Clinical trial results:
A Placebo-Controlled, Double-Blind, Randomized, Multicenter, Three Arm Phase III Trial to Compare the Efficacy and Safety of Ibrutinib vs. Placebo in Previously Untreated Binet Stage A CLL Patients with Risk of Early Disease Progression

Summary

EudraCT number	2013-003211-22
Trial protocol	DE
Global end of trial date	11 July 2022

Results information

Result version number	v1 (current)
This version publication date	24 August 2023
First version publication date	24 August 2023

Trial information

Trial identification

Sponsor protocol code	CLL12

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02863718
WHO universal trial number (UTN)	-
Other trial identifiers	Board Approval Number: 13-396

Notes:

Sponsors

Sponsor organisation name	University of Cologne
Sponsor organisation address	Albertus-Magnus-Platz 1, Cologne, Germany, 50923
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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	21 December 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 July 2022
Global end of trial reached?	Yes
Global end of trial date	11 July 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to demonstrate superiority of ibrutinib over placebo in prolonging EFS for subjects with treatment-naïve CLL stage A and intermediate or (very) high risk of disease progression. All subjects with intermediate, (very) high risk randomized to the treatment arm will be treated up to active progressive disease with treatment indication according to iwCLL-Guidelines with the objective to demonstrate prolongation of EFS for the ibrutinib arm. EFS is defined as the time between randomization until active progressive disease with treatment indication according to the iwCLL-Guidelines, initiation of subsequent treatment for CLL, or death.

Protection of trial subjects:

Safety measures to prevent or to manage known risks associated with CLL, such as infections or cytopenia or known adverse reactions related to ibrutinib, such as bleeding events, cardiac arrhythmias and cardiac failure, hypertension and diarrhea have been included in the protocol. In chapter 2.4 of the protocol the most frequent risks were described, including recommendations how to prevent and manage these potential adverse events . The protocol includes sections (section 8.6.) regarding permitted and prohibited medication respectively, known interactions and precautions with concomitant medication, especially with CYP3A4 inhibitors or inducers. The protocol provides clear guidance for dose modifications and treatment discontinuation.

Background therapy:

Asymptomatic patients with early-stage disease (Rai 0, Binet A), should be monitored without therapy unless they have evidence of rapid disease progression. So far, studies on early-stage disease were unable to show a benefit of early therapeutic interventions.

Evidence for comparator:

To date no proven effective intervention for Binet A patients exists and watchful waiting should remain state of the art, especially, because published data do not support the concern, that a "delayed" (start only, when disease progresses to a treatment requiring disease according to the iwCLL guidelines) treatment would lead to a disadvantage of patients in early stage disease. Hence, the use of placebo as the comparator arm was considered justified.

Actual start date of recruitment	05 May 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	8 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 515
Worldwide total number of subjects	515
EEA total number of subjects	515

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)	313
From 65 to 84 years	201
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

From 5 May 2014 to 14 February 2019, 648 patients consented to participate in the study and were screened for eligibility, of which 133 patients were excluded. A total of 515 patients were enrolled, 152 low-risk patients were allocated to the observational cohort, 182 and 181 patients were randomly assigned to receive ibrutinib and placebo.

Pre-assignment

Screening details:

From 133 Screening failures, 73 did not meet eligibility criteria, 50 withdrew consent, 4 did not complete risk stratification and 6 were sreening failures due to administrative reasons.

Period 1

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

Blinding implementation details:

The randomization procedure was accomplished by a validated interactive web response system (IWRS). Patients were stratified by TP53 mutation status and risk group. Patients, site staff, and the sponsor's clinical and medical representatives were unaware of treatment group assignments. Ibrutinib and placebo capsules were identical in appearance. The blinding was not broken throughout the study unless it was absolutely considered essential.

Arms

Are arms mutually exclusive?	Yes
Arm title	Ibrutinib

Arm description:

Patients were instructed to take 3 capsules (for a dose of 420 mg Ibrutinib) once daily. One cycle was defined as 28 calendar days. Dose modifications were allowed for the management of adverse events (AEs). Study drug could be paused for a maximum of 28 consecutive days.

Arm type	Experimental
Investigational medicinal product name	Ibrutinib
Investigational medicinal product code	SUB120863
Other name	EU/1/14/945/001
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Ibrutinib 420mg will be administered daily up to active progressive disease with treatment indication according to iwCLL-Guidelines. A cycle is defined as 28 calendar days. Ibrutinib was administered until active progressive disease with treatment indication according to iwCLL guidelines or unacceptable toxicity was assessed. If a subject showed signs of progression, the subject was allowed to continue study drug treatment until active progressive disease with treatment indication according to the iwCLL Guidelines was observed.

Arm title	Placebo

Arm description:

Subjects received placebo. A cycle is defined as 28 calendar days. Placebo was continued until active progressive disease with treatment indication according to iwCLL guidelines or unacceptable toxicity was observed. If a subject showed signs of progression, the subject was allowed to continue study drug treatment until active progressive disease with treatment indication according to the iwCLL guidelines was assessed.

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	PL1
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Placebo to match capsules were also provided as a gray, size 0 hard gelatin capsule for oral administration. Subjects were instructed to take 3 capsules (for a dose of 420 mg), orally once daily.

Arm title	Watch and Wait

Arm description:

Subjects at low risk were not randomized and did not receive treatment but were only followed by watch & wait.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Ibrutinib	Placebo	Watch and Wait
Started	182	181	152
Completed	64	33	152
Not completed	118	148	0
Any study treatment received	15	10	-
Progressive disease requiring treatment	4	66	-
Consent withdrawn by subject	1	4	-
Adverse event, non-fatal	75	40	-
New CLL treatment without progressive disease	1	-	-
Death	1	1	-
Non-compliance	12	21	-
Other reason	9	6	-

Baseline characteristics

Reporting groups	
Reporting group title	Ibrutinib
Reporting group description:	
Patients were instructed to take 3 capsules (for a dose of 420 mg Ibrutinib) once daily. One cycle was defined as 28 calendar days. Dose modifications were allowed for the management of adverse events (AEs). Study drug could be paused for a maximum of 28 consecutive days.	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo. A cycle is defined as 28 calendar days. Placebo was continued until active progressive disease with treatment indication according to iwCLL guidelines or unacceptable toxicity was observed. If a subject showed signs of progression, the subject was allowed to continue study drug treatment until active progressive disease with treatment indication according to the iwCLL guidelines was assessed.	
Reporting group title	Watch and Wait
Reporting group description:	
Subjects at low risk were not randomized and did not receive treatment but were only followed by watch & wait.	

Reporting group values	Ibrutinib	Placebo	Watch and Wait
Number of subjects	182	181	152
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)	100	93	120
From 65-84 years	81	88	32
85 years and over	1	0	0
Age continuous Units: years			
median	64	64	57
inter-quartile range (Q1-Q3)	55 to 70	55 to 70	52 to 63
Gender categorical Units: Subjects			
Female	45	54	85
Male	137	127	67
GCLLSG Prognostic Index Risk Group Units: Subjects			
low	0	0	152
intermediate	137	136	0
high	40	42	0
very high	5	3	0
missing	0	0	0
Binet Stage			

The Binet staging system is one of the two staging systems currently adopted in assessment of chronic lymphocytic leukemia (CLL). It classifies CLL according to the number of involved regions (spleen, liver and the axillary, cervical and inguinal lymph nodes), as well as the presence of anemia or thrombocytopenia.			
Units: Subjects			
Binet A	181	181	152
Binet B	1	0	0
Binet C	0	0	0
Cytogenetic subgroup by hierarchical order			
Döhner et al first published a hierarchical model including five categories for chromosomal abnormalities (deletion 17p, deletion 11q, trisomy 12, no abnormalities according to the Döhner's model, deletion 13q) with prognostic value in CLL, with the shortest survival estimates observed in patients with del(17p), followed by those with del(11q) in the absence of del(17p).			
Units: Subjects			
Deletion 17p	6	7	0
Deletion 11q	21	19	0
Trisomy 12	24	28	4
No abnormalities according to Doehner's model	36	30	27
Deletion 13q	95	97	121
CIRS Score			
The Cumulative Illness Rating Scale (CIRS) is a comprehensive tool to evaluate comorbidities, which has been validated in multiple medical settings and is increasingly used in CLL. 14 organ categories can be scored according to the severeness of potential comorbidities with a score between 0 and 4.			
Units: Score points			
median	2	3	2
inter-quartile range (Q1-Q3)	1.0 to 4.3	1.0 to 4.0	0.0 to 3.0

Reporting group values	Total		
Number of subjects	515		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	313		
From 65-84 years	201		
85 years and over	1		
Age continuous			
Units: years			
median			
inter-quartile range (Q1-Q3)	-		
Gender categorical			
Units: Subjects			
Female	184		
Male	331		
GCLLSG Prognostic Index Risk Group			
Units: Subjects			
low	152		

intermediate	273		
high	82		
very high	8		
missing	0		
Binet Stage			
The Binet staging system is one of the two staging systems currently adopted in assessment of chronic lymphocytic leukemia (CLL). It classifies CLL according to the number of involved regions (spleen, liver and the axillary, cervical and inguinal lymph nodes), as well as the presence of anemia or thrombocytopenia.			
Units: Subjects			
Binet A	514		
Binet B	1		
Binet C	0		
Cytogenetic subgroup by hierarchical order			
Döhner et al first published a hierarchical model including five categories for chromosomal abnormalities (deletion 17p, deletion 11q, trisomy 12, no abnormalities according to the Döhner's model, deletion 13q) with prognostic value in CLL, with the shortest survival estimates observed in patients with del(17p), followed by those with del(11q) in the absence of del(17p).			
Units: Subjects			
Deletion 17p	13		
Deletion 11q	40		
Trisomy 12	56		
No abnormalities according to Doehner's model	93		
Deletion 13q	313		
CIRS Score			
The Cumulative Illness Rating Scale (CIRS) is a comprehensive tool to evaluate comorbidities, which has been validated in multiple medical settings and is increasingly used in CLL. 14 organ categories can be scored according to the severeness of potential comorbidities with a score between 0 and 4.			
Units: Score points			
median			
inter-quartile range (Q1-Q3)	-		

End points

End points reporting groups

Reporting group title	Ibrutinib

Reporting group description:

Patients were instructed to take 3 capsules (for a dose of 420 mg Ibrutinib) once daily. One cycle was defined as 28 calendar days. Dose modifications were allowed for the management of adverse events (AEs). Study drug could be paused for a maximum of 28 consecutive days.

Reporting group title	Placebo

Reporting group description:

Subjects received placebo. A cycle is defined as 28 calendar days. Placebo was continued until active progressive disease with treatment indication according to iwCLL guidelines or unacceptable toxicity was observed. If a subject showed signs of progression, the subject was allowed to continue study drug treatment until active progressive disease with treatment indication according to the iwCLL guidelines was assessed.

Reporting group title	Watch and Wait

Reporting group description:

Subjects at low risk were not randomized and did not receive treatment but were only followed by watch & wait.

Primary: Event-free Survival

End point title	Event-free Survival[1]

End point description:

The analysis of the primary efficacy parameter EFS will be performed on the population of all patients with intermediate, high or very high risk being randomized to receive ibrutinib or placebo using a two-sided stratified log-rank test with risk group as stratification factor (intermediate risk / high risk / very high risk) (at 0.05 significance level; not adjusted).
In addition Kaplan-Meier survival methodology will be used to calculate the median EFS and estimated EFS rates for one, two and three years etc. after randomization. The corresponding hazard ratio and 95% confidence interval will be determined using a stratified (by risk group) Cox proportional hazard regression model.

End point type	Primary

End point timeframe:

The primary efficacy parameter is event-free survival (EFS) defined as the time of randomization until symptomatic disease progression with treatment indication, initiation of subsequent treatment for CLL or death by any cause, whichever occurs first.

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The primary objective of the study is to demonstrate superiority of ibrutinib over placebo in prolonging event-free survival in treatment naïve Binet stage A CLL patients with intermediate to (very) high risk of disease progression. Therefore this analysis was based on randomized patients of the two treatment arms with ibrutinib or placebo.

End point values	Ibrutinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	182[2]	181		
Units: Percentage				
number (not applicable)				
Median EFS (months)	0	51.6		
1-year survival	96.4	88.9		
2-year survival	90.9	74.5		

3-year survival	87.7	61.2		
4-year survival	84.1	52.2		
5-year survival	78.2	48.0		

Notes:

[2] - Median EFS was not reached in this subgroup.

Statistical analyses

Statistical analysis title	Stratified log-rank test regarding EFS

Statistical analysis description:

Treatment comparison for the primary efficacy parameter EFS will be performed using a two-sided stratified log-rank test using the GCLLSG Prognostic Index Risk Group as stratification factor (at 0.05 significance level; not adjusted).

Comparison groups	Ibrutinib v Placebo
Number of subjects included in analysis	363
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	log-rank test

Statistical analysis title	Cox regression regarding EFS

Statistical analysis description:

Estimates of the treatment effect will be expressed by the hazard ratio (HR) including the 95% confidence interval estimated through a stratified (by the GCLLSG Prognostic Index Risk Group) Cox proportional hazard regression model. If the null hypothesis is rejected and the observed HR is favorable for the ibrutinib arm, then it is concluded that early treatment with ibrutinib significantly lowers the risk of EFS events in Binet stage A CLL patients with increased risk of disease progression.

Comparison groups	Ibrutinib v Placebo
Number of subjects included in analysis	363
Analysis specification	Pre-specified
Analysis type	superiority[3]
Parameter estimate	Cox proportional hazard
Point estimate	0.276
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.188
upper limit	0.407

Notes:

[3] - In Cox-regression the Placebo-group was used as reference category (Ibrutinib vs. Placebo).

Secondary: Overall survival

End point title	Overall survival[4]

End point description:

The analysis of the secondary efficacy endpoint OS will be performed on the population of all patients with intermediate, high or very high risk being randomized to receive ibrutinib or placebo using a two-sided stratified log-rank test with risk group as stratification factor (intermediate risk / high risk / very high risk).
In addition Kaplan-Meier survival methodology will be used to calculate the median OS and estimated OS rates for one, two and three years etc. after randomization. The corresponding hazard ratio and 95% confidence interval will be determined using a stratified (by risk group) Cox proportional hazard regression model.

End point type	Secondary

End point timeframe:

Overall survival (OS) will be calculated from the date of randomization to the date of death due to any cause. Subjects who have not yet died at the time of analysis will be censored at the date of last observation they were assessed to be alive.

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The secondary objective of the study is to demonstrate superiority of ibrutinib over placebo in treatment naïve Binet stage A CLL patients with intermediate to (very) high risk of disease progression in prolonging overall survival. Therefore this analysis was based on randomized patients of the two treatment arms with ibrutinib or placebo.

End point values	Ibrutinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	182[5]	181[6]		
Units: Percentage				
number (not applicable)				
Median OS	0	0		
1-year survival	98.8	100.0		
2-year survival	97.6	100.0		
3-year survival	97.0	98.8		
4-year survival	94.1	96.0		
5-year survival	93.3	93.6		

Notes:

[5] - Median OS was not reached in this subgroup.

[6] - Median OS was not reached in this subgroup.

Statistical analyses

Statistical analysis title	Stratified log-rank test regarding OS

Statistical analysis description:

Treatment comparison for the secondary efficacy parameter OS will be performed using a two-sided stratified log-rank test using the GCLLSG Prognostic Index Risk Group as stratification factor.

Comparison groups	Placebo v Ibrutinib
Number of subjects included in analysis	363
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.562
Method	log-rank test

Statistical analysis title	Cox regression regarding OS

Statistical analysis description:

Estimates of the treatment effect will be expressed by the hazard ratio (HR) including the 95% confidence interval estimated through a stratified (by the GCLLSG Prognostic Index Risk Group) Cox proportional hazard regression model.

Comparison groups	Ibrutinib v Placebo

Number of subjects included in analysis	363
Analysis specification	Pre-specified
Analysis type	superiority[7]
Parameter estimate	Cox proportional hazard
Point estimate	0.791
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.358
upper limit	1.748

Notes:

[7] - In Cox-regression the Placebo-group was used as reference category (Ibrutinib vs. Placebo).

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Timeframe for AE

Adverse event reporting additional description:

AE additional description

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Placebo

Reporting group description: -

Reporting group title	Ibrutinib

Reporting group description: -

Serious adverse events	Placebo	Ibrutinib	
Total subjects affected by serious adverse events			
subjects affected / exposed	101 / 168 (60.12%)	102 / 170 (60.00%)	
number of deaths (all causes)	14	11	
number of deaths resulting from adverse events	13	10	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adrenal adenoma	Additional description: Adrenal adenoma		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer	Additional description: Breast cancer		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign neoplasm of bladder	Additional description: Benign neoplasm of bladder		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma	Additional description: Basal cell carcinoma		

subjects affected / exposed	12 / 168 (7.14%)	4 / 170 (2.35%)	
occurrences causally related to treatment / all	2 / 18	3 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clear cell renal cell carcinoma	Additional description: Clear cell renal cell carcinoma		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon adenoma	Additional description: Colon adenoma		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial cancer	Additional description: Endometrial cancer		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal stromal tumour	Additional description: Gastrointestinal stromal tumour		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intraductal papilloma of breast	Additional description: Intraductal papilloma of breast		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma	Additional description: Lung adenocarcinoma		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lung neoplasm malignant	Additional description: Lung neoplasm malignant		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Malignant melanoma	Additional description: Malignant melanoma		

subjects affected / exposed	2 / 168 (1.19%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningioma	Additional description: Meningioma		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelodysplastic syndrome	Additional description: Myelodysplastic syndrome		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liposarcoma	Additional description: Liposarcoma		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuroendocrine carcinoma of the skin	Additional description: Neuroendocrine carcinoma of the skin		
subjects affected / exposed	2 / 168 (1.19%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nodular melanoma	Additional description: Nodular melanoma		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-small cell lung cancer	Additional description: Non-small cell lung cancer		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian adenoma	Additional description: Ovarian adenoma		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cancer	Additional description: Ovarian cancer		

subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Rectal adenocarcinoma	Additional description: Rectal adenocarcinoma		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer	Additional description: Prostate cancer		
subjects affected / exposed	5 / 168 (2.98%)	4 / 170 (2.35%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cancer metastatic	Additional description: Renal cancer metastatic		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Small cell lung cancer	Additional description: Small cell lung cancer		
subjects affected / exposed	0 / 168 (0.00%)	2 / 170 (1.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Richter's syndrome	Additional description: Richter's syndrome		
subjects affected / exposed	5 / 168 (2.98%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 3	0 / 0	
Thyroid cancer	Additional description: Thyroid cancer		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma	Additional description: Squamous cell carcinoma		
subjects affected / exposed	4 / 168 (2.38%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	1 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin	Additional description: Squamous cell carcinoma of skin		

subjects affected / exposed	2 / 168 (1.19%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uveal melanoma	Additional description: Uveal melanoma		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Circulatory collapse	Additional description: Circulatory collapse		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension	Additional description: Hypertension		
subjects affected / exposed	1 / 168 (0.60%)	3 / 170 (1.76%)	
occurrences causally related to treatment / all	1 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma	Additional description: Haematoma		
subjects affected / exposed	0 / 168 (0.00%)	2 / 170 (1.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis	Additional description: Hypertensive crisis		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jugular vein distension	Additional description: Jugular vein distension		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease	Additional description: Peripheral arterial occlusive disease		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haemorrhage	Additional description: Subdural haemorrhage		

subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis limb	Additional description: Venous thrombosis limb		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Cardiac pacemaker replacement	Additional description: Cardiac pacemaker replacement		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac resynchronisation therapy	Additional description: Cardiac resynchronisation therapy		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary arterial stent insertion	Additional description: Coronary arterial stent insertion		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical device removal	Additional description: Medical device removal		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuroprosthesis implantation	Additional description: Neuroprosthesis implantation		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatectomy	Additional description: Prostatectomy		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			

Chest pain	Additional description: Chest pain		
subjects affected / exposed	0 / 168 (0.00%)	2 / 170 (1.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death	Additional description: Death		
subjects affected / exposed	4 / 168 (2.38%)	2 / 170 (1.18%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 4	0 / 2	
Hernia	Additional description: Hernia		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration	Additional description: General physical health deterioration		
subjects affected / exposed	2 / 168 (1.19%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Necrosis	Additional description: Necrosis		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia	Additional description: Pyrexia		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden cardiac death	Additional description: Sudden cardiac death		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ulcer	Additional description: Ulcer		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			

Drug hypersensitivity	Additional description: Drug hypersensitivity		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia	Additional description: Benign prostatic hyperplasia		
subjects affected / exposed	2 / 168 (1.19%)	2 / 170 (1.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic floor muscle weakness	Additional description: Pelvic floor muscle weakness		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal prolapse	Additional description: Vaginal prolapse		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma-chronic obstructive pulmonary disease overlap syndrome	Additional description: Asthma-chronic obstructive pulmonary disease overlap syndrome		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma	Additional description: Asthma		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea	Additional description: Dyspnoea		
subjects affected / exposed	2 / 168 (1.19%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease	Additional description: Interstitial lung disease		

subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal septum deviation	Additional description: Nasal septum deviation		
subjects affected / exposed	0 / 168 (0.00%)	2 / 170 (1.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion	Additional description: Pleural effusion		
subjects affected / exposed	1 / 168 (0.60%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism	Additional description: Pulmonary embolism		
subjects affected / exposed	3 / 168 (1.79%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sleep apnoea syndrome	Additional description: Sleep apnoea syndrome		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Delusion of parasitosis	Additional description: Delusion of parasitosis		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression	Additional description: Depression		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Catheterisation cardiac	Additional description: Catheterisation cardiac		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical observation	Additional description: Medical observation		

subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture	Additional description: Ankle fracture		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fractured sacrum	Additional description: Fractured sacrum		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture	Additional description: Foot fracture		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture	Additional description: Femur fracture		
subjects affected / exposed	1 / 168 (0.60%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture	Additional description: Femoral neck fracture		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial bones fracture	Additional description: Facial bones fracture		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture	Additional description: Humerus fracture		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction	Additional description: Infusion related reaction		

subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation	Additional description: Joint dislocation		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb fracture	Additional description: Limb fracture		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture	Additional description: Lumbar vertebral fracture		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus injury	Additional description: Meniscus injury		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple fractures	Additional description: Multiple fractures		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural nausea	Additional description: Procedural nausea		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture	Additional description: Radius fracture		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture	Additional description: Rib fracture		

subjects affected / exposed	1 / 168 (0.60%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident	Additional description: Road traffic accident		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin laceration	Additional description: Skin laceration		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture	Additional description: Spinal fracture		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic rupture	Additional description: Splenic rupture		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage	Additional description: Subarachnoid haemorrhage		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma	Additional description: Subdural haematoma		
subjects affected / exposed	0 / 168 (0.00%)	2 / 170 (1.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Tendon rupture	Additional description: Tendon rupture		
subjects affected / exposed	0 / 168 (0.00%)	2 / 170 (1.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents	Additional description: Toxicity to various agents		

subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture	Additional description: Tibia fracture		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaccination complication	Additional description: Vaccination complication		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation	Additional description: Atrial fibrillation		
subjects affected / exposed	3 / 168 (1.79%)	11 / 170 (6.47%)	
occurrences causally related to treatment / all	2 / 4	9 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis coronary artery	Additional description: Arteriosclerosis coronary artery		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction	Additional description: Acute myocardial infarction		
subjects affected / exposed	5 / 168 (2.98%)	2 / 170 (1.18%)	
occurrences causally related to treatment / all	1 / 5	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter	Additional description: Atrial flutter		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest	Additional description: Cardiac arrest		
subjects affected / exposed	1 / 168 (0.60%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac aneurysm	Additional description: Cardiac aneurysm		

subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorder	Additional description: Cardiac disorder		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive	Additional description: Cardiac failure congestive		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic coronary syndrome	Additional description: Chronic coronary syndrome		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure	Additional description: Cardiac failure		
subjects affected / exposed	3 / 168 (1.79%)	3 / 170 (1.76%)	
occurrences causally related to treatment / all	0 / 4	1 / 3	
deaths causally related to treatment / all	0 / 1	1 / 1	
Congestive cardiomyopathy	Additional description: Congestive cardiomyopathy		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease	Additional description: Coronary artery disease		
subjects affected / exposed	6 / 168 (3.57%)	6 / 170 (3.53%)	
occurrences causally related to treatment / all	0 / 6	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis	Additional description: Coronary artery stenosis		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve incompetence	Additional description: Mitral valve incompetence		

subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia	Additional description: Sinus tachycardia		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia paroxysmal	Additional description: Tachycardia paroxysmal		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tricuspid valve incompetence	Additional description: Tricuspid valve incompetence		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia	Additional description: Ventricular tachycardia		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Basilar artery thrombosis	Additional description: Basilar artery thrombosis		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal ganglia infarction	Additional description: Basal ganglia infarction		
subjects affected / exposed	1 / 168 (0.60%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal ganglia haemorrhage	Additional description: Basal ganglia haemorrhage		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebellar infarction	Additional description: Cerebellar infarction		

subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage	Additional description: Cerebral haemorrhage		
subjects affected / exposed	1 / 168 (0.60%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia	Additional description: Cerebral ischaemia		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident	Additional description: Cerebrovascular accident		
subjects affected / exposed	3 / 168 (1.79%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervicobrachial syndrome	Additional description: Cervicobrachial syndrome		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dementia	Additional description: Dementia		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness	Additional description: Dizziness		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness postural	Additional description: Dizziness postural		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy	Additional description: Epilepsy		

subjects affected / exposed	1 / 168 (0.60%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolic stroke	Additional description: Embolic stroke		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar radiculopathy	Additional description: Lumbar radiculopathy		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurodegenerative disorder	Additional description: Neurodegenerative disorder		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensory neuropathy	Additional description: Peripheral sensory neuropathy		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Posterior reversible encephalopathy syndrome	Additional description: Posterior reversible encephalopathy syndrome		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiculopathy	Additional description: Radiculopathy		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica	Additional description: Sciatica		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure	Additional description: Seizure		

subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage	Additional description: Subarachnoid haemorrhage		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope	Additional description: Syncope		
subjects affected / exposed	1 / 168 (0.60%)	2 / 170 (1.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombotic stroke	Additional description: Thrombotic stroke		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack	Additional description: Transient ischaemic attack		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia	Additional description: Febrile neutropenia		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolytic anaemia	Additional description: Haemolytic anaemia		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolysis	Additional description: Haemolysis		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis	Additional description: Leukocytosis		

subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia	Additional description: Neutropenia		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic haematoma	Additional description: Splenic haematoma		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Meniere's disease	Additional description: Meniere's disease		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo	Additional description: Vertigo		
subjects affected / exposed	2 / 168 (1.19%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Glaucoma	Additional description: Glaucoma		
subjects affected / exposed	1 / 168 (0.60%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal artery occlusion	Additional description: Retinal artery occlusion		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal degeneration	Additional description: Retinal degeneration		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal haemorrhage	Additional description: Retinal haemorrhage		

subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain	Additional description: Abdominal pain		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ischaemic	Additional description: Colitis ischaemic		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation	Additional description: Constipation		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal inflammation	Additional description: Gastrointestinal inflammation		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiatus hernia	Additional description: Hiatus hernia		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia	Additional description: Inguinal hernia		
subjects affected / exposed	2 / 168 (1.19%)	3 / 170 (1.76%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal stenosis	Additional description: Large intestinal stenosis		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation	Additional description: Large intestine perforation		

subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis	Additional description: Pancreatitis		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia	Additional description: Umbilical hernia		
subjects affected / exposed	1 / 168 (0.60%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stone	Additional description: Bile duct stone		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute	Additional description: Cholecystitis acute		
subjects affected / exposed	0 / 168 (0.00%)	2 / 170 (1.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholestasis	Additional description: Cholestasis		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatotoxicity	Additional description: Hepatotoxicity		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure	Additional description: Hepatic failure		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			

Rash	Additional description: Rash		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer	Additional description: Skin ulcer		
subjects affected / exposed	2 / 168 (1.19%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury	Additional description: Acute kidney injury		
subjects affected / exposed	2 / 168 (1.19%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus urinary	Additional description: Calculus urinary		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis	Additional description: Nephrolithiasis		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postrenal failure	Additional description: Postrenal failure		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal infarct	Additional description: Renal infarct		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic	Additional description: Renal colic		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric stenosis	Additional description: Ureteric stenosis		

subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis	Additional description: Ureterolithiasis		
subjects affected / exposed	2 / 168 (1.19%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral stenosis	Additional description: Urethral stenosis		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary incontinence	Additional description: Urinary incontinence		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Goitre	Additional description: Goitre		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroid haemorrhage	Additional description: Thyroid haemorrhage		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain	Additional description: Back pain		
subjects affected / exposed	1 / 168 (0.60%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis	Additional description: Bursitis		
subjects affected / exposed	1 / 168 (0.60%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Intervertebral disc disorder	Additional description: Intervertebral disc disorder		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Intervertebral disc protrusion	Additional description: Intervertebral disc protrusion		
subjects affected / exposed	2 / 168 (1.19%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Mandibular mass	Additional description: Mandibular mass		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Musculoskeletal chest pain	Additional description: Musculoskeletal chest pain		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Osteoarthritis	Additional description: Osteoarthritis		
subjects affected / exposed	1 / 168 (0.60%)	3 / 170 (1.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

Osteochondritis	Additional description: Osteochondritis		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Periarthritis	Additional description: Periarthritis		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Rotator cuff syndrome	Additional description: Rotator cuff syndrome		
subjects affected / exposed	2 / 168 (1.19%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Spondylolisthesis	Additional description: Spondylolisthesis

subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovial cyst	Additional description: Synovial cyst		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal stenosis	Additional description: Spinal stenosis		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis perforated	Additional description: Appendicitis perforated		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess limb	Additional description: Abscess limb		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess	Additional description: Abscess		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis	Additional description: Bronchitis		
subjects affected / exposed	1 / 168 (0.60%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial prostatitis	Additional description: Bacterial prostatitis		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carbuncle	Additional description: Carbuncle		

subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis infective	Additional description: Bursitis infective		
subjects affected / exposed	0 / 168 (0.00%)	2 / 170 (1.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis	Additional description: Clostridium difficile colitis		
subjects affected / exposed	1 / 168 (0.60%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis	Additional description: Cellulitis		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium colitis	Additional description: Clostridium colitis		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dacryocystitis	Additional description: Dacryocystitis		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection	Additional description: Device related infection		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis	Additional description: Diverticulitis		
subjects affected / exposed	2 / 168 (1.19%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19	Additional description: COVID-19		

subjects affected / exposed	7 / 168 (4.17%)	7 / 170 (4.12%)	
occurrences causally related to treatment / all	0 / 7	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia	Additional description: COVID-19 pneumonia		
subjects affected / exposed	1 / 168 (0.60%)	3 / 170 (1.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cystitis	Additional description: Cystitis		
subjects affected / exposed	1 / 168 (0.60%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis escherichia	Additional description: Cystitis escherichia		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus infection	Additional description: Cytomegalovirus infection		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis	Additional description: Gastroenteritis		
subjects affected / exposed	3 / 168 (1.79%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile infection	Additional description: Febrile infection		
subjects affected / exposed	4 / 168 (2.38%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis	Additional description: Escherichia sepsis		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Erysipelas	Additional description: Erysipelas		

subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epididymitis	Additional description: Epididymitis		
subjects affected / exposed	1 / 168 (0.60%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolic pneumonia	Additional description: Embolic pneumonia		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear infection	Additional description: Ear infection		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster meningoencephalitis	Additional description: Herpes zoster meningoencephalitis		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster	Additional description: Herpes zoster		
subjects affected / exposed	2 / 168 (1.19%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cyst infection	Additional description: Hepatic cyst infection		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Helicobacter gastritis	Additional description: Helicobacter gastritis		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis E	Additional description: Hepatitis E		

subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected dermal cyst	Additional description: Infected dermal cyst		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection	Additional description: Infection		
subjects affected / exposed	2 / 168 (1.19%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza	Additional description: Influenza		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injection site abscess	Additional description: Injection site abscess		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral discitis	Additional description: Intervertebral discitis		
subjects affected / exposed	1 / 168 (0.60%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection	Additional description: Lower respiratory tract infection		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphangitis	Additional description: Lymphangitis		
subjects affected / exposed	1 / 168 (0.60%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mastoiditis	Additional description: Mastoiditis		

subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic infection	Additional description: Neutropenic infection		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis	Additional description: Neutropenic sepsis		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal candidiasis	Additional description: Oesophageal candidiasis		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ophthalmic herpes zoster	Additional description: Ophthalmic herpes zoster		
subjects affected / exposed	1 / 168 (0.60%)	2 / 170 (1.18%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral herpes	Additional description: Oral herpes		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orchitis	Additional description: Orchitis		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis	Additional description: Osteomyelitis		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paronychia	Additional description: Paronychia		

subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis infective	Additional description: Pericarditis infective		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia	Additional description: Pneumonia		
subjects affected / exposed	11 / 168 (6.55%)	8 / 170 (4.71%)	
occurrences causally related to treatment / all	3 / 12	7 / 11	
deaths causally related to treatment / all	0 / 0	0 / 1	
Salmonellosis	Additional description: Salmonellosis		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis	Additional description: Sepsis		
subjects affected / exposed	1 / 168 (0.60%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis	Additional description: Staphylococcal sepsis		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis	Additional description: Urosepsis		
subjects affected / exposed	0 / 168 (0.00%)	2 / 170 (1.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis	Additional description: Tonsillitis		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheobronchitis viral	Additional description: Tracheobronchitis viral		

subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection	Additional description: Upper respiratory tract infection		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection	Additional description: Urinary tract infection		
subjects affected / exposed	0 / 168 (0.00%)	3 / 170 (1.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperphosphataemia	Additional description: Hyperphosphataemia		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia	Additional description: Hyponatraemia		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour lysis syndrome	Additional description: Tumour lysis syndrome		
subjects affected / exposed	1 / 168 (0.60%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 diabetes mellitus	Additional description: Type 2 diabetes mellitus		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Placebo	Ibrutinib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	164 / 168 (97.62%)	164 / 170 (96.47%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenoma benign	Additional description: Adenoma benign		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Angiolipoma	Additional description: Angiolipoma		
subjects affected / exposed	1 / 168 (0.60%)	1 / 170 (0.59%)	
occurrences (all)	1	1	
Bowen's disease	Additional description: Bowen's disease		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Cancer fatigue	Additional description: Cancer fatigue		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Colon adenoma	Additional description: Colon adenoma		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Fibroma	Additional description: Fibroma		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Haemangioma of liver	Additional description: Haemangioma of liver		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Kidney angiomyolipoma	Additional description: Kidney angiomyolipoma		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Lipoma	Additional description: Lipoma		
subjects affected / exposed	1 / 168 (0.60%)	1 / 170 (0.59%)	
occurrences (all)	1	1	
Melanocytic naevus	Additional description: Melanocytic naevus		
subjects affected / exposed	2 / 168 (1.19%)	1 / 170 (0.59%)	
occurrences (all)	2	2	
Seborrhoeic keratosis	Additional description: Seborrhoeic keratosis		

subjects affected / exposed	0 / 168 (0.00%)	2 / 170 (1.18%)	
occurrences (all)	0	2	
Skin papilloma	Additional description: Skin papilloma		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Sweat gland tumour	Additional description: Sweat gland tumour		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Vascular disorders			
Aortic aneurysm	Additional description: Aortic aneurysm		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Arteriosclerosis	Additional description: Arteriosclerosis		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Circulatory collapse	Additional description: Circulatory collapse		
subjects affected / exposed	1 / 168 (0.60%)	2 / 170 (1.18%)	
occurrences (all)	1	2	
Flushing	Additional description: Flushing		
subjects affected / exposed	1 / 168 (0.60%)	2 / 170 (1.18%)	
occurrences (all)	1	3	
Haematoma	Additional description: Haematoma		
subjects affected / exposed	9 / 168 (5.36%)	28 / 170 (16.47%)	
occurrences (all)	11	40	
Hot flush	Additional description: Hot flush		
subjects affected / exposed	3 / 168 (1.79%)	2 / 170 (1.18%)	
occurrences (all)	4	2	
Hypertension	Additional description: Hypertension		
subjects affected / exposed	12 / 168 (7.14%)	28 / 170 (16.47%)	
occurrences (all)	12	31	
Hypertensive crisis	Additional description: Hypertensive crisis		
subjects affected / exposed	1 / 168 (0.60%)	2 / 170 (1.18%)	
occurrences (all)	1	3	
Hypotension	Additional description: Hypotension		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	

Musculoskeletal and connective tissue disorders	Additional description: Musculoskeletal and connective tissue disorders		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Orthostatic hypotension	Additional description: Orthostatic hypotension		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Peripheral vascular disorder	Additional description: Peripheral vascular disorder		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	2	
Thrombophlebitis	Additional description: Thrombophlebitis		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Thrombosis	Additional description: Thrombosis		
subjects affected / exposed	2 / 168 (1.19%)	0 / 170 (0.00%)	
occurrences (all)	2	0	
Varicophlebitis	Additional description: Varicophlebitis		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Varicose vein	Additional description: Varicose vein		
subjects affected / exposed	0 / 168 (0.00%)	2 / 170 (1.18%)	
occurrences (all)	0	2	
Surgical and medical procedures			
Bunion operation	Additional description: Bunion operation		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Carpal tunnel decompression	Additional description: Carpal tunnel decompression		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Dental implantation	Additional description: Dental implantation		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Dental operation	Additional description: Dental operation		
subjects affected / exposed	2 / 168 (1.19%)	1 / 170 (0.59%)	
occurrences (all)	2	1	
Dental prosthesis placement	Additional description: Dental prosthesis placement		

subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Foot operation	Additional description: Foot operation		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Hernia repair	Additional description: Hernia repair		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Jaw operation	Additional description: Jaw operation		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Inguinal hernia repair	Additional description: Inguinal hernia repair		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Lipoma excision	Additional description: Lipoma excision		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Renal stone removal	Additional description: Renal stone removal		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Tooth extraction	Additional description: Tooth extraction		
subjects affected / exposed	2 / 168 (1.19%)	0 / 170 (0.00%)	
occurrences (all)	2	0	
General disorders and administration site conditions			
Asthenia	Additional description: Asthenia		
subjects affected / exposed	1 / 168 (0.60%)	2 / 170 (1.18%)	
occurrences (all)	1	2	
Axillary pain	Additional description: Axillary pain		
subjects affected / exposed	2 / 168 (1.19%)	1 / 170 (0.59%)	
occurrences (all)	2	1	
Chest pain	Additional description: Chest pain		
subjects affected / exposed	7 / 168 (4.17%)	4 / 170 (2.35%)	
occurrences (all)	8	4	
Chills	Additional description: Chills		

subjects affected / exposed	2 / 168 (1.19%)	3 / 170 (1.76%)	
occurrences (all)	2	3	
Discomfort	Additional description: Discomfort		
subjects affected / exposed	1 / 168 (0.60%)	1 / 170 (0.59%)	
occurrences (all)	1	1	
Fatigue	Additional description: Fatigue		
subjects affected / exposed	35 / 168 (20.83%)	47 / 170 (27.65%)	
occurrences (all)	39	61	
Extravasation	Additional description: Extravasation		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Gait disturbance	Additional description: Gait disturbance		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
General physical health deterioration	Additional description: General physical health deterioration		
subjects affected / exposed	5 / 168 (2.98%)	0 / 170 (0.00%)	
occurrences (all)	5	0	
General symptom	Additional description: General symptom		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Ill-defined disorder	Additional description: Ill-defined disorder		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Impaired healing	Additional description: Impaired healing		
subjects affected / exposed	0 / 168 (0.00%)	3 / 170 (1.76%)	
occurrences (all)	0	3	
Inflammation	Additional description: Inflammation		
subjects affected / exposed	0 / 168 (0.00%)	2 / 170 (1.18%)	
occurrences (all)	0	4	
Influenza like illness	Additional description: Influenza like illness		
subjects affected / exposed	0 / 168 (0.00%)	3 / 170 (1.76%)	
occurrences (all)	0	4	
Mucosal inflammation	Additional description: Mucosal inflammation		
subjects affected / exposed	0 / 168 (0.00%)	2 / 170 (1.18%)	
occurrences (all)	0	2	
Malaise	Additional description: Malaise		

subjects affected / exposed	2 / 168 (1.19%)	5 / 170 (2.94%)	
occurrences (all)	2	5	
Oedema	Additional description: Oedema		
subjects affected / exposed	1 / 168 (0.60%)	4 / 170 (2.35%)	
occurrences (all)	1	4	
Oedema peripheral	Additional description: Oedema peripheral		
subjects affected / exposed	3 / 168 (1.79%)	12 / 170 (7.06%)	
occurrences (all)	3	14	
Performance status decreased	Additional description: Performance status decreased		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Pain	Additional description: Pain		
subjects affected / exposed	1 / 168 (0.60%)	4 / 170 (2.35%)	
occurrences (all)	2	6	
Peripheral swelling	Additional description: Peripheral swelling		
subjects affected / exposed	0 / 168 (0.00%)	5 / 170 (2.94%)	
occurrences (all)	0	6	
Polyp	Additional description: Polyp		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Pyrexia	Additional description: Pyrexia		
subjects affected / exposed	3 / 168 (1.79%)	7 / 170 (4.12%)	
occurrences (all)	3	8	
Sensation of foreign body	Additional description: Sensation of foreign body		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Swelling	Additional description: Swelling		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Swelling face	Additional description: Swelling face		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Temperature intolerance	Additional description: Temperature intolerance		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Ulcer	Additional description: Ulcer		

subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Vaccination site reaction	Additional description: Vaccination site reaction		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Allergy to arthropod bite	Additional description: Allergy to arthropod bite		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Autoimmune disorder	Additional description: Autoimmune disorder		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Hypersensitivity	Additional description: Hypersensitivity		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Immunisation reaction	Additional description: Immunisation reaction		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	2	
Seasonal allergy	Additional description: Seasonal allergy		
subjects affected / exposed	0 / 168 (0.00%)	3 / 170 (1.76%)	
occurrences (all)	0	4	
Reproductive system and breast disorders			
Balanoposthitis	Additional description: Balanoposthitis		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Benign prostatic hyperplasia	Additional description: Benign prostatic hyperplasia		
subjects affected / exposed	1 / 168 (0.60%)	6 / 170 (3.53%)	
occurrences (all)	1	6	
Breast cyst	Additional description: Breast cyst		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Breast pain	Additional description: Breast pain		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Endometrial hyperplasia	Additional description: Endometrial hyperplasia		

subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Erectile dysfunction	Additional description: Erectile dysfunction		
subjects affected / exposed	1 / 168 (0.60%)	3 / 170 (1.76%)	
occurrences (all)	1	3	
Genital pain	Additional description: Genital pain		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Gynaecomastia	Additional description: Gynaecomastia		
subjects affected / exposed	1 / 168 (0.60%)	1 / 170 (0.59%)	
occurrences (all)	1	1	
Menopausal symptoms	Additional description: Menopausal symptoms		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Metrorrhagia	Additional description: Metrorrhagia		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Orchitis noninfective	Additional description: Orchitis noninfective		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Postmenopausal haemorrhage	Additional description: Postmenopausal haemorrhage		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Rectocele	Additional description: Rectocele		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Prostatitis	Additional description: Prostatitis		
subjects affected / exposed	0 / 168 (0.00%)	2 / 170 (1.18%)	
occurrences (all)	0	2	
Scrotal pain	Additional description: Scrotal pain		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	2	
Testicular pain	Additional description: Testicular pain		
subjects affected / exposed	0 / 168 (0.00%)	3 / 170 (1.76%)	
occurrences (all)	0	3	
Vulvovaginal pain	Additional description: Vulvovaginal pain		

subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Uterine polyp	Additional description: Uterine polyp		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Allergic cough	Additional description: Allergic cough		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Asthma	Additional description: Asthma		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Bronchitis chronic	Additional description: Bronchitis chronic		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Bronchostenosis	Additional description: Bronchostenosis		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Chronic obstructive pulmonary disease	Additional description: Chronic obstructive pulmonary disease		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Cough	Additional description: Cough		
subjects affected / exposed	13 / 168 (7.74%)	14 / 170 (8.24%)	
occurrences (all)	17	18	
Emphysema	Additional description: Emphysema		
subjects affected / exposed	1 / 168 (0.60%)	1 / 170 (0.59%)	
occurrences (all)	1	1	
Dysphonia	Additional description: Dysphonia		
subjects affected / exposed	1 / 168 (0.60%)	1 / 170 (0.59%)	
occurrences (all)	1	1	
Dyspnoea	Additional description: Dyspnoea		
subjects affected / exposed	9 / 168 (5.36%)	10 / 170 (5.88%)	
occurrences (all)	10	11	
Dyspnoea exertional	Additional description: Dyspnoea exertional		

subjects affected / exposed	7 / 168 (4.17%)	4 / 170 (2.35%)	
occurrences (all)	7	5	
Epistaxis	Additional description: Epistaxis		
subjects affected / exposed	4 / 168 (2.38%)	21 / 170 (12.35%)	
occurrences (all)	4	29	
Haemoptysis	Additional description: Haemoptysis		
subjects affected / exposed	1 / 168 (0.60%)	1 / 170 (0.59%)	
occurrences (all)	2	1	
Increased bronchial secretion	Additional description: Increased bronchial secretion		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Laryngeal haemorrhage	Additional description: Laryngeal haemorrhage		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Lung hypoinflation	Additional description: Lung hypoinflation		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Nasal septum deviation	Additional description: Nasal septum deviation		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Oropharyngeal discomfort	Additional description: Oropharyngeal discomfort		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Oropharyngeal pain	Additional description: Oropharyngeal pain		
subjects affected / exposed	7 / 168 (4.17%)	5 / 170 (2.94%)	
occurrences (all)	9	7	
Pharyngeal oedema	Additional description: Pharyngeal oedema		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Pleural effusion	Additional description: Pleural effusion		
subjects affected / exposed	0 / 168 (0.00%)	3 / 170 (1.76%)	
occurrences (all)	0	3	
Pulmonary pain	Additional description: Pulmonary pain		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Rhinitis allergic	Additional description: Rhinitis allergic		

subjects affected / exposed	1 / 168 (0.60%)	2 / 170 (1.18%)	
occurrences (all)	3	2	
Rhinorrhoea	Additional description: Rhinorrhoea		
subjects affected / exposed	1 / 168 (0.60%)	4 / 170 (2.35%)	
occurrences (all)	1	4	
Sleep apnoea syndrome	Additional description: Sleep apnoea syndrome		
subjects affected / exposed	1 / 168 (0.60%)	1 / 170 (0.59%)	
occurrences (all)	1	1	
Throat clearing	Additional description: Throat clearing		
subjects affected / exposed	0 / 168 (0.00%)	2 / 170 (1.18%)	
occurrences (all)	0	2	
Tonsillar hypertrophy	Additional description: Tonsillar hypertrophy		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Agitation	Additional description: Agitation		
subjects affected / exposed	1 / 168 (0.60%)	2 / 170 (1.18%)	
occurrences (all)	1	2	
Aggression	Additional description: Aggression		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Anxiety disorder	Additional description: Anxiety disorder		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Anxiety	Additional description: Anxiety		
subjects affected / exposed	2 / 168 (1.19%)	0 / 170 (0.00%)	
occurrences (all)	2	0	
Aversion	Additional description: Aversion		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Depressed mood	Additional description: Depressed mood		
subjects affected / exposed	2 / 168 (1.19%)	0 / 170 (0.00%)	
occurrences (all)	2	0	
Confusional state	Additional description: Confusional state		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	

Depression	Additional description: Depression		
subjects affected / exposed	4 / 168 (2.38%)	3 / 170 (1.76%)	
occurrences (all)	4	3	
Initial insomnia	Additional description: Initial insomnia		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Insomnia	Additional description: Insomnia		
subjects affected / exposed	5 / 168 (2.98%)	5 / 170 (2.94%)	
occurrences (all)	6	5	
Libido decreased	Additional description: Libido decreased		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Listless	Additional description: Listless		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Mood altered	Additional description: Mood altered		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Nervousness	Additional description: Nervousness		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Panic attack	Additional description: Panic attack		
subjects affected / exposed	1 / 168 (0.60%)	1 / 170 (0.59%)	
occurrences (all)	1	1	
Psychotic disorder	Additional description: Psychotic disorder		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Restlessness	Additional description: Restlessness		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Sleep disorder	Additional description: Sleep disorder		
subjects affected / exposed	1 / 168 (0.60%)	10 / 170 (5.88%)	
occurrences (all)	1	12	
Investigations			
Alanine aminotransferase increased	Additional description: Alanine aminotransferase increased		

subjects affected / exposed	1 / 168 (0.60%)	3 / 170 (1.76%)	
occurrences (all)	1	6	
Arthroscopy	Additional description: Arthroscopy		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Aspartate aminotransferase increased	Additional description: Aspartate aminotransferase increased		
subjects affected / exposed	1 / 168 (0.60%)	3 / 170 (1.76%)	
occurrences (all)	1	4	
Biopsy prostate	Additional description: Biopsy prostate		
subjects affected / exposed	1 / 168 (0.60%)	1 / 170 (0.59%)	
occurrences (all)	1	1	
Blood alkaline phosphatase increased	Additional description: Blood alkaline phosphatase increased		
subjects affected / exposed	3 / 168 (1.79%)	0 / 170 (0.00%)	
occurrences (all)	3	0	
Blood bilirubin increased	Additional description: Blood bilirubin increased		
subjects affected / exposed	0 / 168 (0.00%)	2 / 170 (1.18%)	
occurrences (all)	0	6	
Blood cholesterol increased	Additional description: Blood cholesterol increased		
subjects affected / exposed	2 / 168 (1.19%)	0 / 170 (0.00%)	
occurrences (all)	2	0	
Blood creatine phosphokinase increased	Additional description: Blood creatine phosphokinase increased		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Blood creatinine increased	Additional description: Blood creatinine increased		
subjects affected / exposed	2 / 168 (1.19%)	3 / 170 (1.76%)	
occurrences (all)	2	3	
Blood glucose increased	Additional description: Blood glucose increased		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Blood immunoglobulin G decreased	Additional description: Blood immunoglobulin G decreased		
subjects affected / exposed	1 / 168 (0.60%)	2 / 170 (1.18%)	
occurrences (all)	1	2	
Blood lactate dehydrogenase increased	Additional description: Blood lactate dehydrogenase increased		

subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Blood potassium decreased	Additional description: Blood potassium decreased		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	2	
Blood thyroid stimulating hormone increased	Additional description: Blood thyroid stimulating hormone increased		
subjects affected / exposed	1 / 168 (0.60%)	1 / 170 (0.59%)	
occurrences (all)	1	1	
Blood uric acid increased	Additional description: Blood uric acid increased		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	2	
Cardiac murmur	Additional description: Cardiac murmur		
subjects affected / exposed	0 / 168 (0.00%)	2 / 170 (1.18%)	
occurrences (all)	0	2	
Blood urea increased	Additional description: Blood urea increased		
subjects affected / exposed	0 / 168 (0.00%)	2 / 170 (1.18%)	
occurrences (all)	0	3	
Electrocardiogram repolarisation abnormality	Additional description: Electrocardiogram repolarisation abnormality		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Electrocardiogram ST segment depression	Additional description: Electrocardiogram ST segment depression		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Gamma-glutamyltransferase increased	Additional description: Gamma-glutamyltransferase increased		
subjects affected / exposed	3 / 168 (1.79%)	3 / 170 (1.76%)	
occurrences (all)	3	4	
Hepatic enzyme increased	Additional description: Hepatic enzyme increased		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Heart rate irregular	Additional description: Heart rate irregular		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Immunoglobulins decreased	Additional description: Immunoglobulins decreased		

subjects affected / exposed	2 / 168 (1.19%)	0 / 170 (0.00%)	
occurrences (all)	2	0	
Lipase increased	Additional description: Lipase increased		
subjects affected / exposed	0 / 168 (0.00%)	2 / 170 (1.18%)	
occurrences (all)	0	2	
Prostatic specific antigen increased	Additional description: Prostatic specific antigen increased		
subjects affected / exposed	0 / 168 (0.00%)	2 / 170 (1.18%)	
occurrences (all)	0	2	
Smear cervix	Additional description: Smear cervix		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Transaminases increased	Additional description: Transaminases increased		
subjects affected / exposed	0 / 168 (0.00%)	3 / 170 (1.76%)	
occurrences (all)	0	4	
Urine uric acid increased	Additional description: Urine uric acid increased		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Weight increased	Additional description: Weight increased		
subjects affected / exposed	0 / 168 (0.00%)	3 / 170 (1.76%)	
occurrences (all)	0	3	
Weight decreased	Additional description: Weight decreased		
subjects affected / exposed	3 / 168 (1.79%)	4 / 170 (2.35%)	
occurrences (all)	4	4	
Injury, poisoning and procedural complications			
Acetabulum fracture	Additional description: Acetabulum fracture		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Accident at work	Additional description: Accident at work		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Animal scratch	Additional description: Animal scratch		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Ankle fracture	Additional description: Ankle fracture		

subjects affected / exposed	0 / 168 (0.00%)	3 / 170 (1.76%)	
occurrences (all)	0	3	
Arthropod bite	Additional description: Arthropod bite		
subjects affected / exposed	2 / 168 (1.19%)	4 / 170 (2.35%)	
occurrences (all)	2	7	
Arthropod sting	Additional description: Arthropod sting		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Bone contusion	Additional description: Bone contusion		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Burn oral cavity	Additional description: Burn oral cavity		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Cartilage injury	Additional description: Cartilage injury		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Concussion	Additional description: Concussion		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Contusion	Additional description: Contusion		
subjects affected / exposed	2 / 168 (1.19%)	8 / 170 (4.71%)	
occurrences (all)	2	10	
Fall	Additional description: Fall		
subjects affected / exposed	2 / 168 (1.19%)	2 / 170 (1.18%)	
occurrences (all)	2	2	
Foot fracture	Additional description: Foot fracture		
subjects affected / exposed	1 / 168 (0.60%)	1 / 170 (0.59%)	
occurrences (all)	1	1	
Fracture	Additional description: Fracture		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Hand fracture	Additional description: Hand fracture		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Ilium fracture	Additional description: Ilium fracture		

subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Joint injury	Additional description: Joint injury		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Infusion related reaction	Additional description: Infusion related reaction		
subjects affected / exposed	1 / 168 (0.60%)	1 / 170 (0.59%)	
occurrences (all)	1	1	
Injury corneal	Additional description: Injury corneal		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Laceration	Additional description: Laceration		
subjects affected / exposed	1 / 168 (0.60%)	1 / 170 (0.59%)	
occurrences (all)	1	1	
Ligament rupture	Additional description: Ligament rupture		
subjects affected / exposed	0 / 168 (0.00%)	4 / 170 (2.35%)	
occurrences (all)	0	4	
Ligament sprain	Additional description: Ligament sprain		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Limb injury	Additional description: Limb injury		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Lumbar vertebral fracture	Additional description: Lumbar vertebral fracture		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Muscle rupture	Additional description: Muscle rupture		
subjects affected / exposed	0 / 168 (0.00%)	2 / 170 (1.18%)	
occurrences (all)	0	2	
Meniscus injury	Additional description: Meniscus injury		
subjects affected / exposed	2 / 168 (1.19%)	2 / 170 (1.18%)	
occurrences (all)	2	2	
Muscle strain	Additional description: Muscle strain		
subjects affected / exposed	0 / 168 (0.00%)	2 / 170 (1.18%)	
occurrences (all)	0	2	
Nail avulsion	Additional description: Nail avulsion		

subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Patella fracture	Additional description: Patella fracture		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Post-traumatic pain	Additional description: Post-traumatic pain		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Skin laceration	Additional description: Skin laceration		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Spinal compression fracture	Additional description: Spinal compression fracture		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Spinal fracture	Additional description: Spinal fracture		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Skin abrasion	Additional description: Skin abrasion		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Sunburn	Additional description: Sunburn		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Traumatic fracture	Additional description: Traumatic fracture		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Traumatic haematoma	Additional description: Traumatic haematoma		
subjects affected / exposed	0 / 168 (0.00%)	2 / 170 (1.18%)	
occurrences (all)	0	3	
Wound complication	Additional description: Wound complication		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Wound	Additional description: Wound		
subjects affected / exposed	0 / 168 (0.00%)	2 / 170 (1.18%)	
occurrences (all)	0	2	
Congenital, familial and genetic			

disorders			
Atrial septal defect	Additional description: Atrial septal defect		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Factor V Leiden mutation	Additional description: Factor V Leiden mutation		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Hereditary motor and sensory neuropathy	Additional description: Hereditary motor and sensory neuropathy		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Hydrocele	Additional description: Hydrocele		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Phimosis	Additional description: Phimosis		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Acute myocardial infarction	Additional description: Acute myocardial infarction		
subjects affected / exposed	2 / 168 (1.19%)	0 / 170 (0.00%)	
occurrences (all)	2	0	
Angina pectoris	Additional description: Angina pectoris		
subjects affected / exposed	2 / 168 (1.19%)	1 / 170 (0.59%)	
occurrences (all)	2	1	
Aortic valve incompetence	Additional description: Aortic valve incompetence		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Arrhythmia	Additional description: Arrhythmia		
subjects affected / exposed	1 / 168 (0.60%)	1 / 170 (0.59%)	
occurrences (all)	1	1	
Arteriosclerosis coronary artery	Additional description: Arteriosclerosis coronary artery		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Atrial fibrillation	Additional description: Atrial fibrillation		
subjects affected / exposed	2 / 168 (1.19%)	16 / 170 (9.41%)	
occurrences (all)	9	16	
Atrioventricular block first degree	Additional description: Atrioventricular block first degree		

subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Cardiovascular disorder	Additional description: Cardiovascular disorder		
subjects affected / exposed	1 / 168 (0.60%)	1 / 170 (0.59%)	
occurrences (all)	1	6	
Bradycardia	Additional description: Bradycardia		
subjects affected / exposed	0 / 168 (0.00%)	2 / 170 (1.18%)	
occurrences (all)	0	2	
Cardiac failure	Additional description: Cardiac failure		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Cardiomegaly	Additional description: Cardiomegaly		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Coronary artery disease	Additional description: Coronary artery disease		
subjects affected / exposed	3 / 168 (1.79%)	1 / 170 (0.59%)	
occurrences (all)	3	1	
Coronary artery stenosis	Additional description: Coronary artery stenosis		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	2	0	
Extrasystoles	Additional description: Extrasystoles		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	2	
Hypertensive heart disease	Additional description: Hypertensive heart disease		
subjects affected / exposed	1 / 168 (0.60%)	1 / 170 (0.59%)	
occurrences (all)	1	1	
Left ventricular hypertrophy	Additional description: Left ventricular hypertrophy		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Mitral valve incompetence	Additional description: Mitral valve incompetence		
subjects affected / exposed	1 / 168 (0.60%)	1 / 170 (0.59%)	
occurrences (all)	1	1	
Palpitations	Additional description: Palpitations		
subjects affected / exposed	5 / 168 (2.98%)	3 / 170 (1.76%)	
occurrences (all)	6	4	
Pericardial effusion	Additional description: Pericardial effusion		

subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Sinus tachycardia	Additional description: Sinus tachycardia		
subjects affected / exposed	2 / 168 (1.19%)	0 / 170 (0.00%)	
occurrences (all)	2	0	
Sinus bradycardia	Additional description: Sinus bradycardia		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Tachyarrhythmia	Additional description: Tachyarrhythmia		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Tachycardia	Additional description: Tachycardia		
subjects affected / exposed	4 / 168 (2.38%)	5 / 170 (2.94%)	
occurrences (all)	4	5	
Tricuspid valve incompetence	Additional description: Tricuspid valve incompetence		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Ventricular extrasystoles	Additional description: Ventricular extrasystoles		
subjects affected / exposed	2 / 168 (1.19%)	1 / 170 (0.59%)	
occurrences (all)	2	1	
Nervous system disorders			
Ageusia	Additional description: Ageusia		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Balance disorder	Additional description: Balance disorder		
subjects affected / exposed	0 / 168 (0.00%)	2 / 170 (1.18%)	
occurrences (all)	0	2	
Basilar migraine	Additional description: Basilar migraine		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Cognitive disorder	Additional description: Cognitive disorder		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Carotid artery stenosis	Additional description: Carotid artery stenosis		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	

Carpal tunnel syndrome	Additional description: Carpal tunnel syndrome		
subjects affected / exposed	1 / 168 (0.60%)	1 / 170 (0.59%)	
occurrences (all)	1	1	
Cervical syndrome	Additional description: Cervical syndrome		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Cervicobrachial syndrome	Additional description: Cervicobrachial syndrome		
subjects affected / exposed	0 / 168 (0.00%)	2 / 170 (1.18%)	
occurrences (all)	0	2	
Convulsion	Additional description: Convulsion		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Dementia	Additional description: Dementia		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Dizziness	Additional description: Dizziness		
subjects affected / exposed	11 / 168 (6.55%)	26 / 170 (15.29%)	
occurrences (all)	13	41	
Diabetic neuropathy	Additional description: Diabetic neuropathy		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Disturbance in attention	Additional description: Disturbance in attention		
subjects affected / exposed	0 / 168 (0.00%)	2 / 170 (1.18%)	
occurrences (all)	0	3	
Dysaesthesia	Additional description: Dysaesthesia		
subjects affected / exposed	1 / 168 (0.60%)	2 / 170 (1.18%)	
occurrences (all)	1	2	
Dysgeusia	Additional description: Dysgeusia		
subjects affected / exposed	0 / 168 (0.00%)	2 / 170 (1.18%)	
occurrences (all)	0	2	
Headache	Additional description: Headache		
subjects affected / exposed	20 / 168 (11.90%)	30 / 170 (17.65%)	
occurrences (all)	39	48	
Hypertonia	Additional description: Hypertonia		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	

Hypoaesthesia	Additional description: Hypoaesthesia		
subjects affected / exposed	1 / 168 (0.60%)	4 / 170 (2.35%)	
occurrences (all)	1	4	
Hypoaesthesia oral	Additional description: Hypoaesthesia oral		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Intercostal neuralgia	Additional description: Intercostal neuralgia		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Loss of consciousness	Additional description: Loss of consciousness		
subjects affected / exposed	0 / 168 (0.00%)	2 / 170 (1.18%)	
occurrences (all)	0	2	
Muscle spasticity	Additional description: Muscle spasticity		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Memory impairment	Additional description: Memory impairment		
subjects affected / exposed	1 / 168 (0.60%)	1 / 170 (0.59%)	
occurrences (all)	1	1	
Migraine	Additional description: Migraine		
subjects affected / exposed	2 / 168 (1.19%)	1 / 170 (0.59%)	
occurrences (all)	3	1	
Neuralgia	Additional description: Neuralgia		
subjects affected / exposed	1 / 168 (0.60%)	2 / 170 (1.18%)	
occurrences (all)	1	2	
Neuropathy peripheral	Additional description: Neuropathy peripheral		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Paraesthesia	Additional description: Paraesthesia		
subjects affected / exposed	1 / 168 (0.60%)	8 / 170 (4.71%)	
occurrences (all)	1	12	
Paraparesis	Additional description: Paraparesis		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Parkinson's disease	Additional description: Parkinson's disease		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	

Parosmia	Additional description: Parosmia		
subjects affected / exposed	2 / 168 (1.19%)	0 / 170 (0.00%)	
occurrences (all)	2	0	
Polyneuropathy	Additional description: Polyneuropathy		
subjects affected / exposed	2 / 168 (1.19%)	6 / 170 (3.53%)	
occurrences (all)	2	6	
Radiculopathy	Additional description: Radiculopathy		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Sciatica	Additional description: Sciatica		
subjects affected / exposed	1 / 168 (0.60%)	2 / 170 (1.18%)	
occurrences (all)	1	2	
Syncope	Additional description: Syncope		
subjects affected / exposed	0 / 168 (0.00%)	3 / 170 (1.76%)	
occurrences (all)	0	3	
Tremor	Additional description: Tremor		
subjects affected / exposed	1 / 168 (0.60%)	1 / 170 (0.59%)	
occurrences (all)	1	1	
Vascular encephalopathy	Additional description: Vascular encephalopathy		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia	Additional description: Anaemia		
subjects affected / exposed	4 / 168 (2.38%)	4 / 170 (2.35%)	
occurrences (all)	4	4	
Coagulopathy	Additional description: Coagulopathy		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Eosinophilia	Additional description: Eosinophilia		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Haemorrhagic diathesis	Additional description: Haemorrhagic diathesis		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Immune thrombocytopenia	Additional description: Immune thrombocytopenia		

subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Iron deficiency anaemia	Additional description: Iron deficiency anaemia		
subjects affected / exposed	1 / 168 (0.60%)	1 / 170 (0.59%)	
occurrences (all)	1	1	
Leukocytosis	Additional description: Leukocytosis		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Lymph node pain	Additional description: Lymph node pain		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Lymphadenopathy	Additional description: Lymphadenopathy		
subjects affected / exposed	1 / 168 (0.60%)	1 / 170 (0.59%)	
occurrences (all)	1	1	
Neutropenia	Additional description: Neutropenia		
subjects affected / exposed	1 / 168 (0.60%)	2 / 170 (1.18%)	
occurrences (all)	1	3	
Splenomegaly	Additional description: Splenomegaly		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Thrombocytopenia	Additional description: Thrombocytopenia		
subjects affected / exposed	3 / 168 (1.79%)	5 / 170 (2.94%)	
occurrences (all)	4	5	
Ear and labyrinth disorders			
Ear disorder	Additional description: Ear disorder		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Ear discomfort	Additional description: Ear discomfort		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Ear pain	Additional description: Ear pain		
subjects affected / exposed	0 / 168 (0.00%)	2 / 170 (1.18%)	
occurrences (all)	0	2	
Ear pruritus	Additional description: Ear pruritus		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	

Ear swelling	Additional description: Ear swelling		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Ear haemorrhage	Additional description: Ear haemorrhage		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Hyperacusis	Additional description: Hyperacusis		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Sudden hearing loss	Additional description: Sudden hearing loss		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Tinnitus	Additional description: Tinnitus		
subjects affected / exposed	2 / 168 (1.19%)	1 / 170 (0.59%)	
occurrences (all)	2	1	
Vertigo	Additional description: Vertigo		
subjects affected / exposed	8 / 168 (4.76%)	12 / 170 (7.06%)	
occurrences (all)	8	17	
Vertigo positional	Additional description: Vertigo positional		
subjects affected / exposed	1 / 168 (0.60%)	1 / 170 (0.59%)	
occurrences (all)	1	1	
Eye disorders			
Blepharitis	Additional description: Blepharitis		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Blepharospasm	Additional description: Blepharospasm		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Blindness	Additional description: Blindness		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Cataract	Additional description: Cataract		
subjects affected / exposed	2 / 168 (1.19%)	6 / 170 (3.53%)	
occurrences (all)	2	6	
Conjunctival haemorrhage	Additional description: Conjunctival haemorrhage		

subjects affected / exposed	2 / 168 (1.19%)	1 / 170 (0.59%)	
occurrences (all)	2	1	
Dacryostenosis acquired	Additional description: Dacryostenosis acquired		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Diplopia	Additional description: Diplopia		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Dry eye	Additional description: Dry eye		
subjects affected / exposed	1 / 168 (0.60%)	2 / 170 (1.18%)	
occurrences (all)	1	2	
Eye haematoma	Additional description: Eye haematoma		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Eye inflammation	Additional description: Eye inflammation		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	2	
Eye pruritus	Additional description: Eye pruritus		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Glaucoma	Additional description: Glaucoma		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Macular degeneration	Additional description: Macular degeneration		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Macular oedema	Additional description: Macular oedema		
subjects affected / exposed	1 / 168 (0.60%)	1 / 170 (0.59%)	
occurrences (all)	1	1	
Posterior capsule opacification	Additional description: Posterior capsule opacification		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Vision blurred	Additional description: Vision blurred		
subjects affected / exposed	0 / 168 (0.00%)	3 / 170 (1.76%)	
occurrences (all)	0	3	
Visual acuity reduced	Additional description: Visual acuity reduced		

subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	2	
Visual impairment	Additional description: Visual impairment		
subjects affected / exposed	1 / 168 (0.60%)	2 / 170 (1.18%)	
occurrences (all)	1	2	
Gastrointestinal disorders			
Abdominal pain lower	Additional description: Abdominal pain lower		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	2	
Abdominal pain	Additional description: Abdominal pain		
subjects affected / exposed	11 / 168 (6.55%)	6 / 170 (3.53%)	
occurrences (all)	12	8	
Abdominal distension	Additional description: Abdominal distension		
subjects affected / exposed	2 / 168 (1.19%)	2 / 170 (1.18%)	
occurrences (all)	2	2	
Abdominal discomfort	Additional description: Abdominal discomfort		
subjects affected / exposed	2 / 168 (1.19%)	2 / 170 (1.18%)	
occurrences (all)	2	2	
Abdominal pain upper	Additional description: Abdominal pain upper		
subjects affected / exposed	13 / 168 (7.74%)	11 / 170 (6.47%)	
occurrences (all)	14	12	
Angular cheilitis	Additional description: Angular cheilitis		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Anal inflammation	Additional description: Anal inflammation		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Anal fistula	Additional description: Anal fistula		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	2	0	
Aphthous ulcer	Additional description: Aphthous ulcer		
subjects affected / exposed	0 / 168 (0.00%)	2 / 170 (1.18%)	
occurrences (all)	0	3	
Ascites	Additional description: Ascites		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	

Cheilitis	Additional description: Cheilitis		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Chronic gastritis	Additional description: Chronic gastritis		
subjects affected / exposed	2 / 168 (1.19%)	0 / 170 (0.00%)	
occurrences (all)	2	0	
Constipation	Additional description: Constipation		
subjects affected / exposed	6 / 168 (3.57%)	9 / 170 (5.29%)	
occurrences (all)	9	9	
Dental caries	Additional description: Dental caries		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Diarrhoea	Additional description: Diarrhoea		
subjects affected / exposed	31 / 168 (18.45%)	58 / 170 (34.12%)	
occurrences (all)	48	101	
Diarrhoea haemorrhagic	Additional description: Diarrhoea haemorrhagic		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Diverticulum	Additional description: Diverticulum		
subjects affected / exposed	1 / 168 (0.60%)	1 / 170 (0.59%)	
occurrences (all)	1	1	
Diverticulum intestinal	Additional description: Diverticulum intestinal		
subjects affected / exposed	1 / 168 (0.60%)	1 / 170 (0.59%)	
occurrences (all)	1	1	
Dry mouth	Additional description: Dry mouth		
subjects affected / exposed	6 / 168 (3.57%)	14 / 170 (8.24%)	
occurrences (all)	7	15	
Dyspepsia	Additional description: Dyspepsia		
subjects affected / exposed	6 / 168 (3.57%)	27 / 170 (15.88%)	
occurrences (all)	7	66	
Dysphagia	Additional description: Dysphagia		
subjects affected / exposed	0 / 168 (0.00%)	3 / 170 (1.76%)	
occurrences (all)	0	3	
Epigastric discomfort	Additional description: Epigastric discomfort		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	

Eructation	Additional description: Eructation		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Gastric disorder	Additional description: Gastric disorder		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Flatulence	Additional description: Flatulence		
subjects affected / exposed	3 / 168 (1.79%)	4 / 170 (2.35%)	
occurrences (all)	3	5	
Frequent bowel movements	Additional description: Frequent bowel movements		
subjects affected / exposed	2 / 168 (1.19%)	0 / 170 (0.00%)	
occurrences (all)	2	0	
Glossodynia	Additional description: Glossodynia		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Gastritis	Additional description: Gastritis		
subjects affected / exposed	0 / 168 (0.00%)	7 / 170 (4.12%)	
occurrences (all)	0	7	
Gastrointestinal disorder	Additional description: Gastrointestinal disorder		
subjects affected / exposed	1 / 168 (0.60%)	1 / 170 (0.59%)	
occurrences (all)	1	1	
Gastrointestinal pain	Additional description: Gastrointestinal pain		
subjects affected / exposed	1 / 168 (0.60%)	2 / 170 (1.18%)	
occurrences (all)	1	2	
Gastrooesophageal reflux disease	Additional description: Gastrooesophageal reflux disease		
subjects affected / exposed	2 / 168 (1.19%)	7 / 170 (4.12%)	
occurrences (all)	2	7	
Gingival bleeding	Additional description: Gingival bleeding		
subjects affected / exposed	1 / 168 (0.60%)	2 / 170 (1.18%)	
occurrences (all)	1	3	
Gingival disorder	Additional description: Gingival disorder		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Gingival swelling	Additional description: Gingival swelling		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	

Gingivitis ulcerative	Additional description: Gingivitis ulcerative		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Glossitis	Additional description: Glossitis		
subjects affected / exposed	0 / 168 (0.00%)	3 / 170 (1.76%)	
occurrences (all)	0	7	
Gastric ulcer	Additional description: Gastric ulcer		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Haematochezia	Additional description: Haematochezia		
subjects affected / exposed	1 / 168 (0.60%)	3 / 170 (1.76%)	
occurrences (all)	1	3	
Haemorrhoids	Additional description: Haemorrhoids		
subjects affected / exposed	4 / 168 (2.38%)	2 / 170 (1.18%)	
occurrences (all)	5	2	
Haemorrhoids thrombosed	Additional description: Haemorrhoids thrombosed		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Hiatus hernia	Additional description: Hiatus hernia		
subjects affected / exposed	3 / 168 (1.79%)	2 / 170 (1.18%)	
occurrences (all)	3	2	
Intestinal polyp	Additional description: Intestinal polyp		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Large intestine polyp	Additional description: Large intestine polyp		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Lip blister	Additional description: Lip blister		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	2	
Loose tooth	Additional description: Loose tooth		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Mouth swelling	Additional description: Mouth swelling		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	

Mouth ulceration	Additional description: Mouth ulceration		
subjects affected / exposed	0 / 168 (0.00%)	2 / 170 (1.18%)	
occurrences (all)	0	4	
Melaena	Additional description: Melaena		
subjects affected / exposed	2 / 168 (1.19%)	1 / 170 (0.59%)	
occurrences (all)	2	1	
Mouth haemorrhage	Additional description: Mouth haemorrhage		
subjects affected / exposed	0 / 168 (0.00%)	2 / 170 (1.18%)	
occurrences (all)	0	3	
Nausea	Additional description: Nausea		
subjects affected / exposed	20 / 168 (11.90%)	32 / 170 (18.82%)	
occurrences (all)	30	57	
Noninfective gingivitis	Additional description: Noninfective gingivitis		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Obstruction gastric	Additional description: Obstruction gastric		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	2	
Oesophageal pain	Additional description: Oesophageal pain		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Oesophagitis	Additional description: Oesophagitis		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Oral disorder	Additional description: Oral disorder		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Oral pain	Additional description: Oral pain		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Pancreatic cyst	Additional description: Pancreatic cyst		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Paraesthesia oral	Additional description: Paraesthesia oral		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	

Proctitis	Additional description: Proctitis		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	2	
Rectal prolapse	Additional description: Rectal prolapse		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Salivary gland enlargement	Additional description: Salivary gland enlargement		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Stomatitis	Additional description: Stomatitis		
subjects affected / exposed	2 / 168 (1.19%)	13 / 170 (7.65%)	
occurrences (all)	2	20	
Subileus	Additional description: Subileus		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Tongue blistering	Additional description: Tongue blistering		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Tongue ulceration	Additional description: Tongue ulceration		
subjects affected / exposed	1 / 168 (0.60%)	1 / 170 (0.59%)	
occurrences (all)	1	1	
Toothache	Additional description: Toothache		
subjects affected / exposed	3 / 168 (1.79%)	3 / 170 (1.76%)	
occurrences (all)	3	4	
Umbilical hernia	Additional description: Umbilical hernia		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Vomiting	Additional description: Vomiting		
subjects affected / exposed	7 / 168 (4.17%)	13 / 170 (7.65%)	
occurrences (all)	9	16	
Hepatobiliary disorders			
Cholecystitis acute	Additional description: Cholecystitis acute		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Cholelithiasis	Additional description: Cholelithiasis		

subjects affected / exposed	1 / 168 (0.60%)	1 / 170 (0.59%)	
occurrences (all)	1	1	
Hepatic cyst	Additional description: Hepatic cyst		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Hepatic steatosis	Additional description: Hepatic steatosis		
subjects affected / exposed	0 / 168 (0.00%)	2 / 170 (1.18%)	
occurrences (all)	0	2	
Hyperbilirubinaemia	Additional description: Hyperbilirubinaemia		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Actinic keratosis	Additional description: Actinic keratosis		
subjects affected / exposed	4 / 168 (2.38%)	2 / 170 (1.18%)	
occurrences (all)	4	4	
Alopecia areata	Additional description: Alopecia areata		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Alopecia	Additional description: Alopecia		
subjects affected / exposed	4 / 168 (2.38%)	5 / 170 (2.94%)	
occurrences (all)	4	5	
Asteatosis	Additional description: Asteatosis		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Blood blister	Additional description: Blood blister		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Butterfly rash	Additional description: Butterfly rash		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Dandruff	Additional description: Dandruff		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Dermatitis	Additional description: Dermatitis		
subjects affected / exposed	0 / 168 (0.00%)	2 / 170 (1.18%)	
occurrences (all)	0	3	

Dermatitis acneiform	Additional description: Dermatitis acneiform		
subjects affected / exposed	0 / 168 (0.00%)	3 / 170 (1.76%)	
occurrences (all)	0	5	
Dermatitis allergic	Additional description: Dermatitis allergic		
subjects affected / exposed	1 / 168 (0.60%)	2 / 170 (1.18%)	
occurrences (all)	1	2	
Dermatitis atopic	Additional description: Dermatitis atopic		
subjects affected / exposed	1 / 168 (0.60%)	1 / 170 (0.59%)	
occurrences (all)	1	1	
Dermatitis bullous	Additional description: Dermatitis bullous		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Dermatosis	Additional description: Dermatosis		
subjects affected / exposed	1 / 168 (0.60%)	1 / 170 (0.59%)	
occurrences (all)	1	1	
Dermal cyst	Additional description: Dermal cyst		
subjects affected / exposed	1 / 168 (0.60%)	3 / 170 (1.76%)	
occurrences (all)	1	3	
Ecchymosis	Additional description: Ecchymosis		
subjects affected / exposed	1 / 168 (0.60%)	2 / 170 (1.18%)	
occurrences (all)	1	3	
Eczema	Additional description: Eczema		
subjects affected / exposed	1 / 168 (0.60%)	7 / 170 (4.12%)	
occurrences (all)	1	9	
Drug eruption	Additional description: Drug eruption		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Dry skin	Additional description: Dry skin		
subjects affected / exposed	5 / 168 (2.98%)	16 / 170 (9.41%)	
occurrences (all)	5	19	
Erythema	Additional description: Erythema		
subjects affected / exposed	1 / 168 (0.60%)	3 / 170 (1.76%)	
occurrences (all)	1	3	
Haemorrhage subcutaneous	Additional description: Haemorrhage subcutaneous		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	

Hair colour changes	Additional description: Hair colour changes		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Hair growth abnormal	Additional description: Hair growth abnormal		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Hyperhidrosis	Additional description: Hyperhidrosis		
subjects affected / exposed	7 / 168 (4.17%)	4 / 170 (2.35%)	
occurrences (all)	10	4	
Hyperkeratosis	Additional description: Hyperkeratosis		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Ingrowing nail	Additional description: Ingrowing nail		
subjects affected / exposed	0 / 168 (0.00%)	5 / 170 (2.94%)	
occurrences (all)	0	5	
Nail atrophy	Additional description: Nail atrophy		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Nail bed inflammation	Additional description: Nail bed inflammation		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Nail disorder	Additional description: Nail disorder		
subjects affected / exposed	0 / 168 (0.00%)	2 / 170 (1.18%)	
occurrences (all)	0	2	
Nail dystrophy	Additional description: Nail dystrophy		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Nail ridging	Additional description: Nail ridging		
subjects affected / exposed	0 / 168 (0.00%)	4 / 170 (2.35%)	
occurrences (all)	0	4	
Night sweats	Additional description: Night sweats		
subjects affected / exposed	9 / 168 (5.36%)	5 / 170 (2.94%)	
occurrences (all)	14	7	
Onychoclasis	Additional description: Onychoclasis		
subjects affected / exposed	3 / 168 (1.79%)	19 / 170 (11.18%)	
occurrences (all)	3	19	

Onycholysis	Additional description: Onycholysis		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Pain of skin	Additional description: Pain of skin		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Petechiae	Additional description: Petechiae		
subjects affected / exposed	0 / 168 (0.00%)	7 / 170 (4.12%)	
occurrences (all)	0	9	
Photosensitivity reaction	Additional description: Photosensitivity reaction		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Polymorphic light eruption	Additional description: Polymorphic light eruption		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Pruritus	Additional description: Pruritus		
subjects affected / exposed	6 / 168 (3.57%)	13 / 170 (7.65%)	
occurrences (all)	7	15	
Psoriasis	Additional description: Psoriasis		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Purpura	Additional description: Purpura		
subjects affected / exposed	0 / 168 (0.00%)	2 / 170 (1.18%)	
occurrences (all)	0	2	
Rash	Additional description: Rash		
subjects affected / exposed	10 / 168 (5.95%)	33 / 170 (19.41%)	
occurrences (all)	15	44	
Rash erythematous	Additional description: Rash erythematous		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Rash maculo-papular	Additional description: Rash maculo-papular		
subjects affected / exposed	1 / 168 (0.60%)	2 / 170 (1.18%)	
occurrences (all)	1	9	
Rash papular	Additional description: Rash papular		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	

Scalp disorder	Additional description: Scalp disorder		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Seborrhoeic dermatitis	Additional description: Seborrhoeic dermatitis		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Skin discolouration	Additional description: Skin discolouration		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Skin disorder	Additional description: Skin disorder		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Skin erosion	Additional description: Skin erosion		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Skin fissures	Additional description: Skin fissures		
subjects affected / exposed	0 / 168 (0.00%)	8 / 170 (4.71%)	
occurrences (all)	0	10	
Skin haemorrhage	Additional description: Skin haemorrhage		
subjects affected / exposed	1 / 168 (0.60%)	2 / 170 (1.18%)	
occurrences (all)	1	2	
Skin hyperpigmentation	Additional description: Skin hyperpigmentation		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Skin induration	Additional description: Skin induration		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Skin irritation	Additional description: Skin irritation		
subjects affected / exposed	0 / 168 (0.00%)	2 / 170 (1.18%)	
occurrences (all)	0	2	
Skin lesion	Additional description: Skin lesion		
subjects affected / exposed	0 / 168 (0.00%)	3 / 170 (1.76%)	
occurrences (all)	0	3	
Skin sensitisation	Additional description: Skin sensitisation		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	

Skin ulcer	Additional description: Skin ulcer		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Swelling face	Additional description: Swelling face		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Urticaria	Additional description: Urticaria		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Chromaturia	Additional description: Chromaturia		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Cystitis noninfective	Additional description: Cystitis noninfective		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Dysuria	Additional description: Dysuria		
subjects affected / exposed	2 / 168 (1.19%)	2 / 170 (1.18%)	
occurrences (all)	2	3	
Haematuria	Additional description: Haematuria		
subjects affected / exposed	3 / 168 (1.79%)	6 / 170 (3.53%)	
occurrences (all)	4	9	
Incontinence	Additional description: Incontinence		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Micturition urgency	Additional description: Micturition urgency		
subjects affected / exposed	1 / 168 (0.60%)	1 / 170 (0.59%)	
occurrences (all)	1	1	
Nocturia	Additional description: Nocturia		
subjects affected / exposed	3 / 168 (1.79%)	1 / 170 (0.59%)	
occurrences (all)	3	1	
Pollakiuria	Additional description: Pollakiuria		
subjects affected / exposed	6 / 168 (3.57%)	0 / 170 (0.00%)	
occurrences (all)	6	0	
Renal cyst	Additional description: Renal cyst		

subjects affected / exposed	0 / 168 (0.00%)	2 / 170 (1.18%)	
occurrences (all)	0	2	
Renal failure	Additional description: Renal failure		
subjects affected / exposed	2 / 168 (1.19%)	3 / 170 (1.76%)	
occurrences (all)	2	3	
Renal pain	Additional description: Renal pain		
subjects affected / exposed	0 / 168 (0.00%)	2 / 170 (1.18%)	
occurrences (all)	0	2	
Urinary incontinence	Additional description: Urinary incontinence		
subjects affected / exposed	1 / 168 (0.60%)	1 / 170 (0.59%)	
occurrences (all)	1	1	
Endocrine disorders			
Goitre	Additional description: Goitre		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Hashimoto's disease	Additional description: Hashimoto's disease		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Hyperparathyroidism	Additional description: Hyperparathyroidism		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Hyperparathyroidism secondary	Additional description: Hyperparathyroidism secondary		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Hypogonadism	Additional description: Hypogonadism		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Hypothyroidism	Additional description: Hypothyroidism		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Thyroid calcification	Additional description: Thyroid calcification		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Thyroid mass	Additional description: Thyroid mass		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	

Type 2 diabetes mellitus	Additional description: Type 2 diabetes mellitus		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia	Additional description: Arthralgia		
subjects affected / exposed	15 / 168 (8.93%)	30 / 170 (17.65%)	
occurrences (all)	18	37	
Arthritis	Additional description: Arthritis		
subjects affected / exposed	1 / 168 (0.60%)	2 / 170 (1.18%)	
occurrences (all)	1	2	
Arthritis reactive	Additional description: Arthritis reactive		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Arthropathy	Additional description: Arthropathy		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Back pain	Additional description: Back pain		
subjects affected / exposed	20 / 168 (11.90%)	20 / 170 (11.76%)	
occurrences (all)	24	24	
Barrel chest	Additional description: Barrel chest		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Bone pain	Additional description: Bone pain		
subjects affected / exposed	2 / 168 (1.19%)	2 / 170 (1.18%)	
occurrences (all)	2	2	
Bursitis	Additional description: Bursitis		
subjects affected / exposed	2 / 168 (1.19%)	2 / 170 (1.18%)	
occurrences (all)	2	2	
Collagen disorder	Additional description: Collagen disorder		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Exostosis	Additional description: Exostosis		
subjects affected / exposed	1 / 168 (0.60%)	2 / 170 (1.18%)	
occurrences (all)	1	2	
Flank pain	Additional description: Flank pain		

subjects affected / exposed	2 / 168 (1.19%)	2 / 170 (1.18%)	
occurrences (all)	2	2	
Foot deformity	Additional description: Foot deformity		
subjects affected / exposed	3 / 168 (1.79%)	1 / 170 (0.59%)	
occurrences (all)	3	1	
Groin pain	Additional description: Groin pain		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Hypercreatinaemia	Additional description: Hypercreatinaemia		
subjects affected / exposed	2 / 168 (1.19%)	1 / 170 (0.59%)	
occurrences (all)	2	1	
Joint effusion	Additional description: Joint effusion		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Joint swelling	Additional description: Joint swelling		
subjects affected / exposed	0 / 168 (0.00%)	2 / 170 (1.18%)	
occurrences (all)	0	2	
Intervertebral disc disorder	Additional description: Intervertebral disc disorder		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Intervertebral disc protrusion	Additional description: Intervertebral disc protrusion		
subjects affected / exposed	2 / 168 (1.19%)	3 / 170 (1.76%)	
occurrences (all)	2	3	
Jaw cyst	Additional description: Jaw cyst		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Limb discomfort	Additional description: Limb discomfort		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Muscle atrophy	Additional description: Muscle atrophy		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Muscle spasms	Additional description: Muscle spasms		
subjects affected / exposed	6 / 168 (3.57%)	25 / 170 (14.71%)	
occurrences (all)	9	52	
Muscle twitching	Additional description: Muscle twitching		

subjects affected / exposed	0 / 168 (0.00%)	2 / 170 (1.18%)	
occurrences (all)	0	2	
Muscular weakness	Additional description: Muscular weakness		
subjects affected / exposed	2 / 168 (1.19%)	3 / 170 (1.76%)	
occurrences (all)	3	3	
Musculoskeletal chest pain	Additional description: Musculoskeletal chest pain		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Musculoskeletal disorder	Additional description: Musculoskeletal disorder		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Musculoskeletal pain	Additional description: Musculoskeletal pain		
subjects affected / exposed	5 / 168 (2.98%)	4 / 170 (2.35%)	
occurrences (all)	6	5	
Musculoskeletal stiffness	Additional description: Musculoskeletal stiffness		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	2	
Myalgia	Additional description: Myalgia		
subjects affected / exposed	8 / 168 (4.76%)	12 / 170 (7.06%)	
occurrences (all)	9	12	
Myositis	Additional description: Myositis		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Neck pain	Additional description: Neck pain		
subjects affected / exposed	4 / 168 (2.38%)	2 / 170 (1.18%)	
occurrences (all)	4	2	
Muscle tightness	Additional description: Muscle tightness		
subjects affected / exposed	1 / 168 (0.60%)	3 / 170 (1.76%)	
occurrences (all)	1	3	
Osteoporosis	Additional description: Osteoporosis		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Pain in extremity	Additional description: Pain in extremity		
subjects affected / exposed	15 / 168 (8.93%)	15 / 170 (8.82%)	
occurrences (all)	17	21	
Pain in jaw	Additional description: Pain in jaw		

subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Osteoarthritis	Additional description: Osteoarthritis		
subjects affected / exposed	11 / 168 (6.55%)	3 / 170 (1.76%)	
occurrences (all)	11	4	
Periarthritis	Additional description: Periarthritis		
subjects affected / exposed	0 / 168 (0.00%)	2 / 170 (1.18%)	
occurrences (all)	0	2	
Periostitis	Additional description: Periostitis		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Plantar fasciitis	Additional description: Plantar fasciitis		
subjects affected / exposed	0 / 168 (0.00%)	2 / 170 (1.18%)	
occurrences (all)	0	2	
Plica syndrome	Additional description: Plica syndrome		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Rheumatic disorder	Additional description: Rheumatic disorder		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Spinal osteoarthritis	Additional description: Spinal osteoarthritis		
subjects affected / exposed	1 / 168 (0.60%)	1 / 170 (0.59%)	
occurrences (all)	1	1	
Spinal pain	Additional description: Spinal pain		
subjects affected / exposed	2 / 168 (1.19%)	0 / 170 (0.00%)	
occurrences (all)	2	0	
Spinal stenosis	Additional description: Spinal stenosis		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Synovial cyst	Additional description: Synovial cyst		
subjects affected / exposed	0 / 168 (0.00%)	2 / 170 (1.18%)	
occurrences (all)	0	2	
Tendon discomfort	Additional description: Tendon discomfort		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Tendonitis	Additional description: Tendonitis		

subjects affected / exposed	1 / 168 (0.60%)	1 / 170 (0.59%)	
occurrences (all)	1	1	
Tenosynovitis	Additional description: Tenosynovitis		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Torticollis	Additional description: Torticollis		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Infections and infestations			
Acne pustular	Additional description: Acne pustular		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Abscess limb	Additional description: Abscess limb		
subjects affected / exposed	0 / 168 (0.00%)	2 / 170 (1.18%)	
occurrences (all)	0	3	
Abscess	Additional description: Abscess		
subjects affected / exposed	1 / 168 (0.60%)	1 / 170 (0.59%)	
occurrences (all)	1	1	
Angular cheilitis	Additional description: Angular cheilitis		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	2	
Alveolar osteitis	Additional description: Alveolar osteitis		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Bacterial diarrhoea	Additional description: Bacterial diarrhoea		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Arthritis infective	Additional description: Arthritis infective		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Atypical pneumonia	Additional description: Atypical pneumonia		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Bacterial rhinitis	Additional description: Bacterial rhinitis		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	

Bacterial vaginosis	Additional description: Bacterial vaginosis		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Bacterial food poisoning	Additional description: Bacterial food poisoning		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Bacterial infection	Additional description: Bacterial infection		
subjects affected / exposed	1 / 168 (0.60%)	1 / 170 (0.59%)	
occurrences (all)	1	1	
Bacterial pyelonephritis	Additional description: Bacterial pyelonephritis		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Bronchitis	Additional description: Bronchitis		
subjects affected / exposed	19 / 168 (11.31%)	26 / 170 (15.29%)	
occurrences (all)	21	30	
Bronchitis bacterial	Additional description: Bronchitis bacterial		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Bronchitis viral	Additional description: Bronchitis viral		
subjects affected / exposed	0 / 168 (0.00%)	2 / 170 (1.18%)	
occurrences (all)	0	2	
Bursitis infective	Additional description: Bursitis infective		
subjects affected / exposed	1 / 168 (0.60%)	1 / 170 (0.59%)	
occurrences (all)	1	1	
Campylobacter infection	Additional description: Campylobacter infection		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Candida infection	Additional description: Candida infection		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	2	
Chronic tonsillitis	Additional description: Chronic tonsillitis		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Chronic sinusitis	Additional description: Chronic sinusitis		
subjects affected / exposed	1 / 168 (0.60%)	2 / 170 (1.18%)	
occurrences (all)	1	2	

Cellulitis	Additional description: Cellulitis		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Conjunctivitis	Additional description: Conjunctivitis		
subjects affected / exposed	3 / 168 (1.79%)	6 / 170 (3.53%)	
occurrences (all)	3	9	
COVID-19	Additional description: COVID-19		
subjects affected / exposed	7 / 168 (4.17%)	7 / 170 (4.12%)	
occurrences (all)	7	7	
Cystitis	Additional description: Cystitis		
subjects affected / exposed	12 / 168 (7.14%)	10 / 170 (5.88%)	
occurrences (all)	20	21	
Cystitis bacterial	Additional description: Cystitis bacterial		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Dermatitis infected	Additional description: Dermatitis infected		
subjects affected / exposed	3 / 168 (1.79%)	0 / 170 (0.00%)	
occurrences (all)	3	0	
Diarrhoea infectious	Additional description: Diarrhoea infectious		
subjects affected / exposed	2 / 168 (1.19%)	3 / 170 (1.76%)	
occurrences (all)	2	3	
Diverticulitis	Additional description: Diverticulitis		
subjects affected / exposed	2 / 168 (1.19%)	1 / 170 (0.59%)	
occurrences (all)	4	1	
Ear infection	Additional description: Ear infection		
subjects affected / exposed	1 / 168 (0.60%)	1 / 170 (0.59%)	
occurrences (all)	1	1	
Epididymitis	Additional description: Epididymitis		
subjects affected / exposed	0 / 168 (0.00%)	2 / 170 (1.18%)	
occurrences (all)	0	6	
Erysipelas	Additional description: Erysipelas		
subjects affected / exposed	1 / 168 (0.60%)	2 / 170 (1.18%)	
occurrences (all)	1	2	
Eye infection	Additional description: Eye infection		
subjects affected / exposed	0 / 168 (0.00%)	2 / 170 (1.18%)	
occurrences (all)	0	2	

Eyelid infection	Additional description: Eyelid infection		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Enterococcal infection	Additional description: Enterococcal infection		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Febrile infection	Additional description: Febrile infection		
subjects affected / exposed	3 / 168 (1.79%)	1 / 170 (0.59%)	
occurrences (all)	3	1	
Folliculitis	Additional description: Folliculitis		
subjects affected / exposed	2 / 168 (1.19%)	3 / 170 (1.76%)	
occurrences (all)	2	3	
Fungal infection	Additional description: Fungal infection		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Fungal pharyngitis	Additional description: Fungal pharyngitis		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Fungal skin infection	Additional description: Fungal skin infection		
subjects affected / exposed	1 / 168 (0.60%)	1 / 170 (0.59%)	
occurrences (all)	1	1	
Gastric infection	Additional description: Gastric infection		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Gastroenteritis	Additional description: Gastroenteritis		
subjects affected / exposed	5 / 168 (2.98%)	5 / 170 (2.94%)	
occurrences (all)	6	7	
Gastroenteritis norovirus	Additional description: Gastroenteritis norovirus		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Gastroenteritis viral	Additional description: Gastroenteritis viral		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Gastrointestinal candidiasis	Additional description: Gastrointestinal candidiasis		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	

Gastrointestinal infection	Additional description: Gastrointestinal infection		
subjects affected / exposed	13 / 168 (7.74%)	15 / 170 (8.82%)	
occurrences (all)	14	26	
Genital herpes	Additional description: Genital herpes		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Genital herpes zoster	Additional description: Genital herpes zoster		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Gingivitis	Additional description: Gingivitis		
subjects affected / exposed	2 / 168 (1.19%)	2 / 170 (1.18%)	
occurrences (all)	2	2	
Haemophilus infection	Additional description: Haemophilus infection		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Helicobacter gastritis	Additional description: Helicobacter gastritis		
subjects affected / exposed	2 / 168 (1.19%)	2 / 170 (1.18%)	
occurrences (all)	2	2	
Hepatitis E	Additional description: Hepatitis E		
subjects affected / exposed	1 / 168 (0.60%)	1 / 170 (0.59%)	
occurrences (all)	1	1	
Herpes simplex	Additional description: Herpes simplex		
subjects affected / exposed	2 / 168 (1.19%)	0 / 170 (0.00%)	
occurrences (all)	3	0	
Herpes virus infection	Additional description: Herpes virus infection		
subjects affected / exposed	1 / 168 (0.60%)	2 / 170 (1.18%)	
occurrences (all)	1	2	
Herpes zoster	Additional description: Herpes zoster		
subjects affected / exposed	10 / 168 (5.95%)	5 / 170 (2.94%)	
occurrences (all)	13	5	
Hepatitis viral	Additional description: Hepatitis viral		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Impetigo	Additional description: Impetigo		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	

Infected bite	Additional description: Infected bite		
subjects affected / exposed	3 / 168 (1.79%)	0 / 170 (0.00%)	
occurrences (all)	3	0	
Infected bites	Additional description: Infected bites		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Infected cyst	Additional description: Infected cyst		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Infection	Additional description: Infection		
subjects affected / exposed	12 / 168 (7.14%)	9 / 170 (5.29%)	
occurrences (all)	13	14	
Influenza	Additional description: Influenza		
subjects affected / exposed	8 / 168 (4.76%)	12 / 170 (7.06%)	
occurrences (all)	13	22	
Injection site abscess	Additional description: Injection site abscess		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Laryngitis	Additional description: Laryngitis		
subjects affected / exposed	0 / 168 (0.00%)	4 / 170 (2.35%)	
occurrences (all)	0	4	
Lip infection	Additional description: Lip infection		
subjects affected / exposed	0 / 168 (0.00%)	2 / 170 (1.18%)	
occurrences (all)	0	4	
Localised infection	Additional description: Localised infection		
subjects affected / exposed	0 / 168 (0.00%)	2 / 170 (1.18%)	
occurrences (all)	0	2	
Lower respiratory tract infection	Additional description: Lower respiratory tract infection		
subjects affected / exposed	1 / 168 (0.60%)	1 / 170 (0.59%)	
occurrences (all)	1	1	
Lyme disease	Additional description: Lyme disease		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Mucosal infection	Additional description: Mucosal infection		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	2	

Nail bed infection	Additional description: Nail bed infection		
subjects affected / exposed	1 / 168 (0.60%)	2 / 170 (1.18%)	
occurrences (all)	1	2	
Nail infection	Additional description: Nail infection		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Nasal herpes	Additional description: Nasal herpes		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis	Additional description: Nasopharyngitis		
subjects affected / exposed	72 / 168 (42.86%)	51 / 170 (30.00%)	
occurrences (all)	126	108	
Neutropenic infection	Additional description: Neutropenic infection		
subjects affected / exposed	2 / 168 (1.19%)	0 / 170 (0.00%)	
occurrences (all)	2	0	
Nosocomial infection	Additional description: Nosocomial infection		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Onychomycosis	Additional description: Onychomycosis		
subjects affected / exposed	1 / 168 (0.60%)	1 / 170 (0.59%)	
occurrences (all)	1	1	
Oral fungal infection	Additional description: Oral fungal infection		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Oral herpes	Additional description: Oral herpes		
subjects affected / exposed	12 / 168 (7.14%)	2 / 170 (1.18%)	
occurrences (all)	18	6	
Oral infection	Additional description: Oral infection		
subjects affected / exposed	0 / 168 (0.00%)	3 / 170 (1.76%)	
occurrences (all)	0	3	
Oral viral infection	Additional description: Oral viral infection		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Orchitis	Additional description: Orchitis		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	

Otitis externa	Additional description: Otitis externa		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Paronychia	Additional description: Paronychia		
subjects affected / exposed	1 / 168 (0.60%)	10 / 170 (5.88%)	
occurrences (all)	3	12	
Parotitis	Additional description: Parotitis		
subjects affected / exposed	1 / 168 (0.60%)	1 / 170 (0.59%)	
occurrences (all)	3	1	
Penile infection	Additional description: Penile infection		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Periodontitis	Additional description: Periodontitis		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Pharyngitis	Additional description: Pharyngitis		
subjects affected / exposed	4 / 168 (2.38%)	4 / 170 (2.35%)	
occurrences (all)	4	4	
Phlebitis infective	Additional description: Phlebitis infective		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Pneumonia	Additional description: Pneumonia		
subjects affected / exposed	7 / 168 (4.17%)	10 / 170 (5.88%)	
occurrences (all)	9	15	
Postoperative wound infection	Additional description: Postoperative wound infection		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Pseudomonas infection	Additional description: Pseudomonas infection		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Purulence	Additional description: Purulence		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Pyelonephritis	Additional description: Pyelonephritis		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	

Pyoderma	Additional description: Pyoderma		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Rash pustular	Additional description: Rash pustular		
subjects affected / exposed	0 / 168 (0.00%)	2 / 170 (1.18%)	
occurrences (all)	0	3	
Respiratory tract infection	Additional description: Respiratory tract infection		
subjects affected / exposed	8 / 168 (4.76%)	13 / 170 (7.65%)	
occurrences (all)	9	23	
Retinitis	Additional description: Retinitis		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Rhinitis	Additional description: Rhinitis		
subjects affected / exposed	3 / 168 (1.79%)	10 / 170 (5.88%)	
occurrences (all)	5	10	
Root canal infection	Additional description: Root canal infection		
subjects affected / exposed	1 / 168 (0.60%)	2 / 170 (1.18%)	
occurrences (all)	1	2	
Scarlet fever	Additional description: Scarlet fever		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Scrotal infection	Additional description: Scrotal infection		
subjects affected / exposed	0 / 168 (0.00%)	2 / 170 (1.18%)	
occurrences (all)	0	5	
Seminal vesicular infection	Additional description: Seminal vesicular infection		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Sialoadenitis	Additional description: Sialoadenitis		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Sinobronchitis	Additional description: Sinobronchitis		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Sinusitis	Additional description: Sinusitis		
subjects affected / exposed	8 / 168 (4.76%)	9 / 170 (5.29%)	
occurrences (all)	11	15	

Sinusitis bacterial	Additional description: Sinusitis bacterial		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Skin infection	Additional description: Skin infection		
subjects affected / exposed	1 / 168 (0.60%)	4 / 170 (2.35%)	
occurrences (all)	2	5	
Subcutaneous abscess	Additional description: Subcutaneous abscess		
subjects affected / exposed	0 / 168 (0.00%)	2 / 170 (1.18%)	
occurrences (all)	0	2	
Tinea infection	Additional description: Tinea infection		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Tinea versicolour	Additional description: Tinea versicolour		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection	Additional description: Upper respiratory tract infection		
subjects affected / exposed	17 / 168 (10.12%)	19 / 170 (11.18%)	
occurrences (all)	20	30	
Tongue fungal infection	Additional description: Tongue fungal infection		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	
Tonsillitis	Additional description: Tonsillitis		
subjects affected / exposed	3 / 168 (1.79%)	3 / 170 (1.76%)	
occurrences (all)	3	5	
Tooth abscess	Additional description: Tooth abscess		
subjects affected / exposed	0 / 168 (0.00%)	2 / 170 (1.18%)	
occurrences (all)	0	2	
Tooth infection	Additional description: Tooth infection		
subjects affected / exposed	4 / 168 (2.38%)	3 / 170 (1.76%)	
occurrences (all)	4	3	
Tracheitis	Additional description: Tracheitis		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Trichomoniasis	Additional description: Trichomoniasis		
subjects affected / exposed	1 / 168 (0.60%)	0 / 170 (0.00%)	
occurrences (all)	1	0	

Tinea pedis	Additional description: Tinea pedis		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Urinary tract infection	Additional description: Urinary tract infection		
subjects affected / exposed	12 / 168 (7.14%)	20 / 170 (11.76%)	
occurrences (all)	14	41	
Vulvovaginal mycotic infection	Additional description: Vulvovaginal mycotic infection		
subjects affected / exposed	1 / 168 (0.60%)	1 / 170 (0.59%)	
occurrences (all)	1	1	
Viral diarrhoea	Additional description: Viral diarrhoea		
subjects affected / exposed	1 / 168 (0.60%)	1 / 170 (0.59%)	
occurrences (all)	1	1	
Viral infection	Additional description: Viral infection		
subjects affected / exposed	5 / 168 (2.98%)	3 / 170 (1.76%)	
occurrences (all)	5	3	
Viral upper respiratory tract infection	Additional description: Viral upper respiratory tract infection		
subjects affected / exposed	2 / 168 (1.19%)	1 / 170 (0.59%)	
occurrences (all)	2	1	
Wound infection bacterial	Additional description: Wound infection bacterial		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Wound infection	Additional description: Wound infection		
subjects affected / exposed	0 / 168 (0.00%)	2 / 170 (1.18%)	
occurrences (all)	0	2	
Wound infection pseudomonas	Additional description: Wound infection pseudomonas		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Decreased appetite	Additional description: Decreased appetite		
subjects affected / exposed	3 / 168 (1.79%)	3 / 170 (1.76%)	
occurrences (all)	5	3	
Diabetes mellitus	Additional description: Diabetes mellitus		
subjects affected / exposed	0 / 168 (0.00%)	2 / 170 (1.18%)	
occurrences (all)	0	2	
Diabetic metabolic decompensation	Additional description: Diabetic metabolic decompensation		

subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Folate deficiency	Additional description: Folate deficiency		
subjects affected / exposed	0 / 168 (0.00%)	3 / 170 (1.76%)	
occurrences (all)	0	3	
Gout	Additional description: Gout		
subjects affected / exposed	1 / 168 (0.60%)	6 / 170 (3.53%)	
occurrences (all)	2	6	
Hypercholesterolaemia	Additional description: Hypercholesterolaemia		
subjects affected / exposed	0 / 168 (0.00%)	2 / 170 (1.18%)	
occurrences (all)	0	3	
Hypercreatininaemia	Additional description: Hypercreatininaemia		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Hyperglycaemia	Additional description: Hyperglycaemia		
subjects affected / exposed	1 / 168 (0.60%)	1 / 170 (0.59%)	
occurrences (all)	1	1	
Hyperkalaemia	Additional description: Hyperkalaemia		
subjects affected / exposed	1 / 168 (0.60%)	1 / 170 (0.59%)	
occurrences (all)	1	1	
Hyperlipasaemia	Additional description: Hyperlipasaemia		
subjects affected / exposed	1 / 168 (0.60%)	1 / 170 (0.59%)	
occurrences (all)	1	1	
Hyperuricaemia	Additional description: Hyperuricaemia		
subjects affected / exposed	0 / 168 (0.00%)	3 / 170 (1.76%)	
occurrences (all)	0	3	
Hypokalaemia	Additional description: Hypokalaemia		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Iron deficiency	Additional description: Iron deficiency		
subjects affected / exposed	1 / 168 (0.60%)	4 / 170 (2.35%)	
occurrences (all)	1	4	
Protein deficiency	Additional description: Protein deficiency		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Type 2 diabetes mellitus	Additional description: Type 2 diabetes mellitus		

subjects affected / exposed	0 / 168 (0.00%)	2 / 170 (1.18%)	
occurrences (all)	0	2	
Vitamin B12 deficiency	Additional description: Vitamin B12 deficiency		
subjects affected / exposed	0 / 168 (0.00%)	1 / 170 (0.59%)	
occurrences (all)	0	1	
Vitamin D deficiency	Additional description: Vitamin D deficiency		
subjects affected / exposed	3 / 168 (1.79%)	4 / 170 (2.35%)	
occurrences (all)	3	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 October 2014	New Information on Ibrutinib and update of protocol and PIC following IB V8.0
04 February 2015	Adaption of sample size calculation with respect to current recruitment rate
15 July 2015	Changes in the protocol, following DSMB recommendation to prohibit concomitant medication with Xa-Inhibitors, alternatively to allow heparines only.
13 January 2016	New Information on Ibrutinib and update of protocol and PIC following IB V9.0;Adaption of statistical assumption to allow confirmatory analyses of overall survival
08 July 2016	New safety information on interstitial lung disease, amendment of PIC accordingly
28 March 2017	New Information on Ibrutinib and update of protocol and PIC following IB V10.0
26 June 2017	New Information on Ibrutinib and update of protocol and PIC following SmPC Februar 2017; administrative changes
09 April 2018	New Information on Ibrutinib and update of protocol and PIC following SmPC August 2017; Adaption of analysis time points and details of statistical analyses

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/34758069