



Clinical trial results:

A multicenter, randomized, double-blind, active controlled study to evaluate the effects of LCZ696 compared to valsartan on cognitive function in patients with chronic heart failure and preserved ejection fraction

Summary

EudraCT number	2016-001254-17
Trial protocol	GB LT DE ES BG NL PL BE HR IT
Global end of trial date	16 May 2022

Results information

Result version number	v1 (current)
This version publication date	18 May 2023
First version publication date	18 May 2023

Trial information

Trial identification

Sponsor protocol code	CLCZ696B2320
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02884206
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	: Novartis Pharma AG
Sponsor organisation address	Novartis Campus, 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	16 May 2022
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	16 May 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the effects of LCZ696 compared to valsartan on cognitive function over 3 years in patients with heart failure and preserved ejection fraction (HFpEF) as assessed by the CogState cognitive assessment battery (Global Cognitive Composite Score (GCCS)).

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	23 November 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	Argentina: 25
Country: Number of subjects enrolled	Australia: 7
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Bulgaria: 17
Country: Number of subjects enrolled	Canada: 7
Country: Number of subjects enrolled	Croatia: 7
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Germany: 71
Country: Number of subjects enrolled	United Kingdom: 27
Country: Number of subjects enrolled	Italy: 39
Country: Number of subjects enrolled	Korea, Republic of: 10
Country: Number of subjects enrolled	Lithuania: 6
Country: Number of subjects enrolled	Netherlands: 17
Country: Number of subjects enrolled	Poland: 68
Country: Number of subjects enrolled	Russian Federation: 39
Country: Number of subjects enrolled	Spain: 23
Country: Number of subjects enrolled	Switzerland: 12
Country: Number of subjects enrolled	Taiwan: 9
Country: Number of subjects enrolled	Turkey: 7

Country: Number of subjects enrolled	United States: 197
Worldwide total number of subjects	592
EEA total number of subjects	252

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)	86
From 65 to 84 years	482
85 years and over	24

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

1200 patients were screened, of which 494 patients discontinued prior to completing the screening epoch. All 706 patients who completed the screening epoch were included in the Enrolled set. A total of 659 patients completed the valsartan run-in epoch and entered the LCZ696 run-in epoch. Overall, 592 patients completed the treatment run-in epoch.

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

Arms

Are arms mutually exclusive?	Yes
Arm title	LCZ696 200 mg bid

Arm description:

Patients who were able to tolerate the treatment during the single-blind treatment run-in epoch. Following the run-in period, patients randomized in this arm were given LCZ696 at 200 mg twice daily for three years.

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 200 mg bid

Arm title	Valsartan 160 mg bid
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Arm description:

Patients who were able to tolerate the treatment during the single-blind treatment run-in epoch. Following the run-in period, patients randomized in this arm were given valsartan at 160 mg twice daily for three years.

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

Dosage and administration details:

Valsartan 160 mg bid

Number of subjects in period 1	LCZ696 200 mg bid	Valsartan 160 mg bid
Started	295	297
Safety set	295	297
PET substudy set	244 ^[1]	247
Completed	251	237
Not completed	44	60
Adverse event, serious fatal	28	39
Physician decision	2	-
Adverse event, non-fatal	-	3
Non-compliance with study treatment	-	1
Patient/guardian decision	10	13
Lost to follow-up	4	4

Notes:

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

Justification: Subset of the SAF patients who participated in the PET substudy and had non-missing baseline assessment.

Baseline characteristics

Reporting groups

Reporting group title	LCZ696 200 mg bid
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Reporting group description:

Patients who were able to tolerate the treatment during the single-blind treatment run-in epoch. Following the run-in period, patients randomized in this arm were given LCZ696 at 200 mg twice daily for three years.

Reporting group title	Valsartan 160 mg bid
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Reporting group description:

Patients who were able to tolerate the treatment during the single-blind treatment run-in epoch. Following the run-in period, patients randomized in this arm were given valsartan at 160 mg twice daily for three years.

Reporting group values	LCZ696 200 mg bid	Valsartan 160 mg bid	Total
Number of subjects	295	297	592
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)	41	45	86
From 65-84 years	243	239	482
85 years and over	11	13	24
Age Continuous			
Units: years			
arithmetic mean	72.27	72.61	
standard deviation	± 6.749	± 7.043	-
Sex: Female, Male			
Units: participants			
Female	134	143	277
Male	161	154	315
Race/Ethnicity, Customized			
Units: Subjects			
Caucasian	273	271	544
Asian	11	12	23
Black	6	9	15
Native American	2	0	2
Unknown	1	2	3
Other	2	3	5

End points

End points reporting groups

Reporting group title	LCZ696 200 mg bid
Reporting group description: Patients who were able to tolerate the treatment during the single-blind treatment run-in epoch. Following the run-in period, patients randomized in this arm were given LCZ696 at 200 mg twice daily for three years.	
Reporting group title	Valsartan 160 mg bid
Reporting group description: Patients who were able to tolerate the treatment during the single-blind treatment run-in epoch. Following the run-in period, patients randomized in this arm were given valsartan at 160 mg twice daily for three years.	

Primary: Change from baseline in the CogState Global Cognitive Composite Score (GCCS)

End point title	Change from baseline in the CogState Global Cognitive Composite Score (GCCS)
End point description: The CogState cognitive battery was composed of 7 tests, which were administered electronically by the patients at scheduled visits. For each test, a standardized z-score was calculated. The GCCS was the average of the non-missing individual test z-scores. A higher score indicated better cognitive function. CogState GCCS changes from baseline (randomization) were analyzed using a repeated measures ANCOVA in which treatment, age stratification factor, Mini mental state examination stratification factor, education level, Apolipoprotein E ϵ 4 allele status, cerebrovascular disease burden at screening, visit and treatment-by-visit interaction are included as fixed-effect factor, and baseline (randomization) GCCS and visit-by-baseline GCCS as covariates with a common unstructured covariance matrix among visits between treatment groups. The analysis was based on a direct likelihood method with an assumption of Missing at random.	
End point type	Primary
End point timeframe: Baseline, month 36	

End point values	LCZ696 200 mg bid	Valsartan 160 mg bid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195	183		
Units: Global Cognitive Composite Score				
least squares mean (standard error)	-0.0902 (\pm 0.0372)	-0.0722 (\pm 0.0383)		

Statistical analyses

Statistical analysis title	LCZ696 vs. Valsartan
Statistical analysis description: Repeated measure ANCOVA	
Comparison groups	LCZ696 200 mg bid v Valsartan 160 mg bid

Number of subjects included in analysis	378
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[1]
P-value	= 0.7363
Method	ANCOVA
Parameter estimate	LSM
Point estimate	-0.018
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.123
upper limit	0.087

Notes:

[1] - To demonstrate non-inferiority that LCZ696 does not lead to a relevant decrease in cognition compared to valsartan at year 3, the lower bound of 95% CI does not include the pre-specified non-inferiority (NI) boundary (Cohen's D) of -0.3. An effect size of 0.3 in Cohen's D is generally considered as small.

Secondary: Change from baseline in cortical composite standardized uptake value ratio (SUVR)

End point title	Change from baseline in cortical composite standardized uptake value ratio (SUVR)
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End point description:

The effects of LCZ696 compared to valsartan on Aβ deposition in the brain over 3 years were evaluated in a subset of patients using amyloid positron emission tomography (PET) imaging by assessing the change from baseline in cortical composite SUVR. PET imaging was performed at selected PET-capable centers on all eligible patients participating in the substudy. Sites with patients performing the PET scan were a subset of the overall patient population and overall sites for the study.

Change from baseline to 3 years was analyzed based on an ANCOVA model with treatment, age, MMSE, amyloid status (+ve/-ve) stratification factors, region, APOE4 status and cerebrovascular disease burden as fixed effects, with baseline SUVR and treatment-by-baseline SUVR interaction as covariates for each of these imputed datasets. Results were obtained by applying Rubin's rules on the estimates from the imputed datasets.

End point type	Secondary
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End point timeframe:

Baseline, month 36

End point values	LCZ696 200 mg bid	Valsartan 160 mg bid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	134		
Units: value ratio (SUVR)				
least squares mean (standard error)				
Global cortical composite	0.0273 (± 0.0114)	0.0564 (± 0.0101)		
Cingulum posterior composite	0.0416 (± 0.0113)	0.0876 (± 0.0109)		
Frontal lobe composite	0.0218 (± 0.0117)	0.0434 (± 0.0104)		
Parietal lobe composite	0.0231 (± 0.0119)	0.0532 (± 0.0104)		
Temporal lobe composite	0.0249 (± 0.0110)	0.0418 (± 0.0097)		
White matter composite	0.0061 (± 0.0094)	-0.0072 (± 0.0083)		

Statistical analyses

Statistical analysis title	LCZ696 vs. Valsartan
Statistical analysis description: Multiple Imputation ANCOVA in Global cortical composite	
Comparison groups	LCZ696 200 mg bid v Valsartan 160 mg bid
Number of subjects included in analysis	281
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[2]
P-value	= 0.0579
Method	ANCOVA
Parameter estimate	Least Squares Mean
Point estimate	-0.0292
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0593
upper limit	0.001

Notes:

[2] - To show that the point estimate of SUVR difference in mean change over 3 years is in favor of LCZ696 and the non-inferiority is demonstrated, with the upper bound of the 95% CI excluding the NI boundary of 0.01.

Secondary: Change from baseline in individual cognitive domains

End point title	Change from baseline in individual cognitive domains
End point description: The effects of LCZ696 compared to valsartan on the individual cognitive domains (memory, executive function, and attention) over 3 years were evaluated by assessing the individual components of the CogState cognitive battery. Composite scores for the 3 individual cognitive domains were generated by combining the standardized z-scores of selected tests from the CogState cognitive battery. Each composite score was the average of the non-missing individual test z-scores. A higher score indicated better cognitive function.	
End point type	Secondary
End point timeframe: Baseline, month 36	

End point values	LCZ696 200 mg bid	Valsartan 160 mg bid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	197	185		
Units: Z-scores				
least squares mean (standard error)				
Memory domain (n= 197, 185)	-0.0573 (± 0.0477)	-0.0580 (± 0.0490)		
Executive function domain (n= 196, 184)	-0.0375 (± 0.0480)	-0.0702 (± 0.0493)		

Attention domain (n= 197, 184)	-0.1836 (\pm 0.0614)	-0.0794 (\pm 0.0634)		
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Statistical analyses

Statistical analysis title	LCZ696 vs. Valsartan for memory domain
Statistical analysis description:	
Repeated measure ANCOVA for memory domain	
Comparison groups	LCZ696 200 mg bid v Valsartan 160 mg bid
Number of subjects included in analysis	382
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.9916
Method	ANCOVA
Parameter estimate	Least Squares Mean
Point estimate	0.0007
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1339
upper limit	0.1353

Statistical analysis title	LCZ696 vs. Valsartan for attention domain
Statistical analysis description:	
Repeated measure ANCOVA for attention domain	
Comparison groups	LCZ696 200 mg bid v Valsartan 160 mg bid
Number of subjects included in analysis	382
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2403
Method	ANCOVA
Parameter estimate	Least Squares Mean
Point estimate	-0.1042
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2783
upper limit	0.07

Statistical analysis title	LCZ696 vs. Valsartan for executive function domain
Statistical analysis description:	
Repeated measure ANCOVA for executive function domain	
Comparison groups	LCZ696 200 mg bid v Valsartan 160 mg bid

Number of subjects included in analysis	382
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.6348
Method	ANCOVA
Parameter estimate	Least Squares Mean
Point estimate	0.0327
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1024
upper limit	0.1677

Secondary: Change from baseline in the summary score of the instrumental activities of daily living (IADL)

End point title	Change from baseline in the summary score of the instrumental activities of daily living (IADL)
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End point description:

The effects of LCZ696 compared to valsartan on the changes in IADL over 3 years were evaluated by as assessing the Functional activities questionnaire (FAQ) summary scores.

The FAQ is a 30-point questionnaire that is made up of 10 questions that reflect a patient's ability to perform activities of daily living and to function independently. A score of 0 represents no impairment and a score of 30 represents severe impairment.

End point type	Secondary
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End point timeframe:

Baseline, month 36

End point values	LCZ696 200 mg bid	Valsartan 160 mg bid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	197	186		
Units: FAQ scores				
least squares mean (standard error)	0.5983 (\pm 0.2064)	0.7089 (\pm 0.2115)		

Statistical analyses

Statistical analysis title	LCZ696 vs. Valsartan
Statistical analysis description:	
Repeated measure ANCOVA	
Comparison groups	LCZ696 200 mg bid v Valsartan 160 mg bid

Number of subjects included in analysis	383
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.7081
Method	ANCOVA
Parameter estimate	Least Squares Mean
Point estimate	-0.1105
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6906
upper limit	0.4696

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from first dose of study treatment until end of study treatment plus 30 days post treatment, up to a maximum duration of 37 months.

Adverse event reporting additional description:

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

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	25.0
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Reporting groups

Reporting group title	LCZ696
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Reporting group description:

LCZ696

Reporting group title	Total
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Reporting group description:

Total

Reporting group title	Valsartan
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Reporting group description:

Valsartan

Serious adverse events	LCZ696	Total	Valsartan
Total subjects affected by serious adverse events			
subjects affected / exposed	145 / 295 (49.15%)	306 / 592 (51.69%)	161 / 297 (54.21%)
number of deaths (all causes)	28	67	39
number of deaths resulting from adverse events	0	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
B-cell lymphoma			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Basal cell carcinoma			
subjects affected / exposed	1 / 295 (0.34%)	7 / 592 (1.18%)	6 / 297 (2.02%)
occurrences causally related to treatment / all	0 / 1	0 / 8	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Benign hepatobiliary neoplasm			

subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder neoplasm			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer recurrent			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Bronchial carcinoma			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Carcinoid tumour in the large intestine			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Colorectal adenoma			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Endometrial cancer			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung adenocarcinoma			

subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Invasive breast carcinoma			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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 neoplasm			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung cancer metastatic			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial stromal sarcoma			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Follicular lymphoma			
subjects affected / exposed	1 / 295 (0.34%)	2 / 592 (0.34%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric cancer			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
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 neoplasm			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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	2 / 295 (0.68%)	3 / 592 (0.51%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to peritoneum			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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 liver			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
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 bone			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Meningioma			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphocytic leukaemia			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Myelodysplastic syndrome			
subjects affected / exposed	1 / 295 (0.34%)	2 / 592 (0.34%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostatic adenoma			

subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	2 / 295 (0.68%)	4 / 592 (0.68%)	2 / 297 (0.67%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cancer			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Oesophageal carcinoma			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Non-Hodgkin's lymphoma			
subjects affected / exposed	1 / 295 (0.34%)	2 / 592 (0.34%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasm prostate			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Refractory cytopenia with unilineage dysplasia			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsil cancer			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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 of lung			

subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
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 cell carcinoma			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
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			
Aneurysm			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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 aneurysm			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Aortic stenosis			
subjects affected / exposed	2 / 295 (0.68%)	2 / 592 (0.34%)	0 / 297 (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
Circulatory collapse			
subjects affected / exposed	0 / 295 (0.00%)	2 / 592 (0.34%)	2 / 297 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Deep vein thrombosis			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Extremity necrosis			

subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
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	0 / 295 (0.00%)	5 / 592 (0.84%)	5 / 297 (1.68%)
occurrences causally related to treatment / all	0 / 0	0 / 5	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	1 / 295 (0.34%)	2 / 592 (0.34%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive urgency			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	3 / 295 (1.02%)	8 / 592 (1.35%)	5 / 297 (1.68%)
occurrences causally related to treatment / all	1 / 3	4 / 9	3 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intermittent claudication			
subjects affected / exposed	1 / 295 (0.34%)	2 / 592 (0.34%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthostatic hypotension			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
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 ischaemia			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral arterial occlusive disease			

subjects affected / exposed	1 / 295 (0.34%)	4 / 592 (0.68%)	3 / 297 (1.01%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock haemorrhagic			
subjects affected / exposed	1 / 295 (0.34%)	2 / 592 (0.34%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Vasculitis			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subclavian artery stenosis			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Venous thrombosis limb			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	2 / 295 (0.68%)	2 / 592 (0.34%)	0 / 297 (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
Cardiac death			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Asthenia			
subjects affected / exposed	0 / 295 (0.00%)	2 / 592 (0.34%)	2 / 297 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalised oedema			

subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Fatigue			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	5 / 295 (1.69%)	8 / 592 (1.35%)	3 / 297 (1.01%)
occurrences causally related to treatment / all	0 / 5	0 / 8	0 / 3
deaths causally related to treatment / all	0 / 5	0 / 8	0 / 3
Impaired healing			
subjects affected / exposed	0 / 295 (0.00%)	2 / 592 (0.34%)	2 / 297 (0.67%)
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			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	8 / 295 (2.71%)	10 / 592 (1.69%)	2 / 297 (0.67%)
occurrences causally related to treatment / all	0 / 8	0 / 10	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			

subjects affected / exposed	0 / 295 (0.00%)	2 / 592 (0.34%)	2 / 297 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Vascular stent stenosis			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Pyrexia			
subjects affected / exposed	0 / 295 (0.00%)	2 / 592 (0.34%)	2 / 297 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden cardiac death			
subjects affected / exposed	2 / 295 (0.68%)	2 / 592 (0.34%)	0 / 297 (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
Immune system disorders			
Allergy to arthropod bite			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug hypersensitivity			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Endometrial hyperplasia			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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

Testicular swelling			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Testicular pain			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
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, thoracic and mediastinal disorders			
Bronchiectasis			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
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	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
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	5 / 295 (1.69%)	10 / 592 (1.69%)	5 / 297 (1.68%)
occurrences causally related to treatment / all	0 / 5	0 / 11	0 / 6
deaths causally related to treatment / all	0 / 1	0 / 2	0 / 1
Central sleep apnoea syndrome			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	9 / 295 (3.05%)	13 / 592 (2.20%)	4 / 297 (1.35%)
occurrences causally related to treatment / all	0 / 14	0 / 19	0 / 5
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Cough			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Haemoptysis			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Epistaxis			
subjects affected / exposed	1 / 295 (0.34%)	4 / 592 (0.68%)	3 / 297 (1.01%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea exertional			
subjects affected / exposed	1 / 295 (0.34%)	3 / 592 (0.51%)	2 / 297 (0.67%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	3 / 295 (1.02%)	10 / 592 (1.69%)	7 / 297 (2.36%)
occurrences causally related to treatment / all	0 / 3	0 / 12	0 / 9
deaths causally related to treatment / all	0 / 1	0 / 2	0 / 1
Hiccups			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	3 / 295 (1.02%)	4 / 592 (0.68%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 5	0 / 6	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Hypercapnia			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Hydrothorax			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Interstitial lung disease			

subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Pleuritic pain			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Pneumothorax			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Pulmonary alveolar haemorrhage			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
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 / 295 (0.34%)	4 / 592 (0.68%)	3 / 297 (1.01%)
occurrences causally related to treatment / all	0 / 2	0 / 5	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 2
Pulmonary toxicity			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
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 mass			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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 hypertension			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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 embolism			

subjects affected / exposed	1 / 295 (0.34%)	5 / 592 (0.84%)	4 / 297 (1.35%)
occurrences causally related to treatment / all	0 / 1	0 / 5	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Sleep apnoea syndrome			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	1 / 295 (0.34%)	2 / 592 (0.34%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angiocardiogram			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
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 creatinine increased			
subjects affected / exposed	2 / 295 (0.68%)	2 / 592 (0.34%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood glucose increased			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

C-reactive protein increased subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Catheterisation cardiac abnormal subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
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 enzyme increased subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronavirus test positive subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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 increased subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Viral test positive subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SARS-CoV-2 test positive subjects affected / exposed	0 / 295 (0.00%)	3 / 592 (0.51%)	3 / 297 (1.01%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procalcitonin increased			

subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Weight decreased			
subjects affected / exposed	1 / 295 (0.34%)	2 / 592 (0.34%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight increased			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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			
Ankle fracture			
subjects affected / exposed	1 / 295 (0.34%)	3 / 592 (0.51%)	2 / 297 (0.67%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	1 / 295 (0.34%)	3 / 592 (0.51%)	2 / 297 (0.67%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	2 / 295 (0.68%)	9 / 592 (1.52%)	7 / 297 (2.36%)
occurrences causally related to treatment / all	0 / 2	1 / 9	1 / 7
deaths causally related to treatment / all	0 / 0	1 / 1	1 / 1
Cranio-cerebral injury			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Concussion			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Cervical vertebral fracture			

subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Brain contusion			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Epicondylitis			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
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	1 / 295 (0.34%)	2 / 592 (0.34%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Haematuria traumatic			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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 / 295 (0.34%)	2 / 592 (0.34%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	1 / 1	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot fracture			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fibula fracture			

subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	2 / 295 (0.68%)	7 / 592 (1.18%)	5 / 297 (1.68%)
occurrences causally related to treatment / all	0 / 2	0 / 7	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	0 / 295 (0.00%)	2 / 592 (0.34%)	2 / 297 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural complication			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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 pulmonary embolism			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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 haemorrhage			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Periprosthetic fracture			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Pelvic fracture			
subjects affected / exposed	0 / 295 (0.00%)	2 / 592 (0.34%)	2 / 297 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			

subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Humerus fracture			
subjects affected / exposed	2 / 295 (0.68%)	3 / 592 (0.51%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin laceration			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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 compression fracture			
subjects affected / exposed	0 / 295 (0.00%)	2 / 592 (0.34%)	2 / 297 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 5	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sternal fracture			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
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	2 / 295 (0.68%)	2 / 592 (0.34%)	0 / 297 (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
Thoracic vertebral fracture			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Transfusion reaction			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic fracture			

subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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	0 / 295 (0.00%)	2 / 592 (0.34%)	2 / 297 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Acute myocardial infarction			
subjects affected / exposed	8 / 295 (2.71%)	20 / 592 (3.38%)	12 / 297 (4.04%)
occurrences causally related to treatment / all	0 / 8	0 / 21	0 / 13
deaths causally related to treatment / all	0 / 0	0 / 3	0 / 3
Acute left ventricular failure			
subjects affected / exposed	3 / 295 (1.02%)	4 / 592 (0.68%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 3	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Acute right ventricular failure			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia			
subjects affected / exposed	0 / 295 (0.00%)	3 / 592 (0.51%)	3 / 297 (1.01%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Aortic valve stenosis			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Angina unstable			
subjects affected / exposed	3 / 295 (1.02%)	8 / 592 (1.35%)	5 / 297 (1.68%)
occurrences causally related to treatment / all	0 / 3	1 / 8	1 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			

subjects affected / exposed	2 / 295 (0.68%)	5 / 592 (0.84%)	3 / 297 (1.01%)
occurrences causally related to treatment / all	0 / 2	0 / 7	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	14 / 295 (4.75%)	25 / 592 (4.22%)	11 / 297 (3.70%)
occurrences causally related to treatment / all	1 / 15	1 / 28	0 / 13
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	1 / 295 (0.34%)	3 / 592 (0.51%)	2 / 297 (0.67%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular dissociation			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
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	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Atrioventricular block			
subjects affected / exposed	2 / 295 (0.68%)	3 / 592 (0.51%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial tachycardia			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradyarrhythmia			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
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 failure chronic			

subjects affected / exposed	4 / 295 (1.36%)	7 / 592 (1.18%)	3 / 297 (1.01%)
occurrences causally related to treatment / all	0 / 5	0 / 9	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure acute			
subjects affected / exposed	5 / 295 (1.69%)	10 / 592 (1.69%)	5 / 297 (1.68%)
occurrences causally related to treatment / all	0 / 7	0 / 14	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	15 / 295 (5.08%)	30 / 592 (5.07%)	15 / 297 (5.05%)
occurrences causally related to treatment / all	1 / 18	2 / 38	1 / 20
deaths causally related to treatment / all	0 / 3	0 / 6	0 / 3
Cardiac arrest			
subjects affected / exposed	0 / 295 (0.00%)	6 / 592 (1.01%)	6 / 297 (2.02%)
occurrences causally related to treatment / all	0 / 0	0 / 6	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 3	0 / 3
Cardiac amyloidosis			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Bradycardia			
subjects affected / exposed	0 / 295 (0.00%)	3 / 592 (0.51%)	3 / 297 (1.01%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	8 / 295 (2.71%)	16 / 592 (2.70%)	8 / 297 (2.69%)
occurrences causally related to treatment / all	0 / 10	0 / 20	0 / 10
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 2
Cardiac valve disease			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			

subjects affected / exposed	1 / 295 (0.34%)	3 / 592 (0.51%)	2 / 297 (0.67%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 3	0 / 2
Cardiogenic shock			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Cardiovascular insufficiency			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Chronic left ventricular failure			
subjects affected / exposed	0 / 295 (0.00%)	2 / 592 (0.34%)	2 / 297 (0.67%)
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	7 / 295 (2.37%)	10 / 592 (1.69%)	3 / 297 (1.01%)
occurrences causally related to treatment / all	0 / 7	0 / 10	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Left ventricular failure			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
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 infarction			
subjects affected / exposed	3 / 295 (1.02%)	10 / 592 (1.69%)	7 / 297 (2.36%)
occurrences causally related to treatment / all	0 / 3	0 / 10	0 / 7
deaths causally related to treatment / all	0 / 2	0 / 7	0 / 5
Myocardial ischaemia			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			

subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Right ventricular failure			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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 bradycardia			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Tachyarrhythmia			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			
subjects affected / exposed	1 / 295 (0.34%)	2 / 592 (0.34%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	1 / 1	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular fibrillation			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Ventricular extrasystoles			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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			
Brain stem infarction			

subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
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 oedema			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Bell's palsy			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carotid artery stenosis			
subjects affected / exposed	1 / 295 (0.34%)	2 / 592 (0.34%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic neuropathy			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dementia Alzheimer's type			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	4 / 295 (1.36%)	7 / 592 (1.18%)	3 / 297 (1.01%)
occurrences causally related to treatment / all	0 / 5	0 / 8	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Cerebellar stroke			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
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 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Cerebral haematoma			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Cerebellar haemorrhage			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
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	2 / 295 (0.68%)	2 / 592 (0.34%)	0 / 297 (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
Dysarthria			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalopathy			
subjects affected / exposed	0 / 295 (0.00%)	2 / 592 (0.34%)	2 / 297 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	1 / 295 (0.34%)	3 / 592 (0.51%)	2 / 297 (0.67%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage intracranial			
subjects affected / exposed	0 / 295 (0.00%)	2 / 592 (0.34%)	2 / 297 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic stroke			

subjects affected / exposed	1 / 295 (0.34%)	2 / 592 (0.34%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Headache			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
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 / 295 (0.34%)	2 / 592 (0.34%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	1 / 295 (0.34%)	4 / 592 (0.68%)	3 / 297 (1.01%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 2	0 / 1
Lacunar stroke			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydrocephalus			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Metabolic encephalopathy			
subjects affected / exposed	3 / 295 (1.02%)	4 / 592 (0.68%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 4	0 / 5	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myelopathy			

subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Intracranial aneurysm			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somnolence			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	6 / 295 (2.03%)	11 / 592 (1.86%)	5 / 297 (1.68%)
occurrences causally related to treatment / all	2 / 9	4 / 15	2 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 295 (0.34%)	2 / 592 (0.34%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Status epilepticus			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	1 / 295 (0.34%)	3 / 592 (0.51%)	2 / 297 (0.67%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 295 (1.02%)	9 / 592 (1.52%)	6 / 297 (2.02%)
occurrences causally related to treatment / all	0 / 4	0 / 11	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombasthenia			

subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Splenic infarction			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukocytosis			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Iron deficiency anaemia			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Thrombotic thrombocytopenic purpura			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	0 / 295 (0.00%)	2 / 592 (0.34%)	2 / 297 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertigo			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Chondrodermatitis nodularis chronica helicis			

subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Eye disorders			
Diabetic retinopathy			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cataract			
subjects affected / exposed	2 / 295 (0.68%)	4 / 592 (0.68%)	2 / 297 (0.67%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal degeneration			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Macular degeneration			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Glaucoma			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Epiretinal membrane			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
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			
subjects affected / exposed	3 / 295 (1.02%)	3 / 592 (0.51%)	0 / 297 (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
Abdominal pain upper			

subjects affected / exposed	1 / 295 (0.34%)	2 / 592 (0.34%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal fissure			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	1 / 295 (0.34%)	2 / 592 (0.34%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	2 / 295 (0.68%)	2 / 592 (0.34%)	0 / 297 (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
Faeces discoloured			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Diverticulum intestinal haemorrhagic			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticular perforation			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
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	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Colitis ischaemic			

subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
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 inflammation			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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 haemorrhage			
subjects affected / exposed	3 / 295 (1.02%)	6 / 592 (1.01%)	3 / 297 (1.01%)
occurrences causally related to treatment / all	0 / 3	0 / 14	0 / 11
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Gastritis			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Melaena			
subjects affected / exposed	2 / 295 (0.68%)	2 / 592 (0.34%)	0 / 297 (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
Intestinal mass			

subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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 gastrointestinal haemorrhage			
subjects affected / exposed	2 / 295 (0.68%)	2 / 592 (0.34%)	0 / 297 (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
Mesenteric arterial occlusion			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Intestinal haemorrhage			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Nausea			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Retroperitoneal haematoma			
subjects affected / exposed	1 / 295 (0.34%)	2 / 592 (0.34%)	1 / 297 (0.34%)
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 haemorrhage			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngo-oesophageal diverticulum			

subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	2 / 295 (0.68%)	2 / 592 (0.34%)	0 / 297 (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
Pancreatitis			
subjects affected / exposed	0 / 295 (0.00%)	2 / 592 (0.34%)	2 / 297 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mouth haemorrhage			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
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	1 / 295 (0.34%)	2 / 592 (0.34%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Umbilical hernia			
subjects affected / exposed	2 / 295 (0.68%)	3 / 592 (0.51%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 295 (0.34%)	2 / 592 (0.34%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Autoimmune hepatitis			

subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bile duct stone			
subjects affected / exposed	1 / 295 (0.34%)	2 / 592 (0.34%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac cirrhosis			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
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 cirrhosis			
subjects affected / exposed	4 / 295 (1.36%)	4 / 592 (0.68%)	0 / 297 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Cholestasis			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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 acute			
subjects affected / exposed	1 / 295 (0.34%)	2 / 592 (0.34%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic mass			

subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice cholestatic			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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 and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Eczema			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
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	6 / 295 (2.03%)	12 / 592 (2.03%)	6 / 297 (2.02%)
occurrences causally related to treatment / all	1 / 6	2 / 12	1 / 6
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Bladder mass			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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 kidney disease			
subjects affected / exposed	2 / 295 (0.68%)	4 / 592 (0.68%)	2 / 297 (0.67%)
occurrences causally related to treatment / all	1 / 2	2 / 4	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis interstitial			

subjects affected / exposed	2 / 295 (0.68%)	2 / 592 (0.34%)	0 / 297 (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
Diabetic nephropathy			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysuria			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Haematuria			
subjects affected / exposed	2 / 295 (0.68%)	2 / 592 (0.34%)	0 / 297 (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
Hydronephrosis			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prerenal failure			
subjects affected / exposed	1 / 295 (0.34%)	2 / 592 (0.34%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder tamponade			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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 disorder			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Urethral stenosis			

subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureterolithiasis			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
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 tubular necrosis			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Renal impairment			
subjects affected / exposed	0 / 295 (0.00%)	3 / 592 (0.51%)	3 / 297 (1.01%)
occurrences causally related to treatment / all	0 / 0	2 / 3	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	2 / 295 (0.68%)	2 / 592 (0.34%)	0 / 297 (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
Urinary retention			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	2 / 295 (0.68%)	2 / 592 (0.34%)	0 / 297 (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
Arthralgia			
subjects affected / exposed	0 / 295 (0.00%)	3 / 592 (0.51%)	3 / 297 (1.01%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			

subjects affected / exposed	2 / 295 (0.68%)	3 / 592 (0.51%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical spinal stenosis			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Femoroacetabular impingement			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gouty arthritis			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscular weakness			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Loose body in joint			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemarthrosis			
subjects affected / exposed	1 / 295 (0.34%)	2 / 592 (0.34%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	6 / 295 (2.03%)	10 / 592 (1.69%)	4 / 297 (1.35%)
occurrences causally related to treatment / all	0 / 7	0 / 11	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Plantar fasciitis			

subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 295 (0.00%)	2 / 592 (0.34%)	2 / 297 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rheumatic disorder			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal disorder			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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	2 / 295 (0.68%)	3 / 592 (0.51%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Synovitis			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertebral foraminal stenosis			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Infections and infestations			
Abdominal abscess			

subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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 / 295 (1.02%)	4 / 592 (0.68%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 4	0 / 5	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis bacterial			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	2 / 295 (0.68%)	5 / 592 (0.84%)	3 / 297 (1.01%)
occurrences causally related to treatment / all	0 / 2	0 / 5	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 2
COVID-19 pneumonia			
subjects affected / exposed	4 / 295 (1.36%)	8 / 592 (1.35%)	4 / 297 (1.35%)
occurrences causally related to treatment / all	0 / 4	0 / 8	0 / 4
deaths causally related to treatment / all	0 / 1	0 / 2	0 / 1
Candida infection			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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 bacterial			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Diverticulitis			

subjects affected / exposed	0 / 295 (0.00%)	2 / 592 (0.34%)	2 / 297 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	2 / 295 (0.68%)	3 / 592 (0.51%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	1 / 295 (0.34%)	2 / 592 (0.34%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic sinusitis			
subjects affected / exposed	1 / 295 (0.34%)	2 / 592 (0.34%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 295 (0.34%)	2 / 592 (0.34%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carbuncle			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gangrene			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis norovirus			

subjects affected / exposed	2 / 295 (0.68%)	2 / 592 (0.34%)	0 / 297 (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
Enterococcal bacteraemia			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Erysipelas			
subjects affected / exposed	2 / 295 (0.68%)	3 / 592 (0.51%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia urinary tract infection			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Febrile infection			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Kidney infection			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Gastroenteritis viral			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Large intestine infection			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Infected skin ulcer			

subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
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	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Orchitis			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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 abscess			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	10 / 295 (3.39%)	19 / 592 (3.21%)	9 / 297 (3.03%)
occurrences causally related to treatment / all	0 / 14	0 / 23	0 / 9
deaths causally related to treatment / all	0 / 2	0 / 2	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Lymphangitis			

subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Nosocomial infection			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Oral candidiasis			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Sepsis			
subjects affected / exposed	5 / 295 (1.69%)	10 / 592 (1.69%)	5 / 297 (1.68%)
occurrences causally related to treatment / all	0 / 5	0 / 10	0 / 5
deaths causally related to treatment / all	0 / 1	0 / 2	0 / 1
Pneumonia aspiration			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Septic shock			
subjects affected / exposed	2 / 295 (0.68%)	4 / 592 (0.68%)	2 / 297 (0.67%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 2	0 / 1
Post procedural infection			
subjects affected / exposed	1 / 295 (0.34%)	2 / 592 (0.34%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psoas abscess			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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 acute			

subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Respiratory tract infection viral			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
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	6 / 295 (2.03%)	7 / 592 (1.18%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 8	0 / 9	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection bacterial			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Urosepsis			
subjects affected / exposed	2 / 295 (0.68%)	2 / 592 (0.34%)	0 / 297 (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
Viral infection			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			
subjects affected / exposed	1 / 295 (0.34%)	2 / 592 (0.34%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal sepsis			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Metabolism and nutrition disorders			
Cachexia			

subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
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 ketoacidosis			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
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			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	4 / 295 (1.36%)	5 / 592 (0.84%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 4	0 / 5	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gout			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Hypoglycaemia			
subjects affected / exposed	2 / 295 (0.68%)	3 / 592 (0.51%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	2 / 295 (0.68%)	5 / 592 (0.84%)	3 / 297 (1.01%)
occurrences causally related to treatment / all	2 / 2	5 / 5	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	1 / 295 (0.34%)	2 / 592 (0.34%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			

subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Lactic acidosis			
subjects affected / exposed	2 / 295 (0.68%)	2 / 592 (0.34%)	0 / 297 (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
Hyponatraemia			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypomagnesaemia			
subjects affected / exposed	1 / 295 (0.34%)	1 / 592 (0.17%)	0 / 297 (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
Metabolic acidosis			
subjects affected / exposed	0 / 295 (0.00%)	1 / 592 (0.17%)	1 / 297 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	LCZ696	Total	Valsartan
Total subjects affected by non-serious adverse events			
subjects affected / exposed	238 / 295 (80.68%)	483 / 592 (81.59%)	245 / 297 (82.49%)
Vascular disorders			
Hypertension			
subjects affected / exposed	21 / 295 (7.12%)	52 / 592 (8.78%)	31 / 297 (10.44%)
occurrences (all)	22	58	36
Hypotension			
subjects affected / exposed	68 / 295 (23.05%)	125 / 592 (21.11%)	57 / 297 (19.19%)
occurrences (all)	99	167	68
General disorders and administration site conditions			

Non-cardiac chest pain subjects affected / exposed occurrences (all)	9 / 295 (3.05%) 10	22 / 592 (3.72%) 23	13 / 297 (4.38%) 13
Fatigue subjects affected / exposed occurrences (all)	16 / 295 (5.42%) 18	39 / 592 (6.59%) 44	23 / 297 (7.74%) 26
Asthenia subjects affected / exposed occurrences (all)	7 / 295 (2.37%) 10	20 / 592 (3.38%) 25	13 / 297 (4.38%) 15
Oedema peripheral subjects affected / exposed occurrences (all)	24 / 295 (8.14%) 32	49 / 592 (8.28%) 59	25 / 297 (8.42%) 27
Pyrexia subjects affected / exposed occurrences (all)	4 / 295 (1.36%) 4	10 / 592 (1.69%) 10	6 / 297 (2.02%) 6
Reproductive system and breast disorders Benign prostatic hyperplasia subjects affected / exposed occurrences (all)	6 / 295 (2.03%) 6	9 / 592 (1.52%) 9	3 / 297 (1.01%) 3
Respiratory, thoracic and mediastinal disorders Chronic obstructive pulmonary disease subjects affected / exposed occurrences (all)	10 / 295 (3.39%) 18	20 / 592 (3.38%) 30	10 / 297 (3.37%) 12
Epistaxis subjects affected / exposed occurrences (all)	6 / 295 (2.03%) 8	12 / 592 (2.03%) 21	6 / 297 (2.02%) 13
Dyspnoea subjects affected / exposed occurrences (all)	21 / 295 (7.12%) 28	55 / 592 (9.29%) 71	34 / 297 (11.45%) 43
Cough subjects affected / exposed occurrences (all)	17 / 295 (5.76%) 20	29 / 592 (4.90%) 33	12 / 297 (4.04%) 13
Psychiatric disorders Depression			

subjects affected / exposed occurrences (all)	13 / 295 (4.41%) 14	25 / 592 (4.22%) 29	12 / 297 (4.04%) 15
Insomnia subjects affected / exposed occurrences (all)	4 / 295 (1.36%) 4	12 / 592 (2.03%) 12	8 / 297 (2.69%) 8
Investigations Blood creatinine increased subjects affected / exposed occurrences (all)	9 / 295 (3.05%) 10	16 / 592 (2.70%) 18	7 / 297 (2.36%) 8
Blood pressure increased subjects affected / exposed occurrences (all)	4 / 295 (1.36%) 6	16 / 592 (2.70%) 20	12 / 297 (4.04%) 14
Glomerular filtration rate decreased subjects affected / exposed occurrences (all)	15 / 295 (5.08%) 16	31 / 592 (5.24%) 32	16 / 297 (5.39%) 16
SARS-CoV-2 test positive subjects affected / exposed occurrences (all)	2 / 295 (0.68%) 2	9 / 592 (1.52%) 9	7 / 297 (2.36%) 7
Injury, poisoning and procedural complications Contusion subjects affected / exposed occurrences (all)	6 / 295 (2.03%) 7	15 / 592 (2.53%) 20	9 / 297 (3.03%) 13
Fall subjects affected / exposed occurrences (all)	19 / 295 (6.44%) 23	34 / 592 (5.74%) 49	15 / 297 (5.05%) 26
Ligament sprain subjects affected / exposed occurrences (all)	7 / 295 (2.37%) 7	10 / 592 (1.69%) 10	3 / 297 (1.01%) 3
Skin laceration subjects affected / exposed occurrences (all)	6 / 295 (2.03%) 10	13 / 592 (2.20%) 17	7 / 297 (2.36%) 7
Cardiac disorders Atrial fibrillation subjects affected / exposed occurrences (all)	17 / 295 (5.76%) 19	39 / 592 (6.59%) 44	22 / 297 (7.41%) 25
Angina pectoris			

subjects affected / exposed	16 / 295 (5.42%)	28 / 592 (4.73%)	12 / 297 (4.04%)
occurrences (all)	17	31	14
Cardiac failure			
subjects affected / exposed	14 / 295 (4.75%)	39 / 592 (6.59%)	25 / 297 (8.42%)
occurrences (all)	16	43	27
Cardiac failure chronic			
subjects affected / exposed	3 / 295 (1.02%)	13 / 592 (2.20%)	10 / 297 (3.37%)
occurrences (all)	3	15	12
Palpitations			
subjects affected / exposed	18 / 295 (6.10%)	24 / 592 (4.05%)	6 / 297 (2.02%)
occurrences (all)	20	26	6
Bradycardia			
subjects affected / exposed	7 / 295 (2.37%)	12 / 592 (2.03%)	5 / 297 (1.68%)
occurrences (all)	7	12	5
Nervous system disorders			
Balance disorder			
subjects affected / exposed	1 / 295 (0.34%)	8 / 592 (1.35%)	7 / 297 (2.36%)
occurrences (all)	1	9	8
Dizziness			
subjects affected / exposed	28 / 295 (9.49%)	59 / 592 (9.97%)	31 / 297 (10.44%)
occurrences (all)	33	68	35
Headache			
subjects affected / exposed	11 / 295 (3.73%)	18 / 592 (3.04%)	7 / 297 (2.36%)
occurrences (all)	11	18	7
Syncope			
subjects affected / exposed	7 / 295 (2.37%)	11 / 592 (1.86%)	4 / 297 (1.35%)
occurrences (all)	7	12	5
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	6 / 295 (2.03%)	7 / 592 (1.18%)	1 / 297 (0.34%)
occurrences (all)	6	7	1
Anaemia			
subjects affected / exposed	24 / 295 (8.14%)	45 / 592 (7.60%)	21 / 297 (7.07%)
occurrences (all)	25	49	24
Eye disorders			

Cataract subjects affected / exposed occurrences (all)	6 / 295 (2.03%) 6	14 / 592 (2.36%) 15	8 / 297 (2.69%) 9
Gastrointestinal disorders			
Constipation subjects affected / exposed occurrences (all)	6 / 295 (2.03%) 6	18 / 592 (3.04%) 18	12 / 297 (4.04%) 12
Large intestine polyp subjects affected / exposed occurrences (all)	4 / 295 (1.36%) 4	10 / 592 (1.69%) 10	6 / 297 (2.02%) 6
Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)	6 / 295 (2.03%) 6	12 / 592 (2.03%) 12	6 / 297 (2.02%) 6
Dyspepsia subjects affected / exposed occurrences (all)	3 / 295 (1.02%) 3	9 / 592 (1.52%) 9	6 / 297 (2.02%) 6
Diarrhoea subjects affected / exposed occurrences (all)	13 / 295 (4.41%) 13	32 / 592 (5.41%) 34	19 / 297 (6.40%) 21
Nausea subjects affected / exposed occurrences (all)	10 / 295 (3.39%) 12	18 / 592 (3.04%) 22	8 / 297 (2.69%) 10
Vomiting subjects affected / exposed occurrences (all)	4 / 295 (1.36%) 5	11 / 592 (1.86%) 13	7 / 297 (2.36%) 8
Skin and subcutaneous tissue disorders			
Skin lesion subjects affected / exposed occurrences (all)	1 / 295 (0.34%) 1	7 / 592 (1.18%) 7	6 / 297 (2.02%) 6
Rash subjects affected / exposed occurrences (all)	3 / 295 (1.02%) 3	12 / 592 (2.03%) 13	9 / 297 (3.03%) 10
Pruritus subjects affected / exposed occurrences (all)	8 / 295 (2.71%) 10	14 / 592 (2.36%) 17	6 / 297 (2.02%) 7
Renal and urinary disorders			

Renal impairment subjects affected / exposed occurrences (all)	26 / 295 (8.81%) 34	57 / 592 (9.63%) 72	31 / 297 (10.44%) 38
Renal failure subjects affected / exposed occurrences (all)	5 / 295 (1.69%) 5	12 / 592 (2.03%) 13	7 / 297 (2.36%) 8
Haematuria subjects affected / exposed occurrences (all)	10 / 295 (3.39%) 12	18 / 592 (3.04%) 20	8 / 297 (2.69%) 8
Chronic kidney disease subjects affected / exposed occurrences (all)	5 / 295 (1.69%) 5	13 / 592 (2.20%) 13	8 / 297 (2.69%) 8
Acute kidney injury subjects affected / exposed occurrences (all)	14 / 295 (4.75%) 15	27 / 592 (4.56%) 29	13 / 297 (4.38%) 14
Musculoskeletal and connective tissue disorders			
Pain in extremity subjects affected / exposed occurrences (all)	12 / 295 (4.07%) 13	23 / 592 (3.89%) 27	11 / 297 (3.70%) 14
Osteoarthritis subjects affected / exposed occurrences (all)	10 / 295 (3.39%) 12	19 / 592 (3.21%) 22	9 / 297 (3.03%) 10
Myalgia subjects affected / exposed occurrences (all)	7 / 295 (2.37%) 7	14 / 592 (2.36%) 16	7 / 297 (2.36%) 9
Muscle spasms subjects affected / exposed occurrences (all)	6 / 295 (2.03%) 6	15 / 592 (2.53%) 18	9 / 297 (3.03%) 12
Joint swelling subjects affected / exposed occurrences (all)	5 / 295 (1.69%) 5	11 / 592 (1.86%) 11	6 / 297 (2.02%) 6
Back pain subjects affected / exposed occurrences (all)	22 / 295 (7.46%) 23	50 / 592 (8.45%) 54	28 / 297 (9.43%) 31
Arthralgia			

subjects affected / exposed occurrences (all)	25 / 295 (8.47%) 30	57 / 592 (9.63%) 67	32 / 297 (10.77%) 37
Infections and infestations			
Bronchitis			
subjects affected / exposed	18 / 295 (6.10%)	31 / 592 (5.24%)	13 / 297 (4.38%)
occurrences (all)	28	42	14
COVID-19			
subjects affected / exposed	12 / 295 (4.07%)	17 / 592 (2.87%)	5 / 297 (1.68%)
occurrences (all)	12	17	5
Pneumonia			
subjects affected / exposed	8 / 295 (2.71%)	19 / 592 (3.21%)	11 / 297 (3.70%)
occurrences (all)	9	21	12
Nasopharyngitis			
subjects affected / exposed	26 / 295 (8.81%)	51 / 592 (8.61%)	25 / 297 (8.42%)
occurrences (all)	40	70	30
Lower respiratory tract infection			
subjects affected / exposed	6 / 295 (2.03%)	12 / 592 (2.03%)	6 / 297 (2.02%)
occurrences (all)	16	28	12
Herpes zoster			
subjects affected / exposed	6 / 295 (2.03%)	8 / 592 (1.35%)	2 / 297 (0.67%)
occurrences (all)	7	9	2
Cystitis			
subjects affected / exposed	6 / 295 (2.03%)	10 / 592 (1.69%)	4 / 297 (1.35%)
occurrences (all)	9	14	5
Cellulitis			
subjects affected / exposed	8 / 295 (2.71%)	17 / 592 (2.87%)	9 / 297 (3.03%)
occurrences (all)	9	19	10
Sinusitis			
subjects affected / exposed	9 / 295 (3.05%)	18 / 592 (3.04%)	9 / 297 (3.03%)
occurrences (all)	10	20	10
Upper respiratory tract infection			
subjects affected / exposed	13 / 295 (4.41%)	19 / 592 (3.21%)	6 / 297 (2.02%)
occurrences (all)	13	20	7
Urinary tract infection			
subjects affected / exposed	26 / 295 (8.81%)	47 / 592 (7.94%)	21 / 297 (7.07%)
occurrences (all)	30	56	26

Metabolism and nutrition disorders			
Type 2 diabetes mellitus			
subjects affected / exposed	7 / 295 (2.37%)	11 / 592 (1.86%)	4 / 297 (1.35%)
occurrences (all)	7	11	4
Iron deficiency			
subjects affected / exposed	4 / 295 (1.36%)	10 / 592 (1.69%)	6 / 297 (2.02%)
occurrences (all)	4	10	6
Hyponatraemia			
subjects affected / exposed	6 / 295 (2.03%)	15 / 592 (2.53%)	9 / 297 (3.03%)
occurrences (all)	9	18	9
Hypokalaemia			
subjects affected / exposed	14 / 295 (4.75%)	19 / 592 (3.21%)	5 / 297 (1.68%)
occurrences (all)	16	21	5
Vitamin D deficiency			
subjects affected / exposed	7 / 295 (2.37%)	13 / 592 (2.20%)	6 / 297 (2.02%)
occurrences (all)	7	13	6
Gout			
subjects affected / exposed	9 / 295 (3.05%)	21 / 592 (3.55%)	12 / 297 (4.04%)
occurrences (all)	12	27	15
Diabetes mellitus			
subjects affected / exposed	7 / 295 (2.37%)	15 / 592 (2.53%)	8 / 297 (2.69%)
occurrences (all)	7	16	9
Vitamin B12 deficiency			
subjects affected / exposed	6 / 295 (2.03%)	9 / 592 (1.52%)	3 / 297 (1.01%)
occurrences (all)	6	9	3
Hyperkalaemia			
subjects affected / exposed	31 / 295 (10.51%)	72 / 592 (12.16%)	41 / 297 (13.80%)
occurrences (all)	49	115	66

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 June 2017	<p>The key purpose of this amendment was to revise some of the study inclusion and exclusion criteria to remove unnecessary restrictions and to ensure the study population reflected the HFpEF population in the community. Although CLCZ696B2320 study was designed as an independent study to evaluate cognitive function and cerebral amyloid accretion in HFpEF patients, most of the inclusion and exclusion criteria were derived from the PARAGON-HF trial (an event-driven trial) as they were thought not to impact the objectives of the CLCZ696B2320 study. The initial screen failure rate was considerably higher than originally anticipated and many of the failures were because patients did not meet the MRI cerebrovascular criteria, which were intended to exclude patients with significant cerebrovascular pathology in whom the rate of change in cognitive function over time may differ from that in patients without significant background vascular disease.</p> <p>Based on CLCZ696B2320 study screening experience as well as available literature, the prevalence of cerebrovascular disease appeared to be significantly higher than originally anticipated and the existing exclusion criteria appeared to limit the population to the extent that the study cohort might not truly reflect the heart failure patient population seen in the community. Therefore, the following changes to the inclusion/exclusion criteria were made:</p> <p>Removed the requirement to meet MRI criteria for cerebrovascular and white matter lesions. Clinically significant cerebral pathology that may impact cognition remained as an exclusion criterion.</p> <p>Removed the existing exclusion criterion to allow participation of patients with a history of cardiomyopathies with an ejection fraction of >40% because exclusion of these patients was not relevant to the study objectives and these patients may benefit from treatment with LCZ696.</p>
18 August 2017	The purpose of this amendment was to correct a typographical error.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported