Clinical trial results:
Randomized, Double-blind, Placebo-controlled Phase 3 Study of Ibrutinib, a Bruton's Tyrosine Kinase (BTK) Inhibitor, in Combination with Bendamustine and Rituximab (BR) in Subjects With Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Summary

EudraCT number	2012-000600-15
Trial protocol	SE BE ES PT GB DE GR PL
Global end of trial date	23 January 2019

Results information

Result version number	v1 (current)
This version publication date	08 February 2020
First version publication date	08 February 2020

Trial information

Trial identification

Sponsor protocol code	PCI-32765CLL3001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01611090
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen Research & Development, LLC
Sponsor organisation address	920 Route 202, Raritan, United States, NJ 08869
Public contact	Janssen Research & Development, LLC, Clinical Registry Group, ClinicalTrialsEU@its.jnj.com
Scientific contact	Janssen Research & Development, LLC, Clinical Registry Group, ClinicalTrialsEU@its.jnj.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	23 January 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 January 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of the study was to determine whether the addition of ibrutinib to bendamustine/rituximab (BR) significantly improved progression-free survival (PFS) compared with BR in subjects with relapsed or refractory chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL).

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practices and applicable regulatory requirements. The safety assessments included adverse events, clinical laboratory tests (hematology and chemistry), vital signs, physical examination results and electrocardiograms.

Background therapy:

Bendamustine hydrochloride and Rituximab

Evidence for comparator: -

Actual start date of recruitment	19 September 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 6
Country: Number of subjects enrolled	Belgium: 28
Country: Number of subjects enrolled	Brazil: 22
Country: Number of subjects enrolled	Canada: 62
Country: Number of subjects enrolled	Colombia: 1
Country: Number of subjects enrolled	Czech Republic: 23
Country: Number of subjects enrolled	Germany: 21
Country: Number of subjects enrolled	Spain: 18
Country: Number of subjects enrolled	France: 27
Country: Number of subjects enrolled	United Kingdom: 14
Country: Number of subjects enrolled	Greece: 17
Country: Number of subjects enrolled	Israel: 26
Country: Number of subjects enrolled	Korea, Republic of: 1
Country: Number of subjects enrolled	Mexico: 3
Country: Number of subjects enrolled	Poland: 39
Country: Number of subjects enrolled	Portugal: 19
Country: Number of subjects enrolled	Russian Federation: 100
Country: Number of subjects enrolled	Sweden: 6

Country: Number of subjects enrolled	Turkey: 51
Country: Number of subjects enrolled	Ukraine: 30
Country: Number of subjects enrolled	United States: 64
Worldwide total number of subjects	578
EEA total number of subjects	212

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)	305
From 65 to 84 years	272
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 578 subjects were enrolled in the study. Among these, 289 subjects were randomized in each ibrutinib + bendamustine/rituximab (BR) treatment group and placebo+BR treatment group.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Ibrutinib+BR

Arm description:

Subjects received ibrutinib 420 milligram (mg) (3 * 140 mg capsules) orally once daily starting on Cycle 1 Day 2 for a maximum of 6 cycles (each cycle of 28 days except Cycle 1 which was of 29 days) along with BR. After 6 cycles ibrutinib alone was administered until disease progression or unacceptable toxicity.

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

Dosage and administration details:

Subjects received ibrutinib 420 milligram (mg) (3 * 140 mg capsules) oral once daily.

Arm title	Placebo+BR

Arm description:

Subjects received placebo (3 capsules) orally once daily starting on Cycle 1 Day 2 for a maximum of 6 cycles (each cycle of 28 days except Cycle 1 which was of 29 days) along with BR. After 6 cycles placebo alone was administered until disease progression or unacceptable toxicity.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received placebo (3 capsules) oral once daily.

Number of subjects in period 1	Ibrutinib+BR	Placebo+BR
Started	289	289
Crossover: Placebo to Ibrutinib	0 [1]	183 [2]
Treated	287	287
Completed	259	260
Not completed	30	29
Consent withdrawn by subject	22	26
Lost to follow-up	8	3

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: Only 183 subjects from Placebo+BR group were crossed over to Ibrutinib group.

[2] - 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: Only 183 subjects from Placebo+BR group were crossed over to Ibrutinib group.

Baseline characteristics

Reporting groups	
Reporting group title	Ibrutinib+BR
Reporting group description:	
Subjects received ibrutinib 420 milligram (mg) (3 * 140 mg capsules) orally once daily starting on Cycle 1 Day 2 for a maximum of 6 cycles (each cycle of 28 days except Cycle 1 which was of 29 days) along with BR. After 6 cycles ibrutinib alone was administered until disease progression or unacceptable toxicity.	
Reporting group title	Placebo+BR
Reporting group description:	
Subjects received placebo (3 capsules) orally once daily starting on Cycle 1 Day 2 for a maximum of 6 cycles (each cycle of 28 days except Cycle 1 which was of 29 days) along with BR. After 6 cycles placebo alone was administered until disease progression or unacceptable toxicity.	

Reporting group values	Ibrutinib+BR	Placebo+BR	Total
Number of subjects	289	289	578
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	145	160	305
From 65 to 84 years	143	129	272
85 years and over	1	0	1
Title for AgeContinuous Units: years			
arithmetic mean	63.7	63.3	
standard deviation	± 9.82	± 9.3	-
Title for Gender Units: subjects			
Female	96	100	196
Male	193	189	382

End points

End points reporting groups

Reporting group title	Ibrutinib+BR

Reporting group description:

Subjects received ibrutinib 420 milligram (mg) (3 * 140 mg capsules) orally once daily starting on Cycle 1 Day 2 for a maximum of 6 cycles (each cycle of 28 days except Cycle 1 which was of 29 days) along with BR. After 6 cycles ibrutinib alone was administered until disease progression or unacceptable toxicity.

Reporting group title	Placebo+BR

Reporting group description:

Subjects received placebo (3 capsules) orally once daily starting on Cycle 1 Day 2 for a maximum of 6 cycles (each cycle of 28 days except Cycle 1 which was of 29 days) along with BR. After 6 cycles placebo alone was administered until disease progression or unacceptable toxicity.

Primary: Progression-free Survival (PFS)

End point title	Progression-free Survival (PFS)

End point description:

PFS was defined as the interval between the date of randomization and the date of disease progression or death, whichever was first reported. IWCLL 2008 criteria for PD: New enlarged nodes >1.5 cm, new hepatomegaly or splenomegaly, or other new organ infiltrates, bone lesion, ascites, or pleural effusion confirmed due to chronic lymphocytic leukemia (CLL); >=50% increase in existing lymph nodes; >=50% increase in enlargement of liver or spleen; >=50% increase from baseline in lymphocyte count (and to >=5*10^9/L) or >=50% increase from nadir count confirmed on >=2 serial assessments if absolute lymphocyte count (ALC) >=30,000 per microliter and lymphocyte doubling time is rapid, unless considered treatment-related lymphocytosis; new cytopenia (Hemoglobin b [Hgb] or platelets) attributable to CLL; and transformation to a more aggressive histology. ITT population included. Here, 99999 indicates that upper limit of CI was not evaluable due to insufficient number of events.

End point type	Primary

End point timeframe:

Up to 5 years

End point values	Ibrutinib+BR	Placebo+BR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	289	289		
Units: Months				
median (confidence interval 95%)	65.12 (55.43 to 99999)	14.32 (13.86 to 16.62)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Ibrutinib+BR v Placebo+BR

Number of subjects included in analysis	578
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.229
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.183
upper limit	0.286

Secondary: Overall Response Rate (ORR)

End point title	Overall Response Rate (ORR)

End point description:

ORR defined as number of subjects achieving a complete response (CR), complete response with incomplete marrow recovery (CRi), nodular partial response (nPR) or partial response (PR). IWCLL 2008 criteria: CR- No lymphadenopathy and hepatosplenomegaly, no constitutional symptoms, neutrophils >1.5*10^9/liter (L), platelets >100*10^9/L, Hgb >11 gram per deciliter (g/dL) and absolute lymphocyte count <4000/microliter (mcL); CRi- CR with incomplete recovery of bone marrow; nPR- subjects meet criteria for CR, but the bone marrow biopsy shows B-lymphoid nodules, may represent a clonal infiltrate; PR-2 of the following when abnormal at baseline: >=50% decrease in ALC, >=50% decrease in sum products of up to 6 lymph nodes, >=50% decrease in enlargement of spleen or liver; and 1 of the following: neutrophils >1.5*10^9/L, Platelets >100*10^9/L and Hgb>11 g/dL or >=50% improvement over baseline in any of these; no new enlarged nodes or new hepatosplenomegaly. ITT population included.

End point type	Secondary

End point timeframe:

Up to 5 years

End point values	Ibrutinib+BR	Placebo+BR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	289	289		
Units: Percentage of subjects				
number (not applicable)	87.2	66.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the interval between the date of randomization and the date of death from any cause. ITT population included all subjects randomized into the study regardless of treatment actually received. Here, '99999' indicates that the data was not estimable due to insufficient number of events.

End point type	Secondary

End point timeframe:

Up to 5 years

End point values	Ibrutinib+BR	Placebo+BR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	289	289		
Units: Months				
median (confidence interval 95%)	99999 (70.93 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Minimal Residual Disease (MRD)-negative Response

End point title	Percentage of Subjects with Minimal Residual Disease (MRD)-negative Response

End point description:

MRD-negative response was defined as the percentage of subjects who reach MRD negative disease status (less than 1 chronic lymphocytic leukemia [CLL] cell per 10,000 leukocytes) in either bone marrow or peripheral blood. All randomized subjects were included in this analysis. Subjects with missing MRD data were considered non-responders. ITT population included all subjects randomized into the study regardless of treatment actually received.

End point type	Secondary

End point timeframe:

Up to 5 years

End point values	Ibrutinib+BR	Placebo+BR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	289	289		
Units: Percentage of subjects				
number (not applicable)	28.7	5.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Sustained Hematologic Improvement

End point title	Percentage of Subjects with Sustained Hematologic Improvement

End point description:

Sustained hematologic improvement was defined as hematological improvement that was sustained continuously for greater than or equal to (>=) 56 days without blood transfusion or growth factors: 1) Platelet counts greater than (>)100* 109/liter (L) if baseline less than or equal to (<=) 100*109/L or increase >= 50 percent (%) over baseline; 2) Hemoglobin >11 gram per deciliters (g/dL) if baseline <= 11 g/dL or increase >= 2 g/dL over baseline. ITT population included all subjects randomized into the study regardless of treatment actually received.

End point type	Secondary

End point timeframe:

At disease progression, up to 5 years after the last subject was randomized

End point values	Ibrutinib+BR	Placebo+BR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	289	289		
Units: Percentage of subjects				
number (not applicable)				
Hemoglobin	36.7	29.1		
Platelets	30.8	21.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Median Time to Clinically Meaningful Improvement in FACIT-Fatigue Scale

End point title	Median Time to Clinically Meaningful Improvement in FACIT-Fatigue Scale

End point description:

Time to improvement is defined as the time interval (months) from randomization to the first observation of improvement. FACIT-Fatigue is an instrument for use as a measure of the effect of fatigue in patients with cancer and other chronic diseases. Responses to the 13-item FACIT Fatigue Scale are reported on a 5point categorical response scale ranging from 0 (not at all) to 4 (very much). The sum of all responses resulted in the FACIT-Fatigue score for a total possible score of 0 (worst score) to 52 (best score). ITT population included all subjects randomized into the study regardless of treatment actually received.

End point type	Secondary

End point timeframe:

Up to 2 years

End point values	Ibrutinib+BR	Placebo+BR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	289	289		
Units: Months				
number (confidence interval 95%)	6.5 (4.7 to 10.7)	4.6 (2.8 to 6.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Clinically Relevant Shifts in Disease-Related Symptoms

End point title	Number of Subjects With Clinically Relevant Shifts in Disease-Related Symptoms

End point description:

The disease-related symptoms included fatigue, weight loss, fevers, night sweats, abdominal discomfort/splenomegaly and anorexia. ITT population included all subjects randomized into the study regardless of treatment actually received.

End point type	Secondary

End point timeframe:

From the date of randomization to disease progression (Up to 2 years)

End point values	Ibrutinib+BR	Placebo+BR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	289	289		
Units: Subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects who Received Subsequent Antineoplastic Therapy

End point title	Number of Subjects who Received Subsequent Antineoplastic Therapy

End point description:

Number of subjects who received subsequent antineoplastic therapy was reported. Safety analysis set included all the randomized subjects who received at least 1 dose of study drug or placebo.

End point type	Secondary

End point timeframe:

Up to 5 years

End point values	Ibrutinib+BR	Placebo+BR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	287	287		
Units: Subjects	52	61		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Beta2 Microglobulin at End of Treatment (EOT)

End point title	Change from Baseline in Beta2 Microglobulin at End of Treatment (EOT)

End point description:

Change from baseline in beta2 microglobulin at end of treatment at time of primary analysis was reported. ITT population included all subjects randomized into the study regardless of treatment actually received. Here, 'N' (number of subjects analyzed) signifies number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline to EOT (Up to 2 years)

End point values	Ibrutinib+BR	Placebo+BR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	106		
Units: milligram per liter (mg/L)				
arithmetic mean (standard deviation)	-0.46 (± 1.77)	-0.23 (± 2.08)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in FACIT-Fatigue Scale at End of Treatment

End point title	Change from Baseline in FACIT-Fatigue Scale at End of Treatment

End point description:

FACIT-Fatigue is an instrument for use as a measure of the effect of fatigue in patients with cancer and other chronic diseases. Responses to the 13-item FACIT Fatigue Scale are reported on a 5point categorical response scale ranging from 0 (not at all) to 4 (very much). The sum of all responses resulted in the FACIT-Fatigue score for a total possible score of 0 (worst score) to 52 (best score). ITT population included all subjects randomized into the study regardless of treatment actually received. Here, 'N' (number of subjects analyzed) signifies number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline to EOT (up to 2 years)

End point values	Ibrutinib+BR	Placebo+BR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	104		
Units: Units on a scale				
arithmetic mean (standard deviation)	-0.9 (± 11.22)	0.0 (± 11.01)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in EORTC QLQ-C30 Physical Functioning Score at End of Treatment

End point title	Change from Baseline in EORTC QLQ-C30 Physical Functioning Score at End of Treatment

End point description:

EORTC QLQ-C30 Physical Functioning Score is a questionnaire to assess quality of life of cancer patients. It is composed of 30 items, multi-item measure (28 items) and 2 single-item measures. For the multiple item measure, 4-point scale is used and the score for each item range from "1 = not at all" to "4 = very much". Higher scores indicate worsening. The 2 single-item measure involves question about the overall health and overall quality of life which was rated on a 7-point scale ranging from "1 = very poor" to "7 = excellent". Lower scores indicate worsening. All scale and item scores were linearly transformed to be in range from 0-100. A higher score represents a higher (better) level of functioning, or a higher (worse) level of symptoms. ITT population included all subjects randomized into the study regardless of treatment actually received. Here, 'N' (number of subjects analyzed) signifies number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline to EOT (up to 2 years)

End point values	Ibrutinib+BR	Placebo+BR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	104		
Units: Units on a scale				
arithmetic mean (standard deviation)	-2.1 (± 16.34)	-4.1 (± 22.52)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in EORTC QLQ-CLL 16 Domain Scores at End of Treatment

End point title	Change from Baseline in EORTC QLQ-CLL 16 Domain Scores at End of Treatment

End point description:

The EORTC QLQ-CLL 16 is a 16-item disease specific module that comprises 5 domains of patient-reported health status important in CLL. There are three multi-item scales that include fatigue (2 items), treatment side effects and disease symptoms (8 items), and infection (4 items), and 2 single-item scales on social activities and future health worries. Responses are measured on a 4 point scale ranging from 1 (not at all) to 4 (very much). ITT population included all subjects randomized into the study regardless of treatment actually received. Here, 'N' (number of subjects analyzed) signifies number of subjects evaluable for this endpoint. Here, 'n' signifies the number of subjects analyzed at a specified time point.

End point type	Secondary

End point timeframe:

Baseline to EOT (up to 2 years)

End point values	Ibrutinib+BR	Placebo+BR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	104		
Units: Units on the scale				
arithmetic mean (standard deviation)				
Lost weight (n=38,104)	0.1 (± 0.86)	0.0 (± 0.74)		
Dry mouth (n=38,104)	0.3 (± 0.96)	0.1 (± 0.85)		
Bruises (n=38,104)	0.1 (± 0.61)	0.0 (± 0.65)		
Abdominal discomfort (n=37,104)	0.1 (± 0.81)	0.0 (± 0.76)		
Temperature going up and down (n=38,104)	0.1 (± 0.93)	0.0 (± 0.72)		
Night sweats (n=38,103)	-0.6 (± 0.92)	-0.3 (± 1.07)		
Skin problems (n=37,104)	0.4 (± 1.14)	0.3 (± 0.96)		
Feel ill (n=38,104)	0.1 (± 1.08)	0.2 (± 0.98)		
Feel lethargic (n=38,104)	0.1 (± 1.01)	0.0 (± 0.91)		
Felt slowed down (n=38,103)	0.3 (± 0.80)	0.0 (± 0.97)		
Limited in planning activities (n=38,103)	0.2 (± 0.97)	0.1 (± 0.90)		
Worried about health in the future (n=38,103)	0.0 (± 0.94)	0.0 (± 0.97)		
Trouble with chest infections (n=38,104)	0.2 (± 1.05)	0.0 (± 0.82)		
Trouble with other infections (n=38,104)	0.7 (± 1.07)	0.1 (± 0.86)		
Repeated courses of antibiotics (n=38,104)	0.9 (± 1.22)	0.0 (± 0.97)		
Worried about picking up infection (n=38,103)	0.3 (± 0.96)	0.2 (± 1.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in EuroQol-5 Dimension-5 Level (EQ-5D-5L) Visual Analog Scale at End of Treatment

End point title	Change from Baseline in EuroQol-5 Dimension-5 Level (EQ-5D-5L) Visual Analog Scale at End of Treatment

End point description:

The EQ-5D questionnaire is a brief, generic health-related quality of life assessment (HRQOL) that can also be used to incorporate subject preferences into health economic evaluations. The EQ-5D questionnaire assesses HRQOL in terms of degree of limitation on 5 health dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) and as overall health using a visual analog scale with response options ranging from 0 (worst imaginable health) to 100 (best imaginable health). ITT population included all subjects randomized into the study regardless of treatment actually received. Here, 'N' (number of subjects analyzed) signifies number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline to EOT (up to 2 years)

End point values	Ibrutinib+BR	Placebo+BR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	110		
Units: Units on a scale				
arithmetic mean (standard deviation)	-4.3 (± 19.58)	4.0 (± 18.21)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in EuroQol-5 Dimension-5 Level (EQ-5D-5L) Utility Score Scale at End of Treatment

End point title	Change from Baseline in EuroQol-5 Dimension-5 Level (EQ-5D-5L) Utility Score Scale at End of Treatment

End point description:

The EuroQol-5 is a five dimensional health state classification. Each dimension is assessed on a 3-point ordinal scale (1=no problems, 2=some problems, 3=extreme problems). The responses to the five EQ-5D dimensions were scored using a utility-weighted algorithm to derive an EQ-5D health status index score between 0 to 1. High score indicating a high level of utility. ITT population included all subjects randomized into the study regardless of treatment actually received. Here, 'N' (number of subjects analyzed) signifies number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline to EOT (up to 2 years)

End point values	Ibrutinib+BR	Placebo+BR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	110		
Units: Units on a scale				
arithmetic mean (standard deviation)	0.0 (± 0.28)	0.0 (± 0.24)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the time a signed and dated informed consent form is obtained until 30 days following the last dose of study treatment or until the start of a subsequent systemic antineoplastic therapy, if earlier (up to 5 years)

Adverse event reporting additional description:

Safety analysis set included all the randomized subjects who received at least 1 dose of study drug or placebo.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Ibrutinib+BR

Reporting group description:

Subjects received ibrutinib 420 milligram (mg) (3 * 140 mg capsules) orally once daily starting on Cycle 1 Day 2 for a maximum of 6 cycles (each cycle of 28 days except Cycle 1 which was of 29 days) along with BR. After 6 cycles ibrutinib alone was administered until disease progression or unacceptable toxicity.

Reporting group title	Placebo+BR

Reporting group description:

Subjects received placebo (3 capsules) orally once daily starting on Cycle 1 Day 2 for a maximum of 6 cycles (each cycle of 28 days except Cycle 1 which was of 29 days) along with BR. After 6 cycles placebo alone was administered until disease progression or unacceptable toxicity.

Reporting group title	Crossover Ibrutinib

Reporting group description:

Subjects in the placebo+BR treatment group could cross over to receive next-line ibrutinib treatment (420 mg [3 * 140 mg capsules] orally once daily on a 28-day cycle) at the discretion of the investigator at the time of disease progression or if IWCLL criteria for treatment were met.

Serious adverse events	Ibrutinib+BR	Placebo+BR	Crossover Ibrutinib
Total subjects affected by serious adverse events			
subjects affected / exposed	198 / 287 (68.99%)	127 / 287 (44.25%)	105 / 183 (57.38%)
number of deaths (all causes)	74	107	57
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute Lymphocytic Leukaemia			
subjects affected / exposed	0 / 287 (0.00%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenosquamous Cell Lung Cancer			

subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Anal Squamous Cell Carcinoma			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Basal Cell Carcinoma			
subjects affected / exposed	5 / 287 (1.74%)	1 / 287 (0.35%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	13 / 13	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder Cancer			
subjects affected / exposed	2 / 287 (0.70%)	0 / 287 (0.00%)	0 / 183 (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
Bronchioloalveolar Carcinoma			
subjects affected / exposed	0 / 287 (0.00%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic Myelomonocytic Leukaemia			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Intestinal Adenocarcinoma			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Intraductal Papilloma of Breast			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Lipoma			

subjects affected / exposed	0 / 287 (0.00%)	1 / 287 (0.35%)	0 / 183 (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
Lung Adenocarcinoma			
subjects affected / exposed	0 / 287 (0.00%)	1 / 287 (0.35%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Malignant Melanoma			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Malignant Melanoma in Situ			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Maxillofacial Sinus Neoplasm			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Metastases to Central Nervous System			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Metastatic Renal Cell Carcinoma			
subjects affected / exposed	0 / 287 (0.00%)	1 / 287 (0.35%)	0 / 183 (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
Myelodysplastic Syndrome			
subjects affected / exposed	2 / 287 (0.70%)	1 / 287 (0.35%)	0 / 183 (0.00%)
occurrences causally related to treatment / all	1 / 3	1 / 1	0 / 0
deaths causally related to treatment / all	1 / 2	0 / 0	0 / 0
Myeloproliferative Neoplasm			

subjects affected / exposed	0 / 287 (0.00%)	1 / 287 (0.35%)	0 / 183 (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
Neuroendocrine Carcinoma			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Prostate Cancer			
subjects affected / exposed	1 / 287 (0.35%)	1 / 287 (0.35%)	2 / 183 (1.09%)
occurrences causally related to treatment / all	1 / 1	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal Cancer			
subjects affected / exposed	0 / 287 (0.00%)	1 / 287 (0.35%)	0 / 183 (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
Renal Cancer Stage I			
subjects affected / exposed	0 / 287 (0.00%)	1 / 287 (0.35%)	0 / 183 (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
Renal Oncocytoma			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Squamous Cell Carcinoma			
subjects affected / exposed	3 / 287 (1.05%)	1 / 287 (0.35%)	2 / 183 (1.09%)
occurrences causally related to treatment / all	5 / 5	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous Cell Carcinoma of Skin			
subjects affected / exposed	0 / 287 (0.00%)	2 / 287 (0.70%)	0 / 183 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Superficial Spreading Melanoma Stage Unspecified			

subjects affected / exposed	0 / 287 (0.00%)	1 / 287 (0.35%)	0 / 183 (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
Transitional Cell Carcinoma			
subjects affected / exposed	0 / 287 (0.00%)	1 / 287 (0.35%)	0 / 183 (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
Vascular disorders			
Aortic Aneurysm Rupture			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Arterial Stenosis			
subjects affected / exposed	0 / 287 (0.00%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep Vein Thrombosis			
subjects affected / exposed	1 / 287 (0.35%)	3 / 287 (1.05%)	0 / 183 (0.00%)
occurrences causally related to treatment / all	1 / 1	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Hypertension			
subjects affected / exposed	2 / 287 (0.70%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	2 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive Crisis			
subjects affected / exposed	2 / 287 (0.70%)	0 / 287 (0.00%)	0 / 183 (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
Hypotension			

subjects affected / exposed	2 / 287 (0.70%)	0 / 287 (0.00%)	0 / 183 (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
Jugular Vein Thrombosis			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Lymphoedema			
subjects affected / exposed	0 / 287 (0.00%)	1 / 287 (0.35%)	0 / 183 (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
Peripheral Arterial Occlusive Disease			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Peripheral Artery Occlusion			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Peripheral Artery Thrombosis			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Peripheral Ischaemia			
subjects affected / exposed	0 / 287 (0.00%)	1 / 287 (0.35%)	0 / 183 (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
Thrombophlebitis			
subjects affected / exposed	1 / 287 (0.35%)	1 / 287 (0.35%)	0 / 183 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosis			

subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Vasculitis			
subjects affected / exposed	0 / 287 (0.00%)	1 / 287 (0.35%)	0 / 183 (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
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Chest Pain			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Chills			
subjects affected / exposed	0 / 287 (0.00%)	1 / 287 (0.35%)	0 / 183 (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
Complication Associated with Device			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Condition Aggravated			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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 / 287 (0.70%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	2 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	2 / 2	0 / 0	1 / 1
Disease Progression			

subjects affected / exposed	1 / 287 (0.35%)	2 / 287 (0.70%)	0 / 183 (0.00%)
occurrences causally related to treatment / all	2 / 2	4 / 4	0 / 0
deaths causally related to treatment / all	1 / 1	2 / 2	0 / 0
Fatigue			
subjects affected / exposed	3 / 287 (1.05%)	1 / 287 (0.35%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	2 / 3	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General Physical Health Deterioration			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Hernia			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Influenza Like Illness			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Infusion Site Extravasation			
subjects affected / exposed	0 / 287 (0.00%)	1 / 287 (0.35%)	0 / 183 (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
Malaise			
subjects affected / exposed	1 / 287 (0.35%)	1 / 287 (0.35%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	1 / 1	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mucosal Inflammation			
subjects affected / exposed	1 / 287 (0.35%)	1 / 287 (0.35%)	0 / 183 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple Organ Dysfunction Syndrome			

subjects affected / exposed	1 / 287 (0.35%)	3 / 287 (1.05%)	3 / 183 (1.64%)
occurrences causally related to treatment / all	2 / 2	4 / 4	5 / 5
deaths causally related to treatment / all	1 / 1	3 / 3	3 / 3
Non-Cardiac Chest Pain			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Oedema Peripheral			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Pneumatosis			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Pyrexia			
subjects affected / exposed	11 / 287 (3.83%)	7 / 287 (2.44%)	4 / 183 (2.19%)
occurrences causally related to treatment / all	13 / 13	11 / 11	3 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden Cardiac Death			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Sudden Death			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Systemic Inflammatory Response Syndrome			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Immune system disorders			
Anaphylactic Reaction			

subjects affected / exposed	0 / 287 (0.00%)	1 / 287 (0.35%)	0 / 183 (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
Reproductive system and breast disorders			
Benign Prostatic Hyperplasia			
subjects affected / exposed	2 / 287 (0.70%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	2 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fibrocystic Breast Disease			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Genital Rash			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Pelvic Floor Muscle Weakness			
subjects affected / exposed	0 / 287 (0.00%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Penile Dysplasia			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Uterine Haemorrhage			
subjects affected / exposed	2 / 287 (0.70%)	0 / 287 (0.00%)	0 / 183 (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
Uterine Prolapse			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Respiratory, thoracic and mediastinal disorders			

Acute Respiratory Failure			
subjects affected / exposed	0 / 287 (0.00%)	1 / 287 (0.35%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Chronic Obstructive Pulmonary Disease			
subjects affected / exposed	0 / 287 (0.00%)	1 / 287 (0.35%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	1 / 287 (0.35%)	3 / 287 (1.05%)	0 / 183 (0.00%)
occurrences causally related to treatment / all	1 / 1	4 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea Exertional			
subjects affected / exposed	0 / 287 (0.00%)	1 / 287 (0.35%)	0 / 183 (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
Haemoptysis			
subjects affected / exposed	0 / 287 (0.00%)	1 / 287 (0.35%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemothorax			
subjects affected / exposed	0 / 287 (0.00%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung Infiltration			
subjects affected / exposed	1 / 287 (0.35%)	1 / 287 (0.35%)	0 / 183 (0.00%)
occurrences causally related to treatment / all	2 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Pleural Effusion			
subjects affected / exposed	3 / 287 (1.05%)	2 / 287 (0.70%)	2 / 183 (1.09%)
occurrences causally related to treatment / all	4 / 5	1 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleuritic Pain			

subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Pneumonitis			
subjects affected / exposed	1 / 287 (0.35%)	1 / 287 (0.35%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	1 / 1	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Pneumothorax			
subjects affected / exposed	0 / 287 (0.00%)	1 / 287 (0.35%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary Congestion			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Pulmonary Mass			
subjects affected / exposed	0 / 287 (0.00%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary Sarcoidosis			
subjects affected / exposed	0 / 287 (0.00%)	1 / 287 (0.35%)	0 / 183 (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
Respiratory Failure			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	3 / 183 (1.64%)
occurrences causally related to treatment / all	1 / 1	0 / 0	3 / 3
deaths causally related to treatment / all	1 / 1	0 / 0	2 / 2
Respiratory Tract Oedema			
subjects affected / exposed	0 / 287 (0.00%)	1 / 287 (0.35%)	0 / 183 (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
Sleep Apnoea Syndrome			

subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Psychiatric disorders			
Acute Stress Disorder			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Alcoholic Psychosis			
subjects affected / exposed	0 / 287 (0.00%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Completed Suicide			
subjects affected / exposed	0 / 287 (0.00%)	1 / 287 (0.35%)	0 / 183 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Confusional State			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Delirium			
subjects affected / exposed	1 / 287 (0.35%)	1 / 287 (0.35%)	0 / 183 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental Status Changes			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Biopsy			
subjects affected / exposed	0 / 287 (0.00%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood Creatinine Increased			

subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Body Temperature Increased			
subjects affected / exposed	0 / 287 (0.00%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutrophil Count Decreased			
subjects affected / exposed	2 / 287 (0.70%)	0 / 287 (0.00%)	0 / 183 (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
Prostatic Specific Antigen Increased			
subjects affected / exposed	0 / 287 (0.00%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight Decreased			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Injury, poisoning and procedural complications			
Abdominal Injury			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Ankle Fracture			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Fall			
subjects affected / exposed	2 / 287 (0.70%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	2 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral Neck Fracture			

subjects affected / exposed	2 / 287 (0.70%)	0 / 287 (0.00%)	2 / 183 (1.09%)
occurrences causally related to treatment / all	2 / 2	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur Fracture			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Hip Fracture			
subjects affected / exposed	1 / 287 (0.35%)	1 / 287 (0.35%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	1 / 1	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incision Site Haemorrhage			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Infusion Related Reaction			
subjects affected / exposed	4 / 287 (1.39%)	5 / 287 (1.74%)	0 / 183 (0.00%)
occurrences causally related to treatment / all	4 / 4	5 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic Fracture			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Pneumoconiosis			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Pneumothorax Traumatic			
subjects affected / exposed	0 / 287 (0.00%)	1 / 287 (0.35%)	0 / 183 (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
Post Procedural Haemorrhage			

subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	2 / 183 (1.09%)
occurrences causally related to treatment / all	1 / 1	0 / 0	2 / 2
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Post Procedural Swelling			
subjects affected / exposed	0 / 287 (0.00%)	1 / 287 (0.35%)	0 / 183 (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	0 / 287 (0.00%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thoracic Vertebral Fracture			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Cardiac disorders			
Acute Coronary Syndrome			
subjects affected / exposed	0 / 287 (0.00%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute Myocardial Infarction			
subjects affected / exposed	0 / 287 (0.00%)	3 / 287 (1.05%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	4 / 4	1 / 1
deaths causally related to treatment / all	0 / 0	1 / 1	1 / 1
Angina Pectoris			
subjects affected / exposed	4 / 287 (1.39%)	1 / 287 (0.35%)	0 / 183 (0.00%)
occurrences causally related to treatment / all	4 / 4	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina Unstable			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia Supraventricular			

subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Atrial Fibrillation			
subjects affected / exposed	16 / 287 (5.57%)	2 / 287 (0.70%)	6 / 183 (3.28%)
occurrences causally related to treatment / all	16 / 19	2 / 2	6 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial Flutter			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular Block			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Cardiac Arrest			
subjects affected / exposed	2 / 287 (0.70%)	0 / 287 (0.00%)	3 / 183 (1.64%)
occurrences causally related to treatment / all	2 / 2	0 / 0	4 / 4
deaths causally related to treatment / all	1 / 1	0 / 0	2 / 2
Cardiac Failure			
subjects affected / exposed	3 / 287 (1.05%)	0 / 287 (0.00%)	0 / 183 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Cardio-Respiratory Arrest			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Cardiopulmonary Failure			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	1 / 1
Cardiovascular Insufficiency			

subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Carditis			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Coronary Artery Occlusion			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Myocardial Infarction			
subjects affected / exposed	2 / 287 (0.70%)	2 / 287 (0.70%)	2 / 183 (1.09%)
occurrences causally related to treatment / all	2 / 2	2 / 2	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Myocarditis			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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	2 / 287 (0.70%)	1 / 287 (0.35%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	1 / 2	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus Node Dysfunction			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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 Tachycardia			
subjects affected / exposed	0 / 287 (0.00%)	1 / 287 (0.35%)	0 / 183 (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
Tachycardia			

subjects affected / exposed	0 / 287 (0.00%)	1 / 287 (0.35%)	0 / 183 (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
Ventricular Fibrillation			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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 Flutter			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Ventricular Tachycardia			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Nervous system disorders			
Carotid Sinus Syndrome			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Cerebral Disorder			
subjects affected / exposed	0 / 287 (0.00%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral Infarction			
subjects affected / exposed	0 / 287 (0.00%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral Ischaemia			
subjects affected / exposed	0 / 287 (0.00%)	1 / 287 (0.35%)	0 / 183 (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
Cerebrovascular Accident			

subjects affected / exposed	3 / 287 (1.05%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	3 / 3	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cognitive Disorder			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Depressed Level of Consciousness			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalopathy			
subjects affected / exposed	0 / 287 (0.00%)	0 / 287 (0.00%)	2 / 183 (1.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Facial Paresis			
subjects affected / exposed	0 / 287 (0.00%)	1 / 287 (0.35%)	0 / 183 (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
Haemorrhage Intracranial			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic Stroke			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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	0 / 287 (0.00%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of Consciousness			

subjects affected / exposed	0 / 287 (0.00%)	1 / 287 (0.35%)	0 / 183 (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
Meningism			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Peripheral Sensory Neuropathy			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Post Herpetic Neuralgia			
subjects affected / exposed	1 / 287 (0.35%)	1 / 287 (0.35%)	0 / 183 (0.00%)
occurrences causally related to treatment / all	2 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radiculopathy			
subjects affected / exposed	0 / 287 (0.00%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 287 (0.00%)	1 / 287 (0.35%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient Global Amnesia			
subjects affected / exposed	0 / 287 (0.00%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular Encephalopathy			
subjects affected / exposed	0 / 287 (0.00%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	3 / 287 (1.05%)	7 / 287 (2.44%)	2 / 183 (1.09%)
occurrences causally related to treatment / all	2 / 3	10 / 11	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aplasia Pure Red Cell			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Aplastic Anaemia			
subjects affected / exposed	0 / 287 (0.00%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Autoimmune Haemolytic Anaemia			
subjects affected / exposed	0 / 287 (0.00%)	5 / 287 (1.74%)	0 / 183 (0.00%)
occurrences causally related to treatment / all	0 / 0	4 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone Marrow Failure			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Cytopenia			
subjects affected / exposed	0 / 287 (0.00%)	1 / 287 (0.35%)	0 / 183 (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
Febrile Neutropenia			
subjects affected / exposed	30 / 287 (10.45%)	22 / 287 (7.67%)	2 / 183 (1.09%)
occurrences causally related to treatment / all	22 / 33	20 / 28	1 / 3
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Haemolytic Anaemia			
subjects affected / exposed	0 / 287 (0.00%)	1 / 287 (0.35%)	0 / 183 (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
Immune Thrombocytopenic Purpura			

subjects affected / exposed	0 / 287 (0.00%)	1 / 287 (0.35%)	0 / 183 (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
Neutropenia			
subjects affected / exposed	7 / 287 (2.44%)	6 / 287 (2.09%)	0 / 183 (0.00%)
occurrences causally related to treatment / all	8 / 9	6 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	2 / 287 (0.70%)	0 / 287 (0.00%)	0 / 183 (0.00%)
occurrences causally related to treatment / all	4 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	4 / 287 (1.39%)	2 / 287 (0.70%)	0 / 183 (0.00%)
occurrences causally related to treatment / all	2 / 4	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Cataract			
subjects affected / exposed	3 / 287 (1.05%)	0 / 287 (0.00%)	2 / 183 (1.09%)
occurrences causally related to treatment / all	3 / 3	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Maculopathy			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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 Haemorrhage			
subjects affected / exposed	0 / 287 (0.00%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Scleral Disorder			
subjects affected / exposed	0 / 287 (0.00%)	1 / 287 (0.35%)	0 / 183 (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
Vitreous Adhesions			

subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Vitreous Haemorrhage			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Gastrointestinal disorders			
Abdominal Hernia			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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 Incarcerated Hernia			
subjects affected / exposed	0 / 287 (0.00%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal Pain			
subjects affected / exposed	0 / 287 (0.00%)	0 / 287 (0.00%)	3 / 183 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal Fistula			
subjects affected / exposed	0 / 287 (0.00%)	1 / 287 (0.35%)	0 / 183 (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
Ascites			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Colitis			
subjects affected / exposed	1 / 287 (0.35%)	2 / 287 (0.70%)	0 / 183 (0.00%)
occurrences causally related to treatment / all	1 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis Ischaemic			

subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Constipation			
subjects affected / exposed	0 / 287 (0.00%)	1 / 287 (0.35%)	0 / 183 (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
Diarrhoea			
subjects affected / exposed	4 / 287 (1.39%)	1 / 287 (0.35%)	0 / 183 (0.00%)
occurrences causally related to treatment / all	3 / 5	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal Ulcer Haemorrhage			
subjects affected / exposed	0 / 287 (0.00%)	1 / 287 (0.35%)	0 / 183 (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
Dyspepsia			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Dysphagia			
subjects affected / exposed	0 / 287 (0.00%)	2 / 287 (0.70%)	0 / 183 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Gastric Haemorrhage			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric Ulcer Perforation			

subjects affected / exposed	0 / 287 (0.00%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	3 / 287 (1.05%)	0 / 287 (0.00%)	0 / 183 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal Disorder			
subjects affected / exposed	0 / 287 (0.00%)	1 / 287 (0.35%)	0 / 183 (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
Gastrointestinal Haemorrhage			
subjects affected / exposed	2 / 287 (0.70%)	0 / 287 (0.00%)	0 / 183 (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
Gastrointestinal Inflammation			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Haematemesis			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Haematochezia			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Inguinal Hernia			
subjects affected / exposed	4 / 287 (1.39%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	5 / 5	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal Obstruction			

subjects affected / exposed	0 / 287 (0.00%)	1 / 287 (0.35%)	0 / 183 (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
Intra-Abdominal Haemorrhage			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Large Intestine Perforation			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Lower Gastrointestinal Haemorrhage			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Mouth Ulceration			
subjects affected / exposed	0 / 287 (0.00%)	1 / 287 (0.35%)	0 / 183 (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
Nausea			
subjects affected / exposed	0 / 287 (0.00%)	1 / 287 (0.35%)	0 / 183 (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
Oesophageal Ulcer			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Oesophagitis			
subjects affected / exposed	0 / 287 (0.00%)	1 / 287 (0.35%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			

subjects affected / exposed	0 / 287 (0.00%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis Acute			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Proctitis			
subjects affected / exposed	0 / 287 (0.00%)	1 / 287 (0.35%)	0 / 183 (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
Small Intestinal Obstruction			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Stomatitis			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Volvulus			
subjects affected / exposed	0 / 287 (0.00%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 287 (0.35%)	2 / 287 (0.70%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 1	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	0 / 287 (0.00%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			

subjects affected / exposed	1 / 287 (0.35%)	1 / 287 (0.35%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	1 / 1	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis Acute			
subjects affected / exposed	0 / 287 (0.00%)	1 / 287 (0.35%)	0 / 183 (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
Cholecystitis Chronic			
subjects affected / exposed	0 / 287 (0.00%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	2 / 287 (0.70%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	3 / 3	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholestasis			
subjects affected / exposed	0 / 287 (0.00%)	1 / 287 (0.35%)	0 / 183 (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
Gallbladder Obstruction			
subjects affected / exposed	0 / 287 (0.00%)	1 / 287 (0.35%)	0 / 183 (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
Hepatic Cirrhosis			
subjects affected / exposed	0 / 287 (0.00%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Hepatitis Toxic			
subjects affected / exposed	0 / 287 (0.00%)	2 / 287 (0.70%)	0 / 183 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatocellular Injury			

subjects affected / exposed	1 / 287 (0.35%)	1 / 287 (0.35%)	0 / 183 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Hepatosplenomegaly			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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 and subcutaneous tissue disorders			
Acute Febrile Neutrophilic Dermatosis			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Cellulitis			
subjects affected / exposed	0 / 287 (0.00%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug Eruption			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Excessive Granulation Tissue			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Hypersensitivity Vasculitis			
subjects affected / exposed	0 / 287 (0.00%)	1 / 287 (0.35%)	0 / 183 (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
Pemphigoid			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Pemphigus			

subjects affected / exposed	0 / 287 (0.00%)	1 / 287 (0.35%)	0 / 183 (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
Rash			
subjects affected / exposed	0 / 287 (0.00%)	2 / 287 (0.70%)	0 / 183 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash Erythematous			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Rash Maculo-Papular			
subjects affected / exposed	0 / 287 (0.00%)	1 / 287 (0.35%)	0 / 183 (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
Skin Necrosis			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Urticaria			
subjects affected / exposed	0 / 287 (0.00%)	1 / 287 (0.35%)	0 / 183 (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
Renal and urinary disorders			
Acute Kidney Injury			
subjects affected / exposed	2 / 287 (0.70%)	1 / 287 (0.35%)	0 / 183 (0.00%)
occurrences causally related to treatment / all	2 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Calculus Bladder			
subjects affected / exposed	0 / 287 (0.00%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysuria			

subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Haematuria			
subjects affected / exposed	0 / 287 (0.00%)	0 / 287 (0.00%)	2 / 183 (1.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephropathy			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Nephropathy Toxic			
subjects affected / exposed	0 / 287 (0.00%)	1 / 287 (0.35%)	0 / 183 (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
Renal Failure			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	2 / 183 (1.09%)
occurrences causally related to treatment / all	1 / 1	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal Impairment			
subjects affected / exposed	2 / 287 (0.70%)	1 / 287 (0.35%)	0 / 183 (0.00%)
occurrences causally related to treatment / all	2 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureteric Stenosis			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Ureterolithiasis			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Urge Incontinence			

subjects affected / exposed	0 / 287 (0.00%)	1 / 287 (0.35%)	0 / 183 (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
Urinary Incontinence			
subjects affected / exposed	0 / 287 (0.00%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary Retention			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Addison's Disease			
subjects affected / exposed	0 / 287 (0.00%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Goitre			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 287 (0.00%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis			
subjects affected / exposed	2 / 287 (0.70%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	3 / 3	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back Pain			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Chondrocalcinosis Pyrophosphate			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Femoroacetabular Impingement			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Groin Pain			
subjects affected / exposed	0 / 287 (0.00%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar Spinal Stenosis			
subjects affected / exposed	0 / 287 (0.00%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscle Haemorrhage			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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	0 / 287 (0.00%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal Pain			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Osteoarthritis			
subjects affected / exposed	3 / 287 (1.05%)	0 / 287 (0.00%)	0 / 183 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis			

subjects affected / exposed	0 / 287 (0.00%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in Extremity			
subjects affected / exposed	0 / 287 (0.00%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abscess Jaw			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Actinomycotic Pulmonary Infection			
subjects affected / exposed	0 / 287 (0.00%)	1 / 287 (0.35%)	0 / 183 (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
Acute Sinusitis			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Appendicitis			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	2 / 183 (1.09%)
occurrences causally related to treatment / all	1 / 1	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis Bacterial			
subjects affected / exposed	2 / 287 (0.70%)	0 / 287 (0.00%)	0 / 183 (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
Ascariasis			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Atypical Pneumonia			

subjects affected / exposed	0 / 287 (0.00%)	1 / 287 (0.35%)	0 / 183 (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
Bacteraemia			
subjects affected / exposed	2 / 287 (0.70%)	0 / 287 (0.00%)	0 / 183 (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
Brain Abscess			
subjects affected / exposed	2 / 287 (0.70%)	0 / 287 (0.00%)	0 / 183 (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
Breast Abscess			
subjects affected / exposed	0 / 287 (0.00%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast Cellulitis			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Bronchitis			
subjects affected / exposed	8 / 287 (2.79%)	5 / 287 (1.74%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	8 / 10	5 / 5	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopulmonary Aspergillosis			
subjects affected / exposed	1 / 287 (0.35%)	1 / 287 (0.35%)	2 / 183 (1.09%)
occurrences causally related to treatment / all	1 / 1	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Campylobacter Infection			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Cellulitis			

subjects affected / exposed	4 / 287 (1.39%)	2 / 287 (0.70%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	4 / 4	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis Staphylococcal			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Central Nervous System Infection			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Chronic Sinusitis			
subjects affected / exposed	1 / 287 (0.35%)	1 / 287 (0.35%)	0 / 183 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium Difficile Colitis			
subjects affected / exposed	0 / 287 (0.00%)	1 / 287 (0.35%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium Difficile Infection			
subjects affected / exposed	0 / 287 (0.00%)	0 / 287 (0.00%)	2 / 183 (1.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Conjunctivitis			
subjects affected / exposed	0 / 287 (0.00%)	1 / 287 (0.35%)	0 / 183 (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
Cystitis			
subjects affected / exposed	0 / 287 (0.00%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cytomegalovirus Colitis			

subjects affected / exposed	0 / 287 (0.00%)	1 / 287 (0.35%)	0 / 183 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cytomegalovirus Infection			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Dacryocystitis			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Dermo-Hypodermitis			
subjects affected / exposed	0 / 287 (0.00%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disseminated Cryptococcosis			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Epstein-Barr Virus Infection			
subjects affected / exposed	0 / 287 (0.00%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	3 / 183 (1.64%)
occurrences causally related to treatment / all	1 / 1	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia Sepsis			
subjects affected / exposed	0 / 287 (0.00%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia Urinary Tract Infection			

subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Fungal Infection			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Gastroenteritis			
subjects affected / exposed	1 / 287 (0.35%)	1 / 287 (0.35%)	0 / 183 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis Viral			
subjects affected / exposed	2 / 287 (0.70%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	2 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal Infection			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Haemophilus Infection			
subjects affected / exposed	0 / 287 (0.00%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis B Reactivation			
subjects affected / exposed	1 / 287 (0.35%)	1 / 287 (0.35%)	0 / 183 (0.00%)
occurrences causally related to treatment / all	1 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Herpes Zoster			
subjects affected / exposed	1 / 287 (0.35%)	2 / 287 (0.70%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	1 / 1	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			

subjects affected / exposed	3 / 287 (1.05%)	2 / 287 (0.70%)	0 / 183 (0.00%)
occurrences causally related to treatment / all	3 / 3	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infectious Pleural Effusion			
subjects affected / exposed	0 / 287 (0.00%)	1 / 287 (0.35%)	0 / 183 (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
Influenza			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Laryngitis			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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 Respiratory Tract Infection			
subjects affected / exposed	0 / 287 (0.00%)	2 / 287 (0.70%)	2 / 183 (1.09%)
occurrences causally related to treatment / all	0 / 0	2 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung Infection			
subjects affected / exposed	3 / 287 (1.05%)	3 / 287 (1.05%)	0 / 183 (0.00%)
occurrences causally related to treatment / all	3 / 3	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphadenitis Bacterial			
subjects affected / exposed	0 / 287 (0.00%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscle Abscess			
subjects affected / exposed	0 / 287 (0.00%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenic Sepsis			

subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Nocardiosis			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Oral Candidiasis			
subjects affected / exposed	0 / 287 (0.00%)	2 / 287 (0.70%)	0 / 183 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Otitis Media			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Periodontitis			
subjects affected / exposed	0 / 287 (0.00%)	1 / 287 (0.35%)	0 / 183 (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
Periorbital Cellulitis			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Peritonsillar Abscess			
subjects affected / exposed	0 / 287 (0.00%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngeal Abscess			

subjects affected / exposed	0 / 287 (0.00%)	1 / 287 (0.35%)	0 / 183 (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
Pharyngitis			
subjects affected / exposed	0 / 287 (0.00%)	1 / 287 (0.35%)	0 / 183 (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
Pharyngitis Streptococcal			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Pneumocystis Jirovecii Pneumonia			
subjects affected / exposed	2 / 287 (0.70%)	0 / 287 (0.00%)	0 / 183 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	48 / 287 (16.72%)	26 / 287 (9.06%)	34 / 183 (18.58%)
occurrences causally related to treatment / all	59 / 64	38 / 38	42 / 46
deaths causally related to treatment / all	1 / 1	3 / 3	4 / 4
Pneumonia Bacterial			
subjects affected / exposed	0 / 287 (0.00%)	1 / 287 (0.35%)	0 / 183 (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
Pneumonia Haemophilus			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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 Pneumococcal			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	2 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia Streptococcal			

subjects affected / exposed	0 / 287 (0.00%)	1 / 287 (0.35%)	2 / 183 (1.09%)
occurrences causally related to treatment / all	0 / 0	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Progressive Multifocal Leukoencephalopathy			
subjects affected / exposed	2 / 287 (0.70%)	0 / 287 (0.00%)	2 / 183 (1.09%)
occurrences causally related to treatment / all	4 / 4	0 / 0	4 / 4
deaths causally related to treatment / all	2 / 2	0 / 0	1 / 1
Pseudomembranous Colitis			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Pulmonary Tuberculoma			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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 Tuberculosis			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Pyelonephritis			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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 Pustular			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Respiratory Syncytial Virus Infection			
subjects affected / exposed	0 / 287 (0.00%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory Tract Infection			

subjects affected / exposed	5 / 287 (1.74%)	2 / 287 (0.70%)	5 / 183 (2.73%)
occurrences causally related to treatment / all	6 / 6	2 / 2	5 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	8 / 287 (2.79%)	4 / 287 (1.39%)	4 / 183 (2.19%)
occurrences causally related to treatment / all	9 / 9	5 / 7	6 / 6
deaths causally related to treatment / all	1 / 1	2 / 3	2 / 2
Septic Shock			
subjects affected / exposed	6 / 287 (2.09%)	2 / 287 (0.70%)	5 / 183 (2.73%)
occurrences causally related to treatment / all	9 / 9	1 / 3	7 / 7
deaths causally related to treatment / all	4 / 4	0 / 1	5 / 5
Sinusitis			
subjects affected / exposed	1 / 287 (0.35%)	2 / 287 (0.70%)	2 / 183 (1.09%)
occurrences causally related to treatment / all	1 / 1	2 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin Candida			
subjects affected / exposed	0 / 287 (0.00%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin Infection			
subjects affected / exposed	2 / 287 (0.70%)	1 / 287 (0.35%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	2 / 2	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Soft Tissue Infection			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Splenic Abscess			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Staphylococcal Infection			

subjects affected / exposed	2 / 287 (0.70%)	0 / 287 (0.00%)	0 / 183 (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
Staphylococcal Skin Infection			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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 Abscess			
subjects affected / exposed	3 / 287 (1.05%)	1 / 287 (0.35%)	0 / 183 (0.00%)
occurrences causally related to treatment / all	3 / 3	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tooth Abscess			
subjects affected / exposed	0 / 287 (0.00%)	1 / 287 (0.35%)	0 / 183 (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
Tuberculosis of Central Nervous System			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Upper Respiratory Tract Infection			
subjects affected / exposed	3 / 287 (1.05%)	3 / 287 (1.05%)	0 / 183 (0.00%)
occurrences causally related to treatment / all	4 / 4	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary Tract Infection			
subjects affected / exposed	6 / 287 (2.09%)	1 / 287 (0.35%)	2 / 183 (1.09%)
occurrences causally related to treatment / all	5 / 6	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varicella			

subjects affected / exposed	1 / 287 (0.35%)	1 / 287 (0.35%)	0 / 183 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varicella Zoster Virus Infection			
subjects affected / exposed	0 / 287 (0.00%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral Infection			
subjects affected / exposed	0 / 287 (0.00%)	1 / 287 (0.35%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Dehydration			
subjects affected / exposed	2 / 287 (0.70%)	1 / 287 (0.35%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	2 / 2	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes Mellitus			
subjects affected / exposed	1 / 287 (0.35%)	0 / 287 (0.00%)	0 / 183 (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
Hypercalcaemia			
subjects affected / exposed	0 / 287 (0.00%)	0 / 287 (0.00%)	1 / 183 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperuricaemia			
subjects affected / exposed	0 / 287 (0.00%)	1 / 287 (0.35%)	0 / 183 (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
Hyponatraemia			

subjects affected / exposed	0 / 287 (0.00%)	1 / 287 (0.35%)	0 / 183 (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
Hypophosphataemia			
subjects affected / exposed	0 / 287 (0.00%)	1 / 287 (0.35%)	0 / 183 (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
Tumour Lysis Syndrome			
subjects affected / exposed	6 / 287 (2.09%)	1 / 287 (0.35%)	0 / 183 (0.00%)
occurrences causally related to treatment / all	4 / 6	1 / 1	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+BR	Placebo+BR	Crossover Ibrutinib
Total subjects affected by non-serious adverse events			
subjects affected / exposed	268 / 287 (93.38%)	271 / 287 (94.43%)	157 / 183 (85.79%)
Vascular disorders			
Haematoma			
subjects affected / exposed	26 / 287 (9.06%)	3 / 287 (1.05%)	14 / 183 (7.65%)
occurrences (all)	58	3	18
Hypertension			
subjects affected / exposed	47 / 287 (16.38%)	14 / 287 (4.88%)	27 / 183 (14.75%)
occurrences (all)	70	17	38
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	26 / 287 (9.06%)	24 / 287 (8.36%)	5 / 183 (2.73%)
occurrences (all)	39	36	5
Chills			
subjects affected / exposed	33 / 287 (11.50%)	31 / 287 (10.80%)	5 / 183 (2.73%)
occurrences (all)	45	35	6
Fatigue			
subjects affected / exposed	69 / 287 (24.04%)	66 / 287 (23.00%)	32 / 183 (17.49%)
occurrences (all)	145	121	45
Influenza Like Illness			

subjects affected / exposed	9 / 287 (3.14%)	10 / 287 (3.48%)	12 / 183 (6.56%)
occurrences (all)	11	14	16
Mucosal Inflammation			
subjects affected / exposed	15 / 287 (5.23%)	7 / 287 (2.44%)	3 / 183 (1.64%)
occurrences (all)	27	11	3
Non-Cardiac Chest Pain			
subjects affected / exposed	17 / 287 (5.92%)	13 / 287 (4.53%)	3 / 183 (1.64%)
occurrences (all)	22	16	3
Oedema Peripheral			
subjects affected / exposed	49 / 287 (17.07%)	34 / 287 (11.85%)	21 / 183 (11.48%)
occurrences (all)	82	40	24
Pyrexia			
subjects affected / exposed	74 / 287 (25.78%)	60 / 287 (20.91%)	22 / 183 (12.02%)
occurrences (all)	140	93	29
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	74 / 287 (25.78%)	75 / 287 (26.13%)	27 / 183 (14.75%)
occurrences (all)	116	106	41
Dyspnoea			
subjects affected / exposed	22 / 287 (7.67%)	29 / 287 (10.10%)	11 / 183 (6.01%)
occurrences (all)	30	43	13
Epistaxis			
subjects affected / exposed	22 / 287 (7.67%)	10 / 287 (3.48%)	15 / 183 (8.20%)
occurrences (all)	46	15	16
Nasal Congestion			
subjects affected / exposed	16 / 287 (5.57%)	9 / 287 (3.14%)	4 / 183 (2.19%)
occurrences (all)	21	14	5
Oropharyngeal Pain			
subjects affected / exposed	30 / 287 (10.45%)	20 / 287 (6.97%)	8 / 183 (4.37%)
occurrences (all)	42	23	8
Productive Cough			
subjects affected / exposed	21 / 287 (7.32%)	18 / 287 (6.27%)	9 / 183 (4.92%)
occurrences (all)	30	31	12
Viral Upper Respiratory Tract Infection			

subjects affected / exposed	30 / 287 (10.45%)	20 / 287 (6.97%)	13 / 183 (7.10%)
occurrences (all)	47	27	19
Psychiatric disorders			
Anxiety			
subjects affected / exposed	22 / 287 (7.67%)	11 / 287 (3.83%)	9 / 183 (4.92%)
occurrences (all)	30	12	10
Depression			
subjects affected / exposed	18 / 287 (6.27%)	8 / 287 (2.79%)	4 / 183 (2.19%)
occurrences (all)	18	9	5
Insomnia			
subjects affected / exposed	27 / 287 (9.41%)	21 / 287 (7.32%)	10 / 183 (5.46%)
occurrences (all)	36	26	10
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	15 / 287 (5.23%)	12 / 287 (4.18%)	3 / 183 (1.64%)
occurrences (all)	17	19	4
Blood Creatinine Increased			
subjects affected / exposed	17 / 287 (5.92%)	7 / 287 (2.44%)	6 / 183 (3.28%)
occurrences (all)	24	7	7
Neutrophil Count Decreased			
subjects affected / exposed	21 / 287 (7.32%)	16 / 287 (5.57%)	3 / 183 (1.64%)
occurrences (all)	47	60	5
Platelet Count Decreased			
subjects affected / exposed	17 / 287 (5.92%)	9 / 287 (3.14%)	2 / 183 (1.09%)
occurrences (all)	38	23	2
Weight Decreased			
subjects affected / exposed	18 / 287 (6.27%)	18 / 287 (6.27%)	5 / 183 (2.73%)
occurrences (all)	24	28	5
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	30 / 287 (10.45%)	9 / 287 (3.14%)	15 / 183 (8.20%)
occurrences (all)	56	13	27
Infusion Related Reaction			
subjects affected / exposed	45 / 287 (15.68%)	64 / 287 (22.30%)	1 / 183 (0.55%)
occurrences (all)	66	111	2
Cardiac disorders			

Atrial Fibrillation			
subjects affected / exposed	23 / 287 (8.01%)	5 / 287 (1.74%)	19 / 183 (10.38%)
occurrences (all)	35	6	23
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	15 / 287 (5.23%)	15 / 287 (5.23%)	3 / 183 (1.64%)
occurrences (all)	16	15	3
Headache			
subjects affected / exposed	49 / 287 (17.07%)	47 / 287 (16.38%)	18 / 183 (9.84%)
occurrences (all)	81	74	24
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	73 / 287 (25.44%)	79 / 287 (27.53%)	33 / 183 (18.03%)
occurrences (all)	154	200	56
Leukopenia			
subjects affected / exposed	15 / 287 (5.23%)	18 / 287 (6.27%)	2 / 183 (1.09%)
occurrences (all)	26	62	3
Neutropenia			
subjects affected / exposed	170 / 287 (59.23%)	159 / 287 (55.40%)	40 / 183 (21.86%)
occurrences (all)	659	722	82
Thrombocytopenia			
subjects affected / exposed	90 / 287 (31.36%)	69 / 287 (24.04%)	24 / 183 (13.11%)
occurrences (all)	273	223	51
Eye disorders			
Cataract			
subjects affected / exposed	20 / 287 (6.97%)	3 / 287 (1.05%)	8 / 183 (4.37%)
occurrences (all)	32	3	9
Dry Eye			
subjects affected / exposed	15 / 287 (5.23%)	9 / 287 (3.14%)	6 / 183 (3.28%)
occurrences (all)	15	12	7
Vision Blurred			
subjects affected / exposed	19 / 287 (6.62%)	19 / 287 (6.62%)	3 / 183 (1.64%)
occurrences (all)	21	20	3
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	39 / 287 (13.59%)	24 / 287 (8.36%)	3 / 183 (1.64%)
occurrences (all)	45	35	3

Abdominal Pain Upper			
subjects affected / exposed	23 / 287 (8.01%)	16 / 287 (5.57%)	11 / 183 (6.01%)
occurrences (all)	33	23	12
Constipation			
subjects affected / exposed	61 / 287 (21.25%)	50 / 287 (17.42%)	15 / 183 (8.20%)
occurrences (all)	97	71	23
Diarrhoea			
subjects affected / exposed	115 / 287 (40.07%)	68 / 287 (23.69%)	47 / 183 (25.68%)
occurrences (all)	248	115	87
Dyspepsia			
subjects affected / exposed	24 / 287 (8.36%)	21 / 287 (7.32%)	8 / 183 (4.37%)
occurrences (all)	31	30	15
Gastrooesophageal Reflux Disease			
subjects affected / exposed	15 / 287 (5.23%)	12 / 287 (4.18%)	4 / 183 (2.19%)
occurrences (all)	19	12	4
Nausea			
subjects affected / exposed	108 / 287 (37.63%)	101 / 287 (35.19%)	16 / 183 (8.74%)
occurrences (all)	192	204	22
Toothache			
subjects affected / exposed	15 / 287 (5.23%)	5 / 287 (1.74%)	3 / 183 (1.64%)
occurrences (all)	15	8	3
Vomiting			
subjects affected / exposed	42 / 287 (14.63%)	45 / 287 (15.68%)	15 / 183 (8.20%)
occurrences (all)	63	86	26
Skin and subcutaneous tissue disorders			
Dry Skin			
subjects affected / exposed	27 / 287 (9.41%)	17 / 287 (5.92%)	7 / 183 (3.83%)
occurrences (all)	32	17	8
Ecchymosis			
subjects affected / exposed	14 / 287 (4.88%)	2 / 287 (0.70%)	10 / 183 (5.46%)
occurrences (all)	20	2	15
Onychoclasis			
subjects affected / exposed	10 / 287 (3.48%)	0 / 287 (0.00%)	10 / 183 (5.46%)
occurrences (all)	11	0	10
Pruritus			

subjects affected / exposed	34 / 287 (11.85%)	33 / 287 (11.50%)	9 / 183 (4.92%)
occurrences (all)	43	56	10
Rash			
subjects affected / exposed	63 / 287 (21.95%)	35 / 287 (12.20%)	15 / 183 (8.20%)
occurrences (all)	104	61	18
Rash Maculo-Papular			
subjects affected / exposed	17 / 287 (5.92%)	11 / 287 (3.83%)	7 / 183 (3.83%)
occurrences (all)	25	16	7
Skin Lesion			
subjects affected / exposed	30 / 287 (10.45%)	5 / 287 (1.74%)	11 / 183 (6.01%)
occurrences (all)	40	8	14
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	47 / 287 (16.38%)	29 / 287 (10.10%)	25 / 183 (13.66%)
occurrences (all)	81	41	43
Back Pain			
subjects affected / exposed	41 / 287 (14.29%)	22 / 287 (7.67%)	23 / 183 (12.57%)
occurrences (all)	55	31	30
Muscle Spasms			
subjects affected / exposed	44 / 287 (15.33%)	14 / 287 (4.88%)	17 / 183 (9.29%)
occurrences (all)	75	19	26
Myalgia			
subjects affected / exposed	28 / 287 (9.76%)	15 / 287 (5.23%)	9 / 183 (4.92%)
occurrences (all)	42	24	12
Pain in Extremity			
subjects affected / exposed	21 / 287 (7.32%)	15 / 287 (5.23%)	12 / 183 (6.56%)
occurrences (all)	32	20	13
Infections and infestations			
Bronchitis			
subjects affected / exposed	51 / 287 (17.77%)	29 / 287 (10.10%)	19 / 183 (10.38%)
occurrences (all)	75	41	28
Cellulitis			
subjects affected / exposed	16 / 287 (5.57%)	8 / 287 (2.79%)	10 / 183 (5.46%)
occurrences (all)	21	12	11
Conjunctivitis			

subjects affected / exposed	20 / 287 (6.97%)	15 / 287 (5.23%)	10 / 183 (5.46%)
occurrences (all)	28	20	14
Herpes Zoster			
subjects affected / exposed	24 / 287 (8.36%)	17 / 287 (5.92%)	7 / 183 (3.83%)
occurrences (all)	31	23	7
Influenza			
subjects affected / exposed	22 / 287 (7.67%)	16 / 287 (5.57%)	7 / 183 (3.83%)
occurrences (all)	30	19	11
Oral Herpes			
subjects affected / exposed	15 / 287 (5.23%)	18 / 287 (6.27%)	7 / 183 (3.83%)
occurrences (all)	26	27	13
Pharyngitis			
subjects affected / exposed	18 / 287 (6.27%)	13 / 287 (4.53%)	2 / 183 (1.09%)
occurrences (all)	19	13	3
Pneumonia			
subjects affected / exposed	40 / 287 (13.94%)	25 / 287 (8.71%)	21 / 183 (11.48%)
occurrences (all)	55	29	34
Respiratory Tract Infection			
subjects affected / exposed	19 / 287 (6.62%)	10 / 287 (3.48%)	15 / 183 (8.20%)
occurrences (all)	30	12	31
Sinusitis			
subjects affected / exposed	38 / 287 (13.24%)	24 / 287 (8.36%)	25 / 183 (13.66%)
occurrences (all)	67	34	33
Upper Respiratory Tract Infection			
subjects affected / exposed	69 / 287 (24.04%)	50 / 287 (17.42%)	36 / 183 (19.67%)
occurrences (all)	135	79	61
Urinary Tract Infection			
subjects affected / exposed	28 / 287 (9.76%)	15 / 287 (5.23%)	26 / 183 (14.21%)
occurrences (all)	56	20	39
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	42 / 287 (14.63%)	42 / 287 (14.63%)	16 / 183 (8.74%)
occurrences (all)	58	65	20
Hyperuricaemia			
subjects affected / exposed	36 / 287 (12.54%)	20 / 287 (6.97%)	7 / 183 (3.83%)
occurrences (all)	60	24	12

Hypokalaemia subjects affected / exposed occurrences (all)	24 / 287 (8.36%) 40	12 / 287 (4.18%) 18	8 / 183 (4.37%) 14

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 December 2012	• Clarified management of study drug with concomitant cytochrome (CYP) CYP3A4/5 inhibitors/inducers and warfarin or other anticoagulants during the study to reflect updated standard language across the ibrutinib development program • Removed the eligibility restriction for subjects requiring treatment with strong CYP2D6 inhibitors in the exclusion criteria • Clarified management of study drug during the perioperative periods • Incorporated feedback from investigators, health authorities, and the study steering committee with regard to the platelet cutoff eligibility criteria, and bone marrow and MRD sampling for subjects reaching CR
13 September 2013	• Updated the protocol with safety information in the investigator's brochure • Implemented a recommendation from the DMC to use anti-microbial prophylaxis • Added that data related to the occurrence of other malignancies or transformation to a more aggressive histology (Richter's transformation) during the follow-up phase should be collected
30 January 2014	• Provided access to next-line treatment with ibrutinib for subjects initially assigned to placebo who had IRC-confirmed disease progression (that is each subject had met the primary endpoint), at investigator's discretion, and with medical monitor approval
13 April 2015	• Unblinded study and removed the Amendment 3 requirement for IRC-confirmed disease progression providing access to next-line treatment with ibrutinib for subjects initially assigned to placebo at the discretion of the investigator at the time the subject had progression or met IWCLL criteria for treatment • End of study definition was revised to change the length of time from last subject in study from 4 years to 5 years so that estimated median PFS could be reached • Clarified that all responding subjects were to have peripheral blood MRD evaluations performed every 12 weeks until PD

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Study was planned to end when 80% of randomized participants died or 5 years after last participant randomized, whichever was first. Sponsor terminated study on 23-Jan-2019 (5 year after last participant randomized) and study was considered completed

Notes: