Clinical trial results:
An Open-label Extension Study in Patients 65 Years or Older With Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL) Who Participated in Study PCYC-1115-CA (Ibrutinib Versus Chlorambucil)

Summary

EudraCT number	2012-003968-44
Trial protocol	BE GB IE CZ ES IT
Global end of trial date	18 August 2023

Results information

Result version number	v2 (current)
This version publication date	12 October 2024
First version publication date	03 August 2024
Version creation reason	• Correction of full data set Clarifying text in reporting group descriptions and milestone information in participant flow.

Trial information

Trial identification

Sponsor protocol code	PCYC-1116-CA

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01724346
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AbbVie Deutschland GmbH & Co. KG
Sponsor organisation address	AbbVie House, Vanwall Business Park, Vanwall Road, Maidenhead, Berkshire, United Kingdom, SL6 4UB
Public contact	Global Medical Services, AbbVie, 001 8006339110, abbvieclinicaltrials@abbvie.com
Scientific contact	Global Medical Services, AbbVie, 001 8006339110, abbvieclinicaltrials@abbvie.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 August 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 August 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- To monitor progression free survival (PFS)
- To continue treatment and safety assessment of patients randomized to Arm B (ibrutinib) in Study PCYC-1115-CA (the parent study) who have not progressed at the time of parent study closure
- To follow patients for long-term outcome
- To capture overall response rate (ORR), duration of response (DOR), PFS, and overall survival (OS), and time to next therapy
- To fulfill long-term follow-up requirements of randomized patients after closure of the parent study, including OS.

Protection of trial subjects:

Subject and/or legal guardian read and understood the information provided about the study and gave written permission.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 December 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 12
Country: Number of subjects enrolled	Canada: 10
Country: Number of subjects enrolled	China: 11
Country: Number of subjects enrolled	Czechia: 10
Country: Number of subjects enrolled	Spain: 12
Country: Number of subjects enrolled	United Kingdom: 30
Country: Number of subjects enrolled	Ireland: 5
Country: Number of subjects enrolled	Israel: 16
Country: Number of subjects enrolled	Italy: 27
Country: Number of subjects enrolled	New Zealand: 13
Country: Number of subjects enrolled	Poland: 20
Country: Number of subjects enrolled	Russian Federation: 1
Country: Number of subjects enrolled	Türkiye: 10
Country: Number of subjects enrolled	Ukraine: 13
Country: Number of subjects enrolled	United States: 61
Country: Number of subjects enrolled	Australia: 18

Worldwide total number of subjects	269
EEA total number of subjects	86

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)	0
From 65 to 84 years	258
85 years and over	11

Subject disposition

Recruitment

Recruitment details:

This extension study provided ongoing treatment and follow-up for participants previously enrolled in the parent study (PCYC-1115-CA; Study 1115; NCT01722487). Participants entered this study upon Independent Review Committee (IRC)-confirmed progressive disease (PD) or the closure of Study 1115, whichever was earlier.

Pre-assignment

Screening details:

All participants randomized to chlorambucil in Study 1115 completed or discontinued their first-line treatment prior to rollover. Participants randomized to ibrutinib in Study 1115 with no PD could continue their firstline treatment in this study. Next-line treatment with ibrutinib after PD was a subsequent-therapy option for the chlorambucil arm.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Ibrutinib

Arm description:

Participants who received ibrutinib 420 mg daily in Study 1115 received ibrutinib orally once daily. Participants continuing in first-line ibrutinib therapy entered Study 1116 at the ibrutinib dose tolerated in Study 1115.

Arm type	Experimental
Investigational medicinal product name	Ibrutinib
Investigational medicinal product code	
Other name	PCI-32765
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Ibrutinib is administered orally once daily

Arm title	Chlorambucil

Arm description:

Participants who received chlorambucil 0.5 mg/kg (to maximum 0.8 mg/kg) Days 1 and 15 of 28-day cycle up to 12 cycles in Study 1115. In Study 1116, participants had the option to receive next-line ibrutinib 420 mg/day
after PD.

Arm type	Experimental
Investigational medicinal product name	Ibrutinib
Investigational medicinal product code	
Other name	PCI-32765
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Ibrutinib is administered orally once daily

Number of subjects in period 1	Ibrutinib	Chlorambucil
Started	136	133
Received Next- Line Ibrutinib After PD	0 [1]	78
Completed	57	63
Not completed	79	70
Consent withdrawn by subject	27	19
Death	42	42
Eligible but didn't rollover after completing 1115	5	8
Lost to follow-up	5	1

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Next-line treatment with ibrutinib after PD was a subsequent-therapy option for participants enrolled in the chlorambucil arm only.

Baseline characteristics

Reporting groups	
Reporting group title	Ibrutinib
Reporting group description:	
Participants who received ibrutinib 420 mg daily in Study 1115 received ibrutinib orally once daily. Participants continuing in first-line ibrutinib therapy entered Study 1116 at the ibrutinib dose tolerated in Study 1115.	
Reporting group title	Chlorambucil
Reporting group description:	
Participants who received chlorambucil 0.5 mg/kg (to maximum 0.8 mg/kg) Days 1 and 15 of 28-day cycle up to 12 cycles in Study 1115. In Study 1116, participants had the option to receive next-line ibrutinib 420 mg/day after PD.	

Reporting group values	Ibrutinib	Chlorambucil	Total
Number of subjects	136	133	269
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	73.1	73.4	
standard deviation	± 5.67	± 5.95	-
Gender categorical Units: Subjects			
Female	48	52	100
Male	88	81	169
Ethnicity Units: Subjects			
Hispanic or Latino	3	2	5
Not Hispanic or Latino	132	129	261
Unknown or Not Reported	1	2	3
Race Units: Subjects			
White	120	125	245
Asian	9	4	13
Black or African American	5	3	8
Native Hawaiian or Other Pacific Islander	0	1	1
Subject declined to answer/ unknown	2	0	2

End points

End points reporting groups

Reporting group title	Ibrutinib

Reporting group description:

Participants who received ibrutinib 420 mg daily in Study 1115 received ibrutinib orally once daily. Participants continuing in first-line ibrutinib therapy entered Study 1116 at the ibrutinib dose tolerated in Study 1115.

Reporting group title	Chlorambucil

Reporting group description:

Participants who received chlorambucil 0.5 mg/kg (to maximum 0.8 mg/kg) Days 1 and 15 of 28-day cycle up to 12 cycles in Study 1115. In Study 1116, participants had the option to receive next-line ibrutinib 420 mg/day
after PD.

Primary: Progression Free Survival (PFS) Based on Investigator Assessment

End point title	Progression Free Survival (PFS) Based on Investigator Assessment

End point description:

PFS is defined as the time from the date of randomization to the date of disease progression determined by the investigator or date of death from any cause, whichever occurs first, regardless of the use of subsequent antineoplastic therapy prior to disease progression (PD) or death. Estimated by Kaplan-Meier method.

Intent-to-Treat (ITT) Population: All randomized participants in Study 1115.

End point type	Primary

End point timeframe:

Median overall follow-up of 82.7 months

End point values	Ibrutinib	Chlorambucil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136[1]	133		
Units: months				
median (confidence interval 95%)	106.9 (83.4 to 99999)	15.0 (10.2 to 19.4)		

Notes:

[1] - 99999=Not estimable because there were not enough PFS events to get a reliable upper bound of 95% CI

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Ibrutinib v Chlorambucil

Number of subjects included in analysis	269
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.155
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.11
upper limit	0.22

Notes:

[2] - P-value is from stratified log-rank test.

Secondary: Progression Free Survival After Initiation of Subsequent Anticancer Therapy (PFS2)

End point title	Progression Free Survival After Initiation of Subsequent Anticancer Therapy (PFS2)

End point description:

PFS2 is defined as the time from the date of randomization to the earliest occurrence of the following three types of
events:
• PD per investigator response assessment after initiation of the first subsequent anti-cancer therapy
• Initiation of second subsequent anti-cancer therapy
• Death due to any cause, regardless of administration of subsequent anticancer therapy.
Kaplan-Meier landmark estimate of the PFS2 rate at 60 months (that is, the estimated percentage of participants with PFS2 at Month 60) is presented.

ITT Population: All randomized participants in Study 1115.

End point type	Secondary

End point timeframe:

Median overall follow-up of 82.7 months

End point values	Ibrutinib	Chlorambucil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	133		
Units: percentage of participants				
number (confidence interval 95%)	79.3 (71.1 to 85.4)	58.4 (48.8 to 66.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS is defined as the time from randomization to death due to any cause. Kaplan-Meier landmark

estimate of the OS rate at 60 months (that is, the estimated percentage of participants with OS at Month 60) is presented.

ITT Population: All randomized participants in Study 1115.

End point type	Secondary

End point timeframe:

Median overall follow-up of 82.7 months

End point values	Ibrutinib	Chlorambucil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	133		
Units: percentage of participants				
number (confidence interval 95%)	82.8 (75.0 to 88.3)	68.4 (59.1 to 75.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Next Treatment (TTNT)

End point title	Time to Next Treatment (TTNT)

End point description:

Time from randomization to initiation of any subsequent treatment for chronic lymphocytic leukemia (CLL).

End point type	Secondary

End point timeframe:

Median overall follow-up of 82.7 months

End point values	Ibrutinib	Chlorambucil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136[3]	133		
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	25.1 (21.8 to 27.9)		

Notes:

[3] - 99999=Not estimable because there were not enough TTNT events.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Ibrutinib v Chlorambucil

Number of subjects included in analysis	269
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [4]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.087
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.054
upper limit	0.141

Notes:

[4] - P value is from stratified log-rank test.

Secondary: Overall Response Rate (ORR)

End point title	Overall Response Rate (ORR)

End point description:

ORR is defined as the percentage of participants who achieve complete response (CR), complete response with an incomplete marrow recovery (CRi), nodular partial response (nPR), or partial response (PR), as determined by the investigator at or prior to initiation of subsequent antineoplastic therapy according to the International Workshop on CLL (iwCLL) 2008 criteria with the 2012 iwCLL modification stating that treatment-related lymphocytosis in the setting of improvement in other parameters was not considered as PD and the 2013 iwCLL clarification of criteria for a partial response to therapy.

ITT Population: All randomized participants in Study 1115.

End point type	Secondary

End point timeframe:

Median overall follow-up of 82.7 months

End point values	Ibrutinib	Chlorambucil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	133		
Units: percentage of participants				
number (not applicable)	91.2	36.8		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Ibrutinib v Chlorambucil
Number of subjects included in analysis	269
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [5]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Rate Ratio
Point estimate	2.496

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.99
upper limit	3.131

Notes:

[5] - Rate ratio and p-value are based on Cochran-Mantel-Haenszel chi-square test stratified by Eastern Cooperative Oncology Group (ECOG; 0-1 vs 2) and Rai stage (0/I/II vs III/IV) at baseline.

Secondary: Rate of Minimal Residual Disease (MRD) Negativity

End point title	Rate of Minimal Residual Disease (MRD) Negativity

End point description:

Percentage of participants who achieved MRD-negative response defined as < 1 CLL cell per 10,000 leukocytes as assessed by flow cytometry of a bone marrow aspirate and/or peripheral blood sample per central laboratory at or prior to initiation of subsequent antineoplastic therapy.

ITT Population: All randomized participants in Study 1115.

End point type	Secondary

End point timeframe:

Median overall follow-up of 82.7 months

End point values	Ibrutinib	Chlorambucil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	133		
Units: percentage of participants				
number (not applicable)	5.1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)

End point description:

DOR will be calculated for the participants achieving a protocol-defined response (Halleck 2008; CR, CRi, nPR, PR) per investigator assessment and is defined as time from the date of initial response including PR with lymphocytosis to the date of disease progression or the date of death from any cause, whichever occurs first.

ITT Participants Achieving Response (Partial Response or Better) per protocol definitions (Halleck 2008).

End point type	Secondary

End point timeframe:

Median overall follow-up of 82.7 months

End point values	Ibrutinib	Chlorambucil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124[6]	49		
Units: months				
median (confidence interval 95%)	99999 (84.0 to 99999)	29.7 (15.2 to 40.4)		

Notes:

[6] - 99999=Not estimable because there were not enough DOR events.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From 1st dose of any study treatment to 30 days after last dose of study treatment or initiation of subsequent therapy, whichever was earlier. Median treatment duration: Ibrutinib=74.0 months; Chlorambucil=7.1 months; Next-line Ibrutinib=26.9 months.

Adverse event reporting additional description:

Safety Population: participants in the ITT population who received >= 1 dose of either chlorambucil or ibrutinib as the first-line therapy in the parent Study 1115. The crossover analysis set used for next-line ibrutinib treatment included all chlorambucil arm participants who received at least 1 dose of ibrutinib as the next-line study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	Ibrutinib

Reporting group description:

Participants who received ibrutinib 420 mg daily in Study 1115 received ibrutinib orally once daily. Participants continuing in first-line ibrutinib therapy entered Study 1116 at the ibrutinib dose tolerated in Study 1115.

Reporting group title	Chlorambucil Participants Crossed Over to Ibrutinib

Reporting group description:

Participants who received chlorambucil treatment in Study 1115 and crossed over to next-line ibrutinib 420 mg/day in Study 1116.

Reporting group title	Chlorambucil

Reporting group description:

Participants who received chlorambucil 0.5 mg/kg (to maximum 0.8 mg/kg) Days 1 and 15 of 28-day cycle up to 12 cycles in Study 1115.

Serious adverse events	Ibrutinib	Chlorambucil Participants Crossed Over to Ibrutinib	Chlorambucil
Total subjects affected by serious adverse events			
subjects affected / exposed	111 / 135 (82.22%)	49 / 78 (62.82%)	33 / 132 (25.00%)
number of deaths (all causes)	42	24	44
number of deaths resulting from adverse events	25	9	4
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
ADENOCARCINOMA			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ADENOCARCINOMA OF COLON			

subjects affected / exposed	0 / 135 (0.00%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BASAL CELL CARCINOMA			
subjects affected / exposed	9 / 135 (6.67%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	1 / 12	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BASOSQUAMOUS CARCINOMA OF SKIN			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BLADDER CANCER			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BLADDER TRANSITIONAL CELL CARCINOMA			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BOWEN'S DISEASE			
subjects affected / exposed	0 / 135 (0.00%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BRAIN NEOPLASM			
subjects affected / exposed	0 / 135 (0.00%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
BREAST CANCER			
subjects affected / exposed	2 / 135 (1.48%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CHRONIC LYMPHOCYTIC LEUKAEMIA			

subjects affected / exposed	2 / 135 (1.48%)	0 / 78 (0.00%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 1
COLORECTAL ADENOMA			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LUNG NEOPLASM			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LUNG CANCER METASTATIC			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
LUNG ADENOCARCINOMA			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LUNG NEOPLASM MALIGNANT			
subjects affected / exposed	2 / 135 (1.48%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
MUCINOUS ADENOCARCINOMA OF APPENDIX			
subjects affected / exposed	0 / 135 (0.00%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NON-SMALL CELL LUNG CANCER			
subjects affected / exposed	1 / 135 (0.74%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NON-SMALL CELL LUNG CANCER METASTATIC			

subjects affected / exposed	0 / 135 (0.00%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PROSTATE CANCER			
subjects affected / exposed	4 / 135 (2.96%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RECTAL ADENOCARCINOMA			
subjects affected / exposed	0 / 135 (0.00%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RICHTER'S SYNDROME			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SPINDLE CELL SARCOMA			
subjects affected / exposed	0 / 135 (0.00%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
SQUAMOUS CELL CARCINOMA			
subjects affected / exposed	2 / 135 (1.48%)	2 / 78 (2.56%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	0 / 2	0 / 5	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SQUAMOUS CELL CARCINOMA OF SKIN			
subjects affected / exposed	2 / 135 (1.48%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
AORTIC ANEURYSM			
subjects affected / exposed	0 / 135 (0.00%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
AORTIC STENOSIS			

subjects affected / exposed	0 / 135 (0.00%)	0 / 78 (0.00%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HAEMATOMA			
subjects affected / exposed	0 / 135 (0.00%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPERTENSION			
subjects affected / exposed	4 / 135 (2.96%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	1 / 4	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPOTENSION			
subjects affected / exposed	0 / 135 (0.00%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ORTHOSTATIC HYPOTENSION			
subjects affected / exposed	2 / 135 (1.48%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PERIPHERAL ARTERY ANEURYSM			
subjects affected / exposed	0 / 135 (0.00%)	0 / 78 (0.00%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PERIPHERAL ISCHAEMIA			
subjects affected / exposed	0 / 135 (0.00%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
General disorders and administration site conditions			
CHILLS			
subjects affected / exposed	0 / 135 (0.00%)	0 / 78 (0.00%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CHEST PAIN			

subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DEATH			
subjects affected / exposed	2 / 135 (1.48%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
MULTIPLE ORGAN DYSFUNCTION SYNDROME			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
FATIGUE			
subjects affected / exposed	0 / 135 (0.00%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NON-CARDIAC CHEST PAIN			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PAIN			
subjects affected / exposed	0 / 135 (0.00%)	0 / 78 (0.00%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OEDEMA PERIPHERAL			
subjects affected / exposed	3 / 135 (2.22%)	0 / 78 (0.00%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	2 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PYREXIA			
subjects affected / exposed	4 / 135 (2.96%)	1 / 78 (1.28%)	5 / 132 (3.79%)
occurrences causally related to treatment / all	3 / 6	0 / 2	3 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PHYSICAL DECONDITIONING			

subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SUDDEN DEATH			
subjects affected / exposed	1 / 135 (0.74%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	1 / 1	0 / 0
Immune system disorders			
HYPOGAMMAGLOBULINAEMIA			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
IMMUNODEFICIENCY			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
BENIGN PROSTATIC HYPERPLASIA			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PERINEAL FISTULA			
subjects affected / exposed	0 / 135 (0.00%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
ACUTE RESPIRATORY DISTRESS SYNDROME			
subjects affected / exposed	0 / 135 (0.00%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ACUTE RESPIRATORY FAILURE			

subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ASTHMA			
subjects affected / exposed	0 / 135 (0.00%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BRONCHIECTASIS			
subjects affected / exposed	0 / 135 (0.00%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
CHRONIC OBSTRUCTIVE PULMONARY DISEASE			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COUGH			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DYSPNOEA			
subjects affected / exposed	1 / 135 (0.74%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HAEMOPTYSIS			
subjects affected / exposed	0 / 135 (0.00%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPERCAPNIA			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPOXIA			

subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LUNG INFILTRATION			
subjects affected / exposed	0 / 135 (0.00%)	0 / 78 (0.00%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PLEURAL EFFUSION			
subjects affected / exposed	5 / 135 (3.70%)	2 / 78 (2.56%)	2 / 132 (1.52%)
occurrences causally related to treatment / all	1 / 8	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMOMEDIASTINUM			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONITIS			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMOTHORAX			
subjects affected / exposed	0 / 135 (0.00%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RESPIRATORY FAILURE			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PULMONARY OEDEMA			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PULMONARY FIBROSIS			

subjects affected / exposed	2 / 135 (1.48%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
PULMONARY EMBOLISM			
subjects affected / exposed	0 / 135 (0.00%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
PULMONARY CONGESTION			
subjects affected / exposed	0 / 135 (0.00%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PULMONARY ARTERIAL HYPERTENSION			
subjects affected / exposed	0 / 135 (0.00%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
WHEEZING			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
CARDIOVASCULAR SOMATIC SYMPTOM DISORDER			
subjects affected / exposed	0 / 135 (0.00%)	0 / 78 (0.00%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CONFUSIONAL STATE			
subjects affected / exposed	1 / 135 (0.74%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DELIRIUM			
subjects affected / exposed	3 / 135 (2.22%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PSYCHOTIC DISORDER			

subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
FIBRIN D DIMER INCREASED			
subjects affected / exposed	0 / 135 (0.00%)	0 / 78 (0.00%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEPATIC ENZYME INCREASED			
subjects affected / exposed	0 / 135 (0.00%)	0 / 78 (0.00%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEART RATE IRREGULAR			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
WEIGHT DECREASED			
subjects affected / exposed	0 / 135 (0.00%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
FALL			
subjects affected / exposed	3 / 135 (2.22%)	2 / 78 (2.56%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ANIMAL BITE			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ANKLE FRACTURE			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

FEMORAL NECK FRACTURE			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FEMUR FRACTURE			
subjects affected / exposed	1 / 135 (0.74%)	2 / 78 (2.56%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FRACTURED SACRUM			
subjects affected / exposed	0 / 135 (0.00%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEAD INJURY			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEAT STROKE			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPHAEMA			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LIMB TRAUMATIC AMPUTATION			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LOWER LIMB FRACTURE			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LUMBAR VERTEBRAL FRACTURE			

subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MUSCLE STRAIN			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OVERDOSE			
subjects affected / exposed	0 / 135 (0.00%)	0 / 78 (0.00%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PELVIC FRACTURE			
subjects affected / exposed	1 / 135 (0.74%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
POSTOPERATIVE WOUND COMPLICATION			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
POST PROCEDURAL HAEMORRHAGE			
subjects affected / exposed	2 / 135 (1.48%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RADIUS FRACTURE			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RIB FRACTURE			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ROAD TRAFFIC ACCIDENT			

subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SHOULDER FRACTURE			
subjects affected / exposed	0 / 135 (0.00%)	0 / 78 (0.00%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SKIN LACERATION			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SPINAL FRACTURE			
subjects affected / exposed	2 / 135 (1.48%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SUBCUTANEOUS HAEMATOMA			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SUBDURAL HAEMORRHAGE			
subjects affected / exposed	0 / 135 (0.00%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SUBDURAL HAEMATOMA			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TOXICITY TO VARIOUS AGENTS			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TRAUMATIC HAEMATOMA			

subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ULNA FRACTURE			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
WRIST FRACTURE			
subjects affected / exposed	1 / 135 (0.74%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URINARY RETENTION POSTOPERATIVE			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
THYROGLOSSAL CYST			
subjects affected / exposed	0 / 135 (0.00%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
ACUTE CORONARY SYNDROME			
subjects affected / exposed	1 / 135 (0.74%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ACUTE MYOCARDIAL INFARCTION			
subjects affected / exposed	2 / 135 (1.48%)	1 / 78 (1.28%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
AORTIC VALVE DISEASE			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

AORTIC VALVE DISEASE MIXED			
subjects affected / exposed	0 / 135 (0.00%)	0 / 78 (0.00%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ARRHYTHMIA			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ATRIAL FIBRILLATION			
subjects affected / exposed	11 / 135 (8.15%)	6 / 78 (7.69%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	9 / 11	6 / 8	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ATRIAL FLUTTER			
subjects affected / exposed	3 / 135 (2.22%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	1 / 3	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ATRIOVENTRICULAR BLOCK COMPLETE			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CARDIAC ARREST			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CARDIAC DYSFUNCTION			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CARDIAC FAILURE			
subjects affected / exposed	5 / 135 (3.70%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	3 / 6	0 / 1	0 / 0
deaths causally related to treatment / all	1 / 2	0 / 0	0 / 0
CARDIAC FAILURE ACUTE			

subjects affected / exposed	0 / 135 (0.00%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CORONARY ARTERY DISEASE			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CARDIOPULMONARY FAILURE			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
CARDIAC TAMPONADE			
subjects affected / exposed	0 / 135 (0.00%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CARDIAC FAILURE CONGESTIVE			
subjects affected / exposed	2 / 135 (1.48%)	0 / 78 (0.00%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LEFT VENTRICULAR FAILURE			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MITRAL VALVE INCOMPETENCE			
subjects affected / exposed	0 / 135 (0.00%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MYOCARDIAL INFARCTION			
subjects affected / exposed	2 / 135 (1.48%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
MYOCARDIAL ISCHAEMIA			

subjects affected / exposed	0 / 135 (0.00%)	0 / 78 (0.00%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PALPITATIONS			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PERICARDIAL EFFUSION			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SINUS NODE DYSFUNCTION			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VENTRICULAR TACHYCARDIA			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
CAUDA EQUINA SYNDROME			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CEREBELLAR INFARCTION			
subjects affected / exposed	0 / 135 (0.00%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CEREBRAL HAEMORRHAGE			
subjects affected / exposed	2 / 135 (1.48%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COGNITIVE DISORDER			

subjects affected / exposed	2 / 135 (1.48%)	0 / 78 (0.00%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CEREBROVASCULAR ACCIDENT			
subjects affected / exposed	3 / 135 (2.22%)	2 / 78 (2.56%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
CEREBRAL INFARCTION			
subjects affected / exposed	0 / 135 (0.00%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
DEMENTIA			
subjects affected / exposed	2 / 135 (1.48%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DEMENTIA ALZHEIMER'S TYPE			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DYSARTHRIA			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
EPILEPSY			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ISCHAEMIC STROKE			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
METABOLIC ENCEPHALOPATHY			

subjects affected / exposed	2 / 135 (1.48%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
POST HERPETIC NEURALGIA			
subjects affected / exposed	0 / 135 (0.00%)	0 / 78 (0.00%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEMIANOPIA HOMONYMOUS			
subjects affected / exposed	0 / 135 (0.00%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PRESYNCOPE			
subjects affected / exposed	0 / 135 (0.00%)	0 / 78 (0.00%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HAEMORRHAGE INTRACRANIAL			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEADACHE			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SYNCOPE			
subjects affected / exposed	5 / 135 (3.70%)	1 / 78 (1.28%)	2 / 132 (1.52%)
occurrences causally related to treatment / all	1 / 7	1 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SUBARACHNOID HAEMORRHAGE			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SEIZURE			

subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TRANSIENT ISCHAEMIC ATTACK			
subjects affected / exposed	5 / 135 (3.70%)	2 / 78 (2.56%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	2 / 6	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
HAEMOLYTIC ANAEMIA			
subjects affected / exposed	0 / 135 (0.00%)	0 / 78 (0.00%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FEBRILE NEUTROPENIA			
subjects affected / exposed	4 / 135 (2.96%)	2 / 78 (2.56%)	2 / 132 (1.52%)
occurrences causally related to treatment / all	3 / 5	1 / 2	1 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
AUTOIMMUNE HAEMOLYTIC ANAEMIA			
subjects affected / exposed	0 / 135 (0.00%)	0 / 78 (0.00%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ANAEMIA			
subjects affected / exposed	3 / 135 (2.22%)	1 / 78 (1.28%)	2 / 132 (1.52%)
occurrences causally related to treatment / all	1 / 3	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PANCYTOPENIA			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NEUTROPENIA			
subjects affected / exposed	1 / 135 (0.74%)	2 / 78 (2.56%)	2 / 132 (1.52%)
occurrences causally related to treatment / all	2 / 2	2 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LYMPHADENOPATHY			

subjects affected / exposed	0 / 135 (0.00%)	0 / 78 (0.00%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
VERTIGO			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
EYE OEDEMA			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CATARACT			
subjects affected / exposed	2 / 135 (1.48%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BLINDNESS UNILATERAL			
subjects affected / exposed	2 / 135 (1.48%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GLAUCOMA			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VITREOUS HAEMORRHAGE			
subjects affected / exposed	1 / 135 (0.74%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RETINAL VEIN OCCLUSION			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RETINAL DETACHMENT			

subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RETINAL VASCULAR OCCLUSION			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	1 / 135 (0.74%)	3 / 78 (3.85%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ABDOMINAL PAIN UPPER			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ABDOMINAL WALL HAEMATOMA			
subjects affected / exposed	0 / 135 (0.00%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COLITIS			
subjects affected / exposed	0 / 135 (0.00%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CONSTIPATION			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	2 / 135 (1.48%)	1 / 78 (1.28%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	1 / 2	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTRITIS			

subjects affected / exposed	1 / 135 (0.74%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIVERTICULUM			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIARRHOEA			
subjects affected / exposed	3 / 135 (2.22%)	2 / 78 (2.56%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	2 / 3	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HIATUS HERNIA			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ILEUS PARALYTIC			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INTESTINAL OBSTRUCTION			
subjects affected / exposed	0 / 135 (0.00%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MELAENA			
subjects affected / exposed	0 / 135 (0.00%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OESOPHAGEAL STENOSIS			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OVERFLOW DIARRHOEA			

subjects affected / exposed	0 / 135 (0.00%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PANCREATITIS			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PANCREATITIS ACUTE			
subjects affected / exposed	2 / 135 (1.48%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
UPPER GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	1 / 135 (0.74%)	2 / 78 (2.56%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
STOMATITIS			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SMALL INTESTINAL OBSTRUCTION			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
VOMITING			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
BILE DUCT STONE			
subjects affected / exposed	1 / 135 (0.74%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CHOLECYSTITIS			

subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CHOLANGITIS			
subjects affected / exposed	3 / 135 (2.22%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	1 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CHOLECYSTITIS ACUTE			
subjects affected / exposed	0 / 135 (0.00%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEPATIC FUNCTION ABNORMAL			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CHOLELITHIASIS			
subjects affected / exposed	1 / 135 (0.74%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEPATITIS			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
JAUNDICE CHOLESTATIC			
subjects affected / exposed	0 / 135 (0.00%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEPATITIS TOXIC			
subjects affected / exposed	0 / 135 (0.00%)	0 / 78 (0.00%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Skin and subcutaneous tissue disorders			
PSORIASIS			

subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ERYTHEMA			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ECZEMA			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DERMATITIS ALLERGIC			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DERMAL CYST			
subjects affected / exposed	0 / 135 (0.00%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RASH MACULAR			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RASH MACULO-PAPULAR			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SKIN ULCER			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SUBCUTANEOUS EMPHYSEMA			

subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
ACUTE KIDNEY INJURY			
subjects affected / exposed	4 / 135 (2.96%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	1 / 5	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BLADDER CYST			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BLADDER TAMPONADE			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CALCULUS BLADDER			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CHRONIC KIDNEY DISEASE			
subjects affected / exposed	1 / 135 (0.74%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CYSTITIS HAEMORRHAGIC			
subjects affected / exposed	0 / 135 (0.00%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HAEMATURIA			
subjects affected / exposed	4 / 135 (2.96%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	1 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYDRONEPHROSIS			

subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RENAL FAILURE			
subjects affected / exposed	2 / 135 (1.48%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RENAL HAEMORRHAGE			
subjects affected / exposed	0 / 135 (0.00%)	0 / 78 (0.00%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RENAL IMPAIRMENT			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URETEROLITHIASIS			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URINARY RETENTION			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ARTHRITIS			
subjects affected / exposed	0 / 135 (0.00%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BACK PAIN			

subjects affected / exposed	1 / 135 (0.74%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HAEMATOMA MUSCLE			
subjects affected / exposed	0 / 135 (0.00%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LUMBAR SPINAL STENOSIS			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MUSCULAR WEAKNESS			
subjects affected / exposed	2 / 135 (1.48%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MUSCULOSKELETAL CHEST PAIN			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NECK PAIN			
subjects affected / exposed	0 / 135 (0.00%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SPINAL PAIN			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RHABDOMYOLYSIS			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
ARTHRITIS BACTERIAL			

subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ANAL ABSCESS			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ACUTE HEPATITIS B			
subjects affected / exposed	0 / 135 (0.00%)	0 / 78 (0.00%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
ABSCESS LIMB			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BACTERAEMIA			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BACTERIAL SEPSIS			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BILIARY SEPSIS			
subjects affected / exposed	0 / 135 (0.00%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BRONCHITIS			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			

subjects affected / exposed	3 / 135 (2.22%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CANDIDA SEPSIS			
subjects affected / exposed	0 / 135 (0.00%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CELLULITIS			
subjects affected / exposed	3 / 135 (2.22%)	2 / 78 (2.56%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	3 / 4	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CAMPYLOBACTER GASTROENTERITIS			
subjects affected / exposed	0 / 135 (0.00%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19 PNEUMONIA			
subjects affected / exposed	4 / 135 (2.96%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
CHOLANGITIS INFECTIVE			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CORONAVIRUS INFECTION			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
EAR INFECTION			
subjects affected / exposed	0 / 135 (0.00%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CHRONIC SINUSITIS			

subjects affected / exposed	0 / 135 (0.00%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CLOSTRIDIUM DIFFICILE COLITIS			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CLOSTRIDIUM DIFFICILE INFECTION			
subjects affected / exposed	2 / 135 (1.48%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ENDOCARDITIS			
subjects affected / exposed	0 / 135 (0.00%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ERYSIPELAS			
subjects affected / exposed	1 / 135 (0.74%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ESCHERICHIA BACTERAEMIA			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ESCHERICHIA INFECTION			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ESCHERICHIA SEPSIS			
subjects affected / exposed	2 / 135 (1.48%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTROENTERITIS			

subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTROENTERITIS VIRAL			
subjects affected / exposed	1 / 135 (0.74%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INFLUENZA			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INFECTED SKIN ULCER			
subjects affected / exposed	0 / 135 (0.00%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
KLEBSIELLA INFECTION			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
LOWER RESPIRATORY TRACT INFECTION VIRAL			
subjects affected / exposed	0 / 135 (0.00%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LOWER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	4 / 135 (2.96%)	2 / 78 (2.56%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	1 / 5	0 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NEUTROPENIC SEPSIS			
subjects affected / exposed	1 / 135 (0.74%)	1 / 78 (1.28%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	0 / 1	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ORCHITIS			

subjects affected / exposed	2 / 135 (1.48%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ORAL HERPES			
subjects affected / exposed	0 / 135 (0.00%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OSTEOMYELITIS			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMOCOCCAL SEPSIS			
subjects affected / exposed	0 / 135 (0.00%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA			
subjects affected / exposed	27 / 135 (20.00%)	7 / 78 (8.97%)	2 / 132 (1.52%)
occurrences causally related to treatment / all	8 / 38	2 / 14	1 / 2
deaths causally related to treatment / all	1 / 4	0 / 1	0 / 0
PNEUMONIA BACTERIAL			
subjects affected / exposed	2 / 135 (1.48%)	1 / 78 (1.28%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	2 / 2	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA FUNGAL			
subjects affected / exposed	0 / 135 (0.00%)	0 / 78 (0.00%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA LEGIONELLA			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA PSEUDOMONAL			

subjects affected / exposed	1 / 135 (0.74%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA STREPTOCOCCAL			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
POST PROCEDURAL PNEUMONIA			
subjects affected / exposed	0 / 135 (0.00%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA VIRAL			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PSEUDOMONAL BACTERAEMIA			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PSEUDOMONAL SEPSIS			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SEPTIC SHOCK			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
SEPSIS			
subjects affected / exposed	5 / 135 (3.70%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	2 / 6	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RESPIRATORY TRACT INFECTION			

subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PYELONEPHRITIS ACUTE			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PULMONARY SEPSIS			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
UROSEPSIS			
subjects affected / exposed	2 / 135 (1.48%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URINARY TRACT INFECTION			
subjects affected / exposed	6 / 135 (4.44%)	5 / 78 (6.41%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	1 / 11	2 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	2 / 135 (1.48%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SUBCUTANEOUS ABSCESS			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VIRAL INFECTION			
subjects affected / exposed	2 / 135 (1.48%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
STAPHYLOCOCCAL SEPSIS			

subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
WOUND INFECTION			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
DEHYDRATION			
subjects affected / exposed	3 / 135 (2.22%)	0 / 78 (0.00%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIABETES MELLITUS INADEQUATE CONTROL			
subjects affected / exposed	0 / 135 (0.00%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FAILURE TO THRIVE			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
HYPOGLYCAEMIA			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPOKALAEMIA			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPONATRAEMIA			
subjects affected / exposed	5 / 135 (3.70%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 7	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPOVOLAEMIA			

subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPOPHOSPHATAEMIA			
subjects affected / exposed	1 / 135 (0.74%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	7 / 7	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Ibrutinib	Chlorambucil Participants Crossed Over to Ibrutinib	Chlorambucil
Total subjects affected by non-serious adverse events			
subjects affected / exposed	134 / 135 (99.26%)	75 / 78 (96.15%)	120 / 132 (90.91%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
BASAL CELL CARCINOMA			
subjects affected / exposed	14 / 135 (10.37%)	5 / 78 (6.41%)	2 / 132 (1.52%)
occurrences (all)	22	6	3
SEBORRHOEIC KERATOSIS			
subjects affected / exposed	7 / 135 (5.19%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences (all)	8	1	0
SQUAMOUS CELL CARCINOMA			
subjects affected / exposed	8 / 135 (5.93%)	1 / 78 (1.28%)	2 / 132 (1.52%)
occurrences (all)	10	1	2
Vascular disorders			
HYPERTENSION			
subjects affected / exposed	37 / 135 (27.41%)	10 / 78 (12.82%)	0 / 132 (0.00%)
occurrences (all)	64	26	0
HYPOTENSION			
subjects affected / exposed	6 / 135 (4.44%)	4 / 78 (5.13%)	6 / 132 (4.55%)
occurrences (all)	6	8	8
General disorders and administration site conditions			
OEDEMA PERIPHERAL			
subjects affected / exposed	39 / 135 (28.89%)	15 / 78 (19.23%)	11 / 132 (8.33%)
occurrences (all)	71	21	11

FATIGUE			
subjects affected / exposed	55 / 135 (40.74%)	18 / 78 (23.08%)	51 / 132 (38.64%)
occurrences (all)	110	35	85
CHEST PAIN			
subjects affected / exposed	10 / 135 (7.41%)	4 / 78 (5.13%)	0 / 132 (0.00%)
occurrences (all)	11	6	0
ASTHENIA			
subjects affected / exposed	17 / 135 (12.59%)	9 / 78 (11.54%)	5 / 132 (3.79%)
occurrences (all)	20	12	7
PYREXIA			
subjects affected / exposed	36 / 135 (26.67%)	9 / 78 (11.54%)	14 / 132 (10.61%)
occurrences (all)	59	20	23
PERIPHERAL SWELLING			
subjects affected / exposed	7 / 135 (5.19%)	4 / 78 (5.13%)	2 / 132 (1.52%)
occurrences (all)	10	5	2
PAIN			
subjects affected / exposed	7 / 135 (5.19%)	3 / 78 (3.85%)	0 / 132 (0.00%)
occurrences (all)	7	4	0
Respiratory, thoracic and mediastinal disorders			
DYSPNOEA EXERTIONAL			
subjects affected / exposed	8 / 135 (5.93%)	4 / 78 (5.13%)	6 / 132 (4.55%)
occurrences (all)	8	4	7
DYSPNOEA			
subjects affected / exposed	21 / 135 (15.56%)	11 / 78 (14.10%)	13 / 132 (9.85%)
occurrences (all)	37	20	16
COUGH			
subjects affected / exposed	52 / 135 (38.52%)	19 / 78 (24.36%)	20 / 132 (15.15%)
occurrences (all)	79	25	24
EPISTAXIS			
subjects affected / exposed	21 / 135 (15.56%)	7 / 78 (8.97%)	5 / 132 (3.79%)
occurrences (all)	26	8	8
NASAL CONGESTION			
subjects affected / exposed	8 / 135 (5.93%)	3 / 78 (3.85%)	2 / 132 (1.52%)
occurrences (all)	9	3	2
OROPHARYNGEAL PAIN			

subjects affected / exposed	16 / 135 (11.85%)	3 / 78 (3.85%)	5 / 132 (3.79%)
occurrences (all)	23	3	5
PLEURAL EFFUSION			
subjects affected / exposed	11 / 135 (8.15%)	4 / 78 (5.13%)	1 / 132 (0.76%)
occurrences (all)	17	5	1
PRODUCTIVE COUGH			
subjects affected / exposed	8 / 135 (5.93%)	3 / 78 (3.85%)	2 / 132 (1.52%)
occurrences (all)	8	3	2
Psychiatric disorders			
ANXIETY			
subjects affected / exposed	16 / 135 (11.85%)	4 / 78 (5.13%)	2 / 132 (1.52%)
occurrences (all)	21	5	2
INSOMNIA			
subjects affected / exposed	18 / 135 (13.33%)	6 / 78 (7.69%)	9 / 132 (6.82%)
occurrences (all)	22	11	11
DEPRESSION			
subjects affected / exposed	11 / 135 (8.15%)	7 / 78 (8.97%)	5 / 132 (3.79%)
occurrences (all)	11	10	5
Investigations			
WEIGHT DECREASED			
subjects affected / exposed	34 / 135 (25.19%)	12 / 78 (15.38%)	16 / 132 (12.12%)
occurrences (all)	47	16	16
PLATELET COUNT DECREASED			
subjects affected / exposed	7 / 135 (5.19%)	1 / 78 (1.28%)	6 / 132 (4.55%)
occurrences (all)	62	6	10
BLOOD CREATININE INCREASED			
subjects affected / exposed	11 / 135 (8.15%)	5 / 78 (6.41%)	2 / 132 (1.52%)
occurrences (all)	16	5	3
Injury, poisoning and procedural complications			
CONTUSION			
subjects affected / exposed	26 / 135 (19.26%)	4 / 78 (5.13%)	2 / 132 (1.52%)
occurrences (all)	40	4	2
FALL			
subjects affected / exposed	25 / 135 (18.52%)	9 / 78 (11.54%)	3 / 132 (2.27%)
occurrences (all)	45	14	5
PROCEDURAL PAIN			

subjects affected / exposed	8 / 135 (5.93%)	1 / 78 (1.28%)	1 / 132 (0.76%)
occurrences (all)	8	1	1
SKIN ABRASION			
subjects affected / exposed	9 / 135 (6.67%)	1 / 78 (1.28%)	1 / 132 (0.76%)
occurrences (all)	10	2	1
SKIN LACERATION			
subjects affected / exposed	5 / 135 (3.70%)	4 / 78 (5.13%)	4 / 132 (3.03%)
occurrences (all)	10	4	5
TRAUMATIC HAEMATOMA			
subjects affected / exposed	6 / 135 (4.44%)	4 / 78 (5.13%)	2 / 132 (1.52%)
occurrences (all)	9	5	2
Cardiac disorders			
ATRIAL FIBRILLATION			
subjects affected / exposed	21 / 135 (15.56%)	6 / 78 (7.69%)	0 / 132 (0.00%)
occurrences (all)	23	7	0
PALPITATIONS			
subjects affected / exposed	11 / 135 (8.15%)	5 / 78 (6.41%)	1 / 132 (0.76%)
occurrences (all)	13	6	1
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	25 / 135 (18.52%)	10 / 78 (12.82%)	16 / 132 (12.12%)
occurrences (all)	29	14	22
HEADACHE			
subjects affected / exposed	19 / 135 (14.07%)	9 / 78 (11.54%)	13 / 132 (9.85%)
occurrences (all)	32	17	23
HYPOAESTHESIA			
subjects affected / exposed	7 / 135 (5.19%)	0 / 78 (0.00%)	1 / 132 (0.76%)
occurrences (all)	10	0	1
PARAESTHESIA			
subjects affected / exposed	7 / 135 (5.19%)	4 / 78 (5.13%)	1 / 132 (0.76%)
occurrences (all)	8	6	1
SYNCOPE			
subjects affected / exposed	7 / 135 (5.19%)	2 / 78 (2.56%)	2 / 132 (1.52%)
occurrences (all)	7	4	2
Blood and lymphatic system disorders			

INCREASED TENDENCY TO BRUISE			
subjects affected / exposed	22 / 135 (16.30%)	8 / 78 (10.26%)	5 / 132 (3.79%)
occurrences (all)	29	8	5
ANAEMIA			
subjects affected / exposed	33 / 135 (24.44%)	14 / 78 (17.95%)	25 / 132 (18.94%)
occurrences (all)	86	29	53
SPONTANEOUS HAEMATOMA			
subjects affected / exposed	7 / 135 (5.19%)	4 / 78 (5.13%)	0 / 132 (0.00%)
occurrences (all)	13	4	0
THROMBOCYTOPENIA			
subjects affected / exposed	20 / 135 (14.81%)	8 / 78 (10.26%)	17 / 132 (12.88%)
occurrences (all)	49	9	29
NEUTROPENIA			
subjects affected / exposed	24 / 135 (17.78%)	7 / 78 (8.97%)	28 / 132 (21.21%)
occurrences (all)	43	17	50
IRON DEFICIENCY ANAEMIA			
subjects affected / exposed	6 / 135 (4.44%)	4 / 78 (5.13%)	0 / 132 (0.00%)
occurrences (all)	9	4	0
Eye disorders			
CATARACT			
subjects affected / exposed	22 / 135 (16.30%)	5 / 78 (6.41%)	2 / 132 (1.52%)
occurrences (all)	27	7	2
CONJUNCTIVAL HAEMORRHAGE			
subjects affected / exposed	14 / 135 (10.37%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences (all)	14	1	0
DRY EYE			
subjects affected / exposed	27 / 135 (20.00%)	5 / 78 (6.41%)	6 / 132 (4.55%)
occurrences (all)	40	6	7
EYE IRRITATION			
subjects affected / exposed	13 / 135 (9.63%)	4 / 78 (5.13%)	5 / 132 (3.79%)
occurrences (all)	23	7	5
EYE PAIN			
subjects affected / exposed	10 / 135 (7.41%)	3 / 78 (3.85%)	2 / 132 (1.52%)
occurrences (all)	14	4	2
LACRIMATION INCREASED			

subjects affected / exposed	20 / 135 (14.81%)	6 / 78 (7.69%)	8 / 132 (6.06%)
occurrences (all)	47	10	10
VITREOUS FLOATERS			
subjects affected / exposed	13 / 135 (9.63%)	2 / 78 (2.56%)	7 / 132 (5.30%)
occurrences (all)	19	4	8
VISUAL ACUITY REDUCED			
subjects affected / exposed	17 / 135 (12.59%)	3 / 78 (3.85%)	3 / 132 (2.27%)
occurrences (all)	24	3	3
VISION BLURRED			
subjects affected / exposed	23 / 135 (17.04%)	8 / 78 (10.26%)	11 / 132 (8.33%)
occurrences (all)	33	11	11
PHOTOPHOBIA			
subjects affected / exposed	8 / 135 (5.93%)	4 / 78 (5.13%)	2 / 132 (1.52%)
occurrences (all)	10	8	2
Gastrointestinal disorders			
ABDOMINAL PAIN UPPER			
subjects affected / exposed	10 / 135 (7.41%)	4 / 78 (5.13%)	6 / 132 (4.55%)
occurrences (all)	13	6	7
ABDOMINAL PAIN			
subjects affected / exposed	22 / 135 (16.30%)	6 / 78 (7.69%)	13 / 132 (9.85%)
occurrences (all)	30	8	13
HAEMORRHOIDS			
subjects affected / exposed	8 / 135 (5.93%)	2 / 78 (2.56%)	3 / 132 (2.27%)
occurrences (all)	9	2	3
GASTROOESOPHAGEAL REFLUX DISEASE			
subjects affected / exposed	17 / 135 (12.59%)	3 / 78 (3.85%)	2 / 132 (1.52%)
occurrences (all)	17	3	2
DYSPEPSIA			
subjects affected / exposed	21 / 135 (15.56%)	11 / 78 (14.10%)	3 / 132 (2.27%)
occurrences (all)	26	11	3
DIARRHOEA			
subjects affected / exposed	67 / 135 (49.63%)	27 / 78 (34.62%)	22 / 132 (16.67%)
occurrences (all)	145	60	33
CONSTIPATION			

subjects affected / exposed	30 / 135 (22.22%)	12 / 78 (15.38%)	21 / 132 (15.91%)
occurrences (all)	48	14	21
APHTHOUS ULCER			
subjects affected / exposed	7 / 135 (5.19%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences (all)	7	0	0
MOUTH ULCERATION			
subjects affected / exposed	9 / 135 (6.67%)	2 / 78 (2.56%)	0 / 132 (0.00%)
occurrences (all)	9	2	0
NAUSEA			
subjects affected / exposed	43 / 135 (31.85%)	13 / 78 (16.67%)	52 / 132 (39.39%)
occurrences (all)	60	22	75
VOMITING			
subjects affected / exposed	29 / 135 (21.48%)	10 / 78 (12.82%)	27 / 132 (20.45%)
occurrences (all)	37	17	42
STOMATITIS			
subjects affected / exposed	13 / 135 (9.63%)	2 / 78 (2.56%)	5 / 132 (3.79%)
occurrences (all)	22	3	5
Hepatobiliary disorders			
HEPATIC FUNCTION ABNORMAL			
subjects affected / exposed	7 / 135 (5.19%)	3 / 78 (3.85%)	0 / 132 (0.00%)
occurrences (all)	24	11	0
Skin and subcutaneous tissue disorders			
DECUBITUS ULCER			
subjects affected / exposed	2 / 135 (1.48%)	5 / 78 (6.41%)	0 / 132 (0.00%)
occurrences (all)	2	8	0
ACTINIC KERATOSIS			
subjects affected / exposed	12 / 135 (8.89%)	2 / 78 (2.56%)	2 / 132 (1.52%)
occurrences (all)	19	2	2
DRY SKIN			
subjects affected / exposed	12 / 135 (8.89%)	4 / 78 (5.13%)	3 / 132 (2.27%)
occurrences (all)	13	7	3
PETECHIAE			
subjects affected / exposed	7 / 135 (5.19%)	5 / 78 (6.41%)	1 / 132 (0.76%)
occurrences (all)	8	5	1
NIGHT SWEATS			

subjects affected / exposed	14 / 135 (10.37%)	3 / 78 (3.85%)	10 / 132 (7.58%)
occurrences (all)	16	3	12
ECCHYMOSIS			
subjects affected / exposed	3 / 135 (2.22%)	9 / 78 (11.54%)	1 / 132 (0.76%)
occurrences (all)	5	12	1
PRURITUS			
subjects affected / exposed	19 / 135 (14.07%)	5 / 78 (6.41%)	7 / 132 (5.30%)
occurrences (all)	29	10	13
SKIN LESION			
subjects affected / exposed	11 / 135 (8.15%)	4 / 78 (5.13%)	1 / 132 (0.76%)
occurrences (all)	13	5	1
RASH MACULO-PAPULAR			
subjects affected / exposed	13 / 135 (9.63%)	6 / 78 (7.69%)	5 / 132 (3.79%)
occurrences (all)	19	17	7
PURPURA			
subjects affected / exposed	7 / 135 (5.19%)	2 / 78 (2.56%)	0 / 132 (0.00%)
occurrences (all)	8	3	0
RASH			
subjects affected / exposed	9 / 135 (6.67%)	3 / 78 (3.85%)	3 / 132 (2.27%)
occurrences (all)	22	3	8
RASH ERYTHEMATOUS			
subjects affected / exposed	17 / 135 (12.59%)	4 / 78 (5.13%)	6 / 132 (4.55%)
occurrences (all)	30	4	6
Renal and urinary disorders			
POLLAKIURIA			
subjects affected / exposed	8 / 135 (5.93%)	0 / 78 (0.00%)	4 / 132 (3.03%)
occurrences (all)	8	0	4
HAEMATURIA			
subjects affected / exposed	13 / 135 (9.63%)	6 / 78 (7.69%)	3 / 132 (2.27%)
occurrences (all)	14	8	3
CHRONIC KIDNEY DISEASE			
subjects affected / exposed	8 / 135 (5.93%)	0 / 78 (0.00%)	1 / 132 (0.76%)
occurrences (all)	12	0	1
ACUTE KIDNEY INJURY			
subjects affected / exposed	9 / 135 (6.67%)	2 / 78 (2.56%)	0 / 132 (0.00%)
occurrences (all)	13	2	0

Musculoskeletal and connective tissue disorders			
JOINT SWELLING			
subjects affected / exposed	7 / 135 (5.19%)	3 / 78 (3.85%)	1 / 132 (0.76%)
occurrences (all)	9	4	1
BACK PAIN			
subjects affected / exposed	27 / 135 (20.00%)	10 / 78 (12.82%)	9 / 132 (6.82%)
occurrences (all)	38	12	9
ARTHRALGIA			
subjects affected / exposed	41 / 135 (30.37%)	22 / 78 (28.21%)	10 / 132 (7.58%)
occurrences (all)	75	40	18
MUSCLE SPASMS			
subjects affected / exposed	28 / 135 (20.74%)	13 / 78 (16.67%)	7 / 132 (5.30%)
occurrences (all)	40	20	7
MUSCULAR WEAKNESS			
subjects affected / exposed	9 / 135 (6.67%)	2 / 78 (2.56%)	2 / 132 (1.52%)
occurrences (all)	10	2	2
MYALGIA			
subjects affected / exposed	11 / 135 (8.15%)	3 / 78 (3.85%)	4 / 132 (3.03%)
occurrences (all)	17	3	6
NECK PAIN			
subjects affected / exposed	8 / 135 (5.93%)	2 / 78 (2.56%)	4 / 132 (3.03%)
occurrences (all)	11	3	5
OSTEOPOROSIS			
subjects affected / exposed	8 / 135 (5.93%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences (all)	8	1	0
PAIN IN EXTREMITY			
subjects affected / exposed	23 / 135 (17.04%)	8 / 78 (10.26%)	7 / 132 (5.30%)
occurrences (all)	27	10	7
Infections and infestations			
BRONCHITIS			
subjects affected / exposed	17 / 135 (12.59%)	5 / 78 (6.41%)	4 / 132 (3.03%)
occurrences (all)	34	7	5
COVID-19			
subjects affected / exposed	15 / 135 (11.11%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences (all)	18	0	0
CELLULITIS			

subjects affected / exposed	13 / 135 (9.63%)	3 / 78 (3.85%)	1 / 132 (0.76%)
occurrences (all)	17	3	1
EYE INFECTION			
subjects affected / exposed	8 / 135 (5.93%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences (all)	9	1	0
CYSTITIS			
subjects affected / exposed	7 / 135 (5.19%)	1 / 78 (1.28%)	0 / 132 (0.00%)
occurrences (all)	11	2	0
CONJUNCTIVITIS			
subjects affected / exposed	22 / 135 (16.30%)	8 / 78 (10.26%)	3 / 132 (2.27%)
occurrences (all)	37	11	3
FOLLICULITIS			
subjects affected / exposed	7 / 135 (5.19%)	0 / 78 (0.00%)	0 / 132 (0.00%)
occurrences (all)	7	0	0
NASOPHARYNGITIS			
subjects affected / exposed	15 / 135 (11.11%)	5 / 78 (6.41%)	6 / 132 (4.55%)
occurrences (all)	27	11	6
INFLUENZA			
subjects affected / exposed	7 / 135 (5.19%)	7 / 78 (8.97%)	4 / 132 (3.03%)
occurrences (all)	11	9	4
HERPES ZOSTER			
subjects affected / exposed	13 / 135 (9.63%)	1 / 78 (1.28%)	7 / 132 (5.30%)
occurrences (all)	14	1	8
SKIN INFECTION			
subjects affected / exposed	13 / 135 (9.63%)	1 / 78 (1.28%)	3 / 132 (2.27%)
occurrences (all)	16	1	3
SINUSITIS			
subjects affected / exposed	9 / 135 (6.67%)	3 / 78 (3.85%)	1 / 132 (0.76%)
occurrences (all)	14	3	1
RHINITIS			
subjects affected / exposed	7 / 135 (5.19%)	0 / 78 (0.00%)	2 / 132 (1.52%)
occurrences (all)	14	0	2
PHARYNGITIS			
subjects affected / exposed	8 / 135 (5.93%)	2 / 78 (2.56%)	0 / 132 (0.00%)
occurrences (all)	9	2	0
PNEUMONIA			

subjects affected / exposed	12 / 135 (8.89%)	5 / 78 (6.41%)	3 / 132 (2.27%)
occurrences (all)	16	9	3
RESPIRATORY TRACT INFECTION			
subjects affected / exposed	6 / 135 (4.44%)	4 / 78 (5.13%)	2 / 132 (1.52%)
occurrences (all)	8	9	3
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	38 / 135 (28.15%)	20 / 78 (25.64%)	23 / 132 (17.42%)
occurrences (all)	73	31	30
URINARY TRACT INFECTION			
subjects affected / exposed	29 / 135 (21.48%)	10 / 78 (12.82%)	10 / 132 (7.58%)
occurrences (all)	87	14	15
Metabolism and nutrition disorders			
HYPERURICAEMIA			
subjects affected / exposed	23 / 135 (17.04%)	2 / 78 (2.56%)	1 / 132 (0.76%)
occurrences (all)	37	5	1
DECREASED APPETITE			
subjects affected / exposed	24 / 135 (17.78%)	7 / 78 (8.97%)	19 / 132 (14.39%)
occurrences (all)	38	10	26
HYPOCALCAEMIA			
subjects affected / exposed	7 / 135 (5.19%)	1 / 78 (1.28%)	3 / 132 (2.27%)
occurrences (all)	25	1	3
IRON DEFICIENCY			
subjects affected / exposed	12 / 135 (8.89%)	5 / 78 (6.41%)	0 / 132 (0.00%)
occurrences (all)	14	5	0
HYPONATRAEMIA			
subjects affected / exposed	7 / 135 (5.19%)	5 / 78 (6.41%)	1 / 132 (0.76%)
occurrences (all)	15	10	1
HYPOKALAEMIA			
subjects affected / exposed	16 / 135 (11.85%)	6 / 78 (7.69%)	2 / 132 (1.52%)
occurrences (all)	26	9	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 May 2014	• Provide a clarification to broaden the eligible timeframe to receive second-line PCI-32765 by removing the 12 month time limit after last chlorambucil dose to obtain second-line PCI-32765 • Allow subjects receiving non-PCI-32765 as second-line therapy are now eligible to receive next-line PCI-32765 but must have recovered from any toxicity from non-PCI-32765 therapy prior to receiving PCI-32765 therapy. • Update safety language and to ensure consistency across PCI-32765 protocols. • All AEs will be collected to strengthen safety monitoring.
29 September 2016	• Revised study duration • Clarified assessment for MRD-possitive and MRD-negative subjects. • Aligned current protocol language with updated protocol template. • Updated safety language per updated Investigator's Brochure version 10. • Allowed for discontinuation and re-initiation of ibrutinib in subjects receiving second-line ibrutinib who reach MRD-negative status.
12 July 2018	• Revised study duration • Revised study objective • Revised study design: o Subjects randomized to first-line chlorambucil once progressed post their first-line therapy will exit the study and the initiation of second-line treatment with ibrutinib will not be available for these subjects on Study 1116. Note, with the implementation of Amendment 3, first-line chlorambucil subjects, who have withdrawn partial consent and are being followed up for overall survival only, will also exit the study. o Subjects randomized to first-line ibrutinib who have withdrawn partial consent and are being followed up for overall survival only will continue their participation in the study. o Subjects randomized to first-line chlorambucil who are receiving ibrutinib on study will exit and will be given the opportunity to enroll into a separate long-term ibrutinib extension study if they meet the eligibility criteria of that study or can continue therapy from commercial source. o Subjects who were randomized to ibrutinib and have progressed will continue to be followed in the study. • Revised second-line ibrutinib criteria. • Revised first-line therapy continuation. • Revised statistical methods. NOTE: after implementation of amendment 3, at a median follow-up of 60 months, post-PD follow-up for Chlorambucil arm was terminated. Subjects in the chlorambucil arm were to exit the study after PD, and those who had crossed over to next-line ibrutinib had the opportunity to roll over to another long-term ibrutinib study (PCYC-1145-CA).
10 October 2022	• Updated the recommendations that are intended to improve tolerability for continued ibrutinib treatment in the study protocol. • Update risks to Cardiac Arrhythmia section.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported