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
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 perforation			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine polyp			
subjects affected / exposed	1 / 1280 (0.08%)	2 / 2564 (0.08%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mallory-Weiss syndrome			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal polyp			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			

subjects affected / exposed	0 / 1280 (0.00%)	2 / 2564 (0.08%)	2 / 1284 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct stenosis			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bile duct stone			
subjects affected / exposed	1 / 1280 (0.08%)	2 / 2564 (0.08%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	1 / 1280 (0.08%)	2 / 2564 (0.08%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	2 / 1280 (0.16%)	3 / 2564 (0.12%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic congestion			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver disorder			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			

Angioedema			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic foot			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin ulcer			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
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	4 / 1280 (0.31%)	11 / 2564 (0.43%)	7 / 1284 (0.55%)
occurrences causally related to treatment / all	0 / 5	3 / 13	3 / 8
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Diabetic nephropathy			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephritic syndrome			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			

subjects affected / exposed	3 / 1280 (0.23%)	3 / 2564 (0.12%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	1 / 3	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal impairment			
subjects affected / exposed	2 / 1280 (0.16%)	2 / 2564 (0.08%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	2 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal injury			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
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 retention			
subjects affected / exposed	0 / 1280 (0.00%)	2 / 2564 (0.08%)	2 / 1284 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 1280 (0.00%)	2 / 2564 (0.08%)	2 / 1284 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone pain			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	3 / 1280 (0.23%)	3 / 2564 (0.12%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			

subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myalgia			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	1 / 1280 (0.08%)	3 / 2564 (0.12%)	2 / 1284 (0.16%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteochondrosis			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoporosis			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pathological fracture			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rheumatoid arthritis			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal pain			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal stenosis			

subjects affected / exposed	0 / 1280 (0.00%)	4 / 2564 (0.16%)	4 / 1284 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spondylolisthesis			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	3 / 1280 (0.23%)	5 / 2564 (0.20%)	2 / 1284 (0.16%)
occurrences causally related to treatment / all	0 / 3	0 / 5	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Campylobacter gastroenteritis			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
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	3 / 1280 (0.23%)	3 / 2564 (0.12%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis infective			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cutaneous leishmaniasis			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			

subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dengue fever			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocarditis			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
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	2 / 1280 (0.16%)	5 / 2564 (0.20%)	3 / 1284 (0.23%)
occurrences causally related to treatment / all	0 / 2	0 / 5	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	2 / 1280 (0.16%)	3 / 2564 (0.12%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis C			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			

subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infectious pleural effusion			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Localised infection			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	3 / 1280 (0.23%)	3 / 2564 (0.12%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasopharyngitis			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumococcal sepsis			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Pneumonia			
subjects affected / exposed	13 / 1280 (1.02%)	26 / 2564 (1.01%)	13 / 1284 (1.01%)
occurrences causally related to treatment / all	0 / 13	0 / 27	0 / 14
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 2
Pneumonia bacterial			

subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural sepsis			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative wound infection			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary sepsis			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	1 / 1280 (0.08%)	2 / 2564 (0.08%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	2 / 1280 (0.16%)	3 / 2564 (0.12%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Upper respiratory tract infection			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			

subjects affected / exposed	4 / 1280 (0.31%)	5 / 2564 (0.20%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 4	0 / 5	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic metabolic decompensation			
subjects affected / exposed	0 / 1280 (0.00%)	1 / 2564 (0.04%)	1 / 1284 (0.08%)
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	1 / 1280 (0.08%)	3 / 2564 (0.12%)	2 / 1284 (0.16%)
occurrences causally related to treatment / all	1 / 1	3 / 3	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	3 / 1280 (0.23%)	3 / 2564 (0.12%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	2 / 1280 (0.16%)	3 / 2564 (0.12%)	1 / 1284 (0.08%)
occurrences causally related to treatment / all	1 / 2	1 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malnutrition			

subjects affected / exposed	1 / 1280 (0.08%)	1 / 2564 (0.04%)	0 / 1284 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	LCZ696	Total	Individualized Medical Therapy Comparator
Total subjects affected by non-serious adverse events			
subjects affected / exposed	964 / 1280 (75.31%)	1796 / 2564 (70.05%)	832 / 1284 (64.80%)
Vascular disorders			
Hypertension			
subjects affected / exposed	42 / 1280 (3.28%)	123 / 2564 (4.80%)	81 / 1284 (6.31%)
occurrences (all)	43	134	91
Hypotension			
subjects affected / exposed	176 / 1280 (13.75%)	245 / 2564 (9.56%)	69 / 1284 (5.37%)
occurrences (all)	203	282	79
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	38 / 1280 (2.97%)	59 / 2564 (2.30%)	21 / 1284 (1.64%)
occurrences (all)	40	62	22
Oedema peripheral			
subjects affected / exposed	43 / 1280 (3.36%)	78 / 2564 (3.04%)	35 / 1284 (2.73%)
occurrences (all)	46	84	38
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	41 / 1280 (3.20%)	66 / 2564 (2.57%)	25 / 1284 (1.95%)
occurrences (all)	42	68	26
Dyspnoea			
subjects affected / exposed	47 / 1280 (3.67%)	93 / 2564 (3.63%)	46 / 1284 (3.58%)
occurrences (all)	48	96	48
Investigations			
Blood creatinine increased			
subjects affected / exposed	27 / 1280 (2.11%)	49 / 2564 (1.91%)	22 / 1284 (1.71%)
occurrences (all)	29	54	25

Blood potassium increased			
subjects affected / exposed	26 / 1280 (2.03%)	36 / 2564 (1.40%)	10 / 1284 (0.78%)
occurrences (all)	33	43	10
Glomerular filtration rate decreased			
subjects affected / exposed	137 / 1280 (10.70%)	287 / 2564 (11.19%)	150 / 1284 (11.68%)
occurrences (all)	153	323	170
Urine albumin/creatinine ratio increased			
subjects affected / exposed	157 / 1280 (12.27%)	254 / 2564 (9.91%)	97 / 1284 (7.55%)
occurrences (all)	162	261	99
Urine protein/creatinine ratio increased			
subjects affected / exposed	66 / 1280 (5.16%)	131 / 2564 (5.11%)	65 / 1284 (5.06%)
occurrences (all)	70	137	67
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	44 / 1280 (3.44%)	87 / 2564 (3.39%)	43 / 1284 (3.35%)
occurrences (all)	47	95	48
Cardiac failure			
subjects affected / exposed	34 / 1280 (2.66%)	77 / 2564 (3.00%)	43 / 1284 (3.35%)
occurrences (all)	38	84	46
Nervous system disorders			
Dizziness			
subjects affected / exposed	70 / 1280 (5.47%)	133 / 2564 (5.19%)	63 / 1284 (4.91%)
occurrences (all)	79	148	69
Headache			
subjects affected / exposed	18 / 1280 (1.41%)	48 / 2564 (1.87%)	30 / 1284 (2.34%)
occurrences (all)	19	51	32
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	17 / 1280 (1.33%)	45 / 2564 (1.76%)	28 / 1284 (2.18%)
occurrences (all)	17	46	29
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	43 / 1280 (3.36%)	85 / 2564 (3.32%)	42 / 1284 (3.27%)
occurrences (all)	52	123	71
Skin and subcutaneous tissue disorders			

Pruritus			
subjects affected / exposed	27 / 1280 (2.11%)	37 / 2564 (1.44%)	10 / 1284 (0.78%)
occurrences (all)	28	40	12
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	145 / 1280 (11.33%)	249 / 2564 (9.71%)	104 / 1284 (8.10%)
occurrences (all)	148	253	105
Microalbuminuria			
subjects affected / exposed	26 / 1280 (2.03%)	45 / 2564 (1.76%)	19 / 1284 (1.48%)
occurrences (all)	27	46	19
Proteinuria			
subjects affected / exposed	121 / 1280 (9.45%)	205 / 2564 (8.00%)	84 / 1284 (6.54%)
occurrences (all)	124	210	86
Renal failure			
subjects affected / exposed	49 / 1280 (3.83%)	87 / 2564 (3.39%)	38 / 1284 (2.96%)
occurrences (all)	54	94	40
Renal impairment			
subjects affected / exposed	148 / 1280 (11.56%)	258 / 2564 (10.06%)	110 / 1284 (8.57%)
occurrences (all)	165	293	128
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	35 / 1280 (2.73%)	56 / 2564 (2.18%)	21 / 1284 (1.64%)
occurrences (all)	36	61	25
Back pain			
subjects affected / exposed	27 / 1280 (2.11%)	53 / 2564 (2.07%)	26 / 1284 (2.02%)
occurrences (all)	28	54	26
Infections and infestations			
Bronchitis			
subjects affected / exposed	29 / 1280 (2.27%)	64 / 2564 (2.50%)	35 / 1284 (2.73%)
occurrences (all)	29	65	36
Influenza			
subjects affected / exposed	33 / 1280 (2.58%)	56 / 2564 (2.18%)	23 / 1284 (1.79%)
occurrences (all)	33	57	24
Nasopharyngitis			
subjects affected / exposed	35 / 1280 (2.73%)	95 / 2564 (3.71%)	60 / 1284 (4.67%)
occurrences (all)	38	100	62

Urinary tract infection			
subjects affected / exposed	49 / 1280 (3.83%)	84 / 2564 (3.28%)	35 / 1284 (2.73%)
occurrences (all)	55	96	41
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	148 / 1280 (11.56%)	286 / 2564 (11.15%)	138 / 1284 (10.75%)
occurrences (all)	187	379	192

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 January 2017	There were no patients randomized at the time of release of this amendment. The purpose of this amendment was to correct a typographic error in the original protocol that stated the eGFR exclusion criteria as eGFR < 15 mL/min/1.73m2 instead of the correct criteria eGFR < 30 mL/min/1.73m2.
12 September 2018	There were approximately 1095 patients randomized into the study at the time of release of this amendment. Key changes in this amendment were: To expand the EF inclusion criteria from the existing ≥ 45% to > 40%, to increase the sample size from existing 2,200 to 2,500 patients, to elevate change in 6MWD as one of the two primary endpoints in a subset of patients and remove it as a secondary endpoint, to include a testing strategy of the primary and secondary efficacy variables in the multiple testing procedure to control the family-wise Type-I error rate.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported