



Clinical trial results:

A Phase 2, Multicenter, Single-Arm Study to Evaluate the Efficacy and Safety of Single-Agent Bruton's Tyrosine Kinase (BTK) Inhibitor, Ibrutinib, in Subjects With Mantle Cell Lymphoma Who Progress After Bortezomib Therapy

Summary

EudraCT number	2012-000711-88
Trial protocol	ES BE GB PL
Global end of trial date	31 May 2015

Results information

Result version number	v1 (current)
This version publication date	06 May 2016
First version publication date	06 May 2016

Trial information

Trial identification

Sponsor protocol code	PCI-32765MCL2001
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01599949
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen-Cilag International NV
Sponsor organisation address	Turnhoutseweg 30, Beerse, Belgium, 2340
Public contact	Clinical Registry Group, Janssen-Cilag International NV, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group, Janssen-Cilag International NV, 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	31 May 2015
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	31 May 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study was to evaluate the overall response rate (ORR) of ibrutinib, as assessed by the Independent Review Committee (IRC), in participants with mantle cell lymphoma (MCL) who received at least 1 prior rituximab-containing chemotherapy regimen and who progressed after bortezomib therapy.

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. Safety evaluations included monitoring of adverse events, clinical laboratory tests, physical examinations, Eastern Cooperative Oncology Group (ECOG) performance status, and cardiac assessments.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 July 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	15 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	Israel: 13
Country: Number of subjects enrolled	Poland: 1
Country: Number of subjects enrolled	Russian Federation: 12
Country: Number of subjects enrolled	United States: 83
Worldwide total number of subjects	120
EEA total number of subjects	12

Notes:

Subjects enrolled per age group

In utero	0
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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)	45
From 65 to 84 years	74
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 110 subjects were to be enrolled in order to have a minimum of 101 subjects evaluable for the primary efficacy analysis.

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Ibrutinib
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Arm description:

The participants received 560 milligram (mg) of ibrutinib orally once per day, as 4 x 140-mg capsules for 21 consecutive days.

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:

The participants received 560 milligram (mg) of ibrutinib orally once per day, as 4 x 140-mg capsules for 21 consecutive days.

Number of subjects in period 1	Ibrutinib
Started	120
Completed	0
Not completed	120
Consent withdrawn by subject	10
Adverse event, non-fatal	5
Death	9
Adverse event, serious non-fatal	4
Progressive disease	61
Physician decision/study terminated by sponsor	31

Baseline characteristics

Reporting groups

Reporting group title	Ibrutinib
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Reporting group description:

The participants received 560 milligram (mg) of ibrutinib orally once per day, as 4 x 140-mg capsules for 21 consecutive days.

Reporting group values	Ibrutinib	Total	
Number of subjects	120	120	
Title for AgeCategorical Units: subjects			
Adults (18-64 years)	45	45	
From 65 to 84 years	74	74	
85 years and over	1	1	
Title for AgeContinuous Units: years			
arithmetic mean	66.7		
standard deviation	± 9.98	-	
Title for Gender Units: subjects			
Female	16	16	
Male	104	104	

End points

End points reporting groups

Reporting group title	Ibrutinib
Reporting group description: The participants received 560 milligram (mg) of ibrutinib orally once per day, as 4 x 140-mg capsules for 21 consecutive days.	

Primary: Overall Response Rate

End point title	Overall Response Rate ^[1]
End point description: ORR is the proportion of evaluable subjects who achieved complete response (CR) or partial response (PR) as assessed by the IRC based upon the Revised Response Criteria for Malignant Lymphoma (Cheson 2007). The efficacy population includes all randomized subjects who received at least 1 dose of the study drug Ibrutinib.	
End point type	Primary
End point timeframe: Time from first dose of study drug until the date of first documented evidence of progressive disease (or relapse for subjects who experience CR during the study) or death, whichever occurred first (up to 2 years)	
Notes: [1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: No statistical analyses has been reported for this end point	

End point values	Ibrutinib			
Subject group type	Reporting group			
Number of subjects analysed	110			
Units: Participants				
number (confidence interval 95%)	62.7 (53.7 to 71.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival Rate

End point title	Progression-Free Survival Rate
End point description: Progression-free survival was defined as the interval between the date of first dose and the date of disease progression or death, whichever occurred first. Participants with no postbaseline disease assessment were to be censored on Day 1. Participants who were progression free and alive, or with unknown status were censored at the last adequate tumor assessment. The distribution of PFS will be estimated using the Kaplan-Meier method. The efficacy population includes all randomized subjects who received at least 1 dose of the study drug Ibrutinib.	
End point type	Secondary
End point timeframe: Time from first dose of study drug until the date of first documented evidence of progressive disease (or relapse for subjects who experience CR during the study) or death, whichever occurred first (up to 2	

End point values	Ibrutinib			
Subject group type	Reporting group			
Number of subjects analysed	120			
Units: months				
median (confidence interval 95%)	10.48 (4.37 to 14.98)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline In The Lym Subscale

End point title	Mean Change From Baseline In The Lym Subscale
End point description:	
<p>The FACT-Lym consisted of a general functional assessment scale (FACT-G) and a subscale that specifically addressed lymphoma-specific concerns (Lym). Responses to all items were rated on a 5-point scale ranging from 0 "not at all" to 4 "very much." The recall period was the previous 7 days. All translations that were not available were completed according to best practices guidelines (Wild 2005). The FACT-G consisted of three 7-item subscales (scored from 0 to 28) that assessed physical, social, and functional well-being plus one 6-item subscale (scored from 0 to 24) that assessed emotional well-being. The Lym subscale included 15 items scored from 0 to 60. The efficacy population includes all randomized subjects who received at least 1 dose of the study drug Ibrutinib.</p>	
End point type	Secondary
End point timeframe:	
<p>From 1st dose to PD by INV, Death, or End of Study whichever comes earlier (up to 2 years) prior to the Target Day of the window.</p>	

End point values	Ibrutinib			
Subject group type	Reporting group			
Number of subjects analysed	120			
Units: Units on scale				
arithmetic mean (standard deviation)				
Baseline (n=111)	44.96 (± 8.948)			
Last evaluation (n=116)	46.96 (± 10.032)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline In The EuroQol-5 Dimension 5-Level Instrument (EQ-5D-5L) Index

End point title	Mean Change From Baseline In The EuroQol-5 Dimension 5-Level Instrument (EQ-5D-5L) Index
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End point description:

The EQ-5D-5L was used to generate utility scores of health outcome for use in cost effectiveness analysis. The EQ 5D-5L is a 5-item questionnaire and a visual analogue scale ranging from 0 (worst imaginable health state) to 100 (best imaginable health state). The efficacy population includes all randomized subjects who received at least 1 dose of the study drug Ibrutinib.

End point type	Secondary
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End point timeframe:

From 1st dose to Death, or End of Study whichever comes earlier (up to 2 years) prior to the Target Day of the window.

End point values	Ibrutinib			
Subject group type	Reporting group			
Number of subjects analysed	120			
Units: Unit on scale				
arithmetic mean (standard deviation)				
Visual Analogue Scale: Baseline (n=111)	68.77 (± 22.253)			
Visual Analogue Scale: last evaluation (n=114)	73.16 (± 20.939)			
UK-Utility Score: Baseline (n=112)	0.71 (± 0.258)			
UK-Utility Score: Last evaluation (n=114)	0.72 (± 0.273)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival Rate

End point title	Overall Survival Rate
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End point description:

Overall survival was defined as the interval between the date of first dose and the date of death from any cause. 999 indicates (NE) i.e. Median OS was not reached due to high censorship rate. The efficacy population includes all randomized subjects who received at least 1 dose of the study drug Ibrutinib.

End point type	Secondary
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End point timeframe:

Every 9 weeks from first dose to death for the first 15 months from the start of ibrutinib treatment, and thereafter, every 24 weeks until disease progression, death, or study end, whichever occurred first.

End point values	Ibrutinib			
Subject group type	Reporting group			
Number of subjects analysed	120			
Units: Months				
median (confidence interval 95%)	999 (18.53 to 999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response

End point title	Duration of Response
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End point description:

Duration of response was defined as the interval between the date of initial documentation of a response and the date of the first documented evidence of progressive disease or death, whichever occurred first. Participants who were progression-free and alive, or who had unknown status were censored at the last adequate tumor assessment. The distribution of the DOR was to be estimated using the Kaplan-Meier method. The efficacy population includes all randomized subjects who received at least 1 dose of the study drug Ibrutinib.

End point type	Secondary
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End point timeframe:

Time from first dose of study drug until the date of first documented evidence of progressive disease (or relapse for subjects who experience CR during the study) or death, whichever occurred first (up to 2 years)

End point values	Ibrutinib			
Subject group type	Reporting group			
Number of subjects analysed	69 ^[2]			
Units: Months				
median (confidence interval 95%)	14.92 (12.35 to 999)			

Notes:

[2] - Included responders only.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Initial Response and Best Response

End point title	Time to Initial Response and Best Response
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End point description:

Time to response/best response was defined as the interval between the date of the first dose and the date of the initial documentation of response/best response. The efficacy population includes all randomized subjects who received at least 1 dose of the study drug Ibrutinib.

End point type	Secondary
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End point timeframe:

Time from first dose of study drug until the date of first documented evidence of progressive disease (or relapse for subjects who experience CR during the study) or death, whichever occurred first (up to 2

End point values	Ibrutinib			
Subject group type	Reporting group			
Number of subjects analysed	69			
Units: months				
arithmetic mean (standard deviation)				
Time to initial response	2.37 (\pm 1.045)			
Time to best response	3.62 (\pm 2.346)			

Statistical analyses

No statistical analyses for this end point

Secondary: The Number Of Participants Affected By An Adverse Event

End point title	The Number Of Participants Affected By An Adverse Event
End point description:	
An AE is any untoward medical occurrence in a participant who received study drug without regard to possibility of causal relationship. An SAE is an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Safety population included all randomized participants who received at least 1 dose of the study drug.	
End point type	Secondary
End point timeframe:	
Time from first dose of study drug until the last dose date + 30 days or the start of a subsequent antineoplastic therapy, whichever occur earlier	

End point values	Ibrutinib			
Subject group type	Reporting group			
Number of subjects analysed	120			
Units: Participants	115			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 2 years.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.0
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Reporting groups

Reporting group title	Ibrutinib
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Reporting group description:

The participants received 560 milligram (mg) of ibrutinib orally once per day, as 4 x 140-mg capsules for 21 consecutive days.

Serious adverse events	Ibrutinib		
Total subjects affected by serious adverse events			
subjects affected / exposed	65 / 120 (54.17%)		
number of deaths (all causes)	57		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Prostate Cancer			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Circulatory Collapse			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Deep Vein Thrombosis			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypotension			

subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Lymphoedema			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	4 / 120 (3.33%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 1		
Chest Pain			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Death			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Fatigue			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Malaise			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oedema Peripheral			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pain			

subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Pyrexia			
subjects affected / exposed	3 / 120 (2.50%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	6 / 120 (5.00%)		
occurrences causally related to treatment / all	1 / 6		
deaths causally related to treatment / all	0 / 0		
Oropharyngeal Pain			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pleural Effusion			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory Failure			
subjects affected / exposed	4 / 120 (3.33%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 3		
Psychiatric disorders			
Confusional State			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Investigations			
Transaminases Increased			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Animal Bite			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fall			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Overdose			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tibia Fracture			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Angina Unstable			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Atrial Fibrillation			
subjects affected / exposed	5 / 120 (4.17%)		
occurrences causally related to treatment / all	4 / 5		
deaths causally related to treatment / all	0 / 0		
Atrial Flutter			

subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac Arrest			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cardiovascular Insufficiency			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Hypertensive Heart Disease			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebrovascular Accident			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Encephalopathy			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Haemorrhage Intracranial			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Headache			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Presyncope			

subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Transient Ischaemic Attack			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Febrile Neutropenia			
subjects affected / exposed	5 / 120 (4.17%)		
occurrences causally related to treatment / all	9 / 9		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Splenic Haemorrhage			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	4 / 120 (3.33%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Aphthous Stomatitis			

subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Colitis			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Bile Duct Stone			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholangitis			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholelithiasis			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			

Rash			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute Kidney Injury			
subjects affected / exposed	4 / 120 (3.33%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Nephrolithiasis			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Gouty Arthritis			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Muscular Weakness			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pain in Extremity			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Abdominal Abscess			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Appendicitis			

subjects affected / exposed	1 / 120 (0.83%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Appendicitis Perforated				
subjects affected / exposed	1 / 120 (0.83%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
subjects affected / exposed	1 / 120 (0.83%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Campylobacter Infection				
subjects affected / exposed	1 / 120 (0.83%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	5 / 120 (4.17%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Clostridium Difficile Colitis				
subjects affected / exposed	1 / 120 (0.83%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	2 / 120 (1.67%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis Viral				
subjects affected / exposed	1 / 120 (0.83%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lower Respiratory Tract Infection				

subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Peritonitis Bacterial			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	15 / 120 (12.50%)		
occurrences causally related to treatment / all	12 / 25		
deaths causally related to treatment / all	2 / 4		
Pneumonia Bacterial			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia Pseudomonal			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	3 / 120 (2.50%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 1		
Staphylococcal Bacteraemia			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Subcutaneous Abscess			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Upper Respiratory Tract Infection			

subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary Tract Infection			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urosepsis			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Hyperuricaemia			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoalbuminaemia			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Ibrutinib		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	113 / 120 (94.17%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal Cell Carcinoma			
subjects affected / exposed	6 / 120 (5.00%)		
occurrences (all)	9		

Acute Myeloid Leukaemia			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Basosquamous Carcinoma of Skin			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Lung Adenocarcinoma			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Prostate Cancer			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Seborrhoeic Keratosis			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Squamous Cell Carcinoma			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	6		
Tumour Flare			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Squamous Cell Carcinoma of Skin			
subjects affected / exposed	3 / 120 (2.50%)		
occurrences (all)	3		
Vascular disorders			
Aortic Arteriosclerosis			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Deep Vein Thrombosis			
subjects affected / exposed	6 / 120 (5.00%)		
occurrences (all)	6		
Flushing			
subjects affected / exposed	3 / 120 (2.50%)		
occurrences (all)	3		
Haematoma			

subjects affected / exposed	4 / 120 (3.33%)		
occurrences (all)	4		
Hot Flush			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	2		
Hypertension			
subjects affected / exposed	14 / 120 (11.67%)		
occurrences (all)	18		
Hypertensive Crisis			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Hypotension			
subjects affected / exposed	6 / 120 (5.00%)		
occurrences (all)	7		
Orthostatic Hypotension			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Lymphoedema			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	2		
Phlebitis			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Peripheral Venous Disease			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Thrombophlebitis Superficial			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	9 / 120 (7.50%)		
occurrences (all)	11		
Chest Discomfort			

subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	2		
Chest Pain			
subjects affected / exposed	8 / 120 (6.67%)		
occurrences (all)	9		
Chills			
subjects affected / exposed	6 / 120 (5.00%)		
occurrences (all)	10		
Early Satiety			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	51 / 120 (42.50%)		
occurrences (all)	68		
Gait Disturbance			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	4		
Generalised Oedema			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	2		
Gravitational Oedema			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Hypothermia			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Influenza Like Illness			
subjects affected / exposed	5 / 120 (4.17%)		
occurrences (all)	6		
Injection Site Bruising			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	2		
Injection Site Haemorrhage			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Local Swelling			

subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Malaise			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Non-Cardiac Chest Pain			
subjects affected / exposed	3 / 120 (2.50%)		
occurrences (all)	4		
Oedema			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Oedema Peripheral			
subjects affected / exposed	27 / 120 (22.50%)		
occurrences (all)	37		
Pain			
subjects affected / exposed	4 / 120 (3.33%)		
occurrences (all)	4		
Peripheral Swelling			
subjects affected / exposed	10 / 120 (8.33%)		
occurrences (all)	16		
Pyrexia			
subjects affected / exposed	24 / 120 (20.00%)		
occurrences (all)	40		
Swelling			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Temperature Intolerance			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Immune system disorders			
Allergy to Arthropod Bite			
subjects affected / exposed	3 / 120 (2.50%)		
occurrences (all)	4		
Food Allergy			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	3		

Hypersensitivity subjects affected / exposed occurrences (all)	1 / 120 (0.83%) 1		
Hypogammaglobulinaemia subjects affected / exposed occurrences (all)	4 / 120 (3.33%) 4		
Reproductive system and breast disorders			
Benign Prostatic Hyperplasia subjects affected / exposed occurrences (all)	2 / 120 (1.67%) 2		
Erectile Dysfunction subjects affected / exposed occurrences (all)	2 / 120 (1.67%) 3		
Genital Erythema subjects affected / exposed occurrences (all)	1 / 120 (0.83%) 1		
Genital Rash subjects affected / exposed occurrences (all)	1 / 120 (0.83%) 1		
Haematospermia subjects affected / exposed occurrences (all)	1 / 120 (0.83%) 1		
Oedema Genital subjects affected / exposed occurrences (all)	1 / 120 (0.83%) 1		
Pelvic Pain subjects affected / exposed occurrences (all)	1 / 120 (0.83%) 1		
Scrotal Swelling subjects affected / exposed occurrences (all)	1 / 120 (0.83%) 1		
Scrotal Mass subjects affected / exposed occurrences (all)	1 / 120 (0.83%) 1		
Testicular Pain			

subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Testicular Swelling			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Atelectasis			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Bronchial Secretion Retention			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Bronchitis Chronic			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	3		
Bronchiectasis			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Chronic Obstructive Pulmonary Disease			
subjects affected / exposed	4 / 120 (3.33%)		
occurrences (all)	5		
Cough			
subjects affected / exposed	33 / 120 (27.50%)		
occurrences (all)	41		
Dysphonia			
subjects affected / exposed	4 / 120 (3.33%)		
occurrences (all)	4		
Dyspnoea Exertional			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Dyspnoea			

subjects affected / exposed	23 / 120 (19.17%)		
occurrences (all)	27		
Emphysema			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Epistaxis			
subjects affected / exposed	9 / 120 (7.50%)		
occurrences (all)	10		
Haemoptysis			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	3		
Hiccups			
subjects affected / exposed	3 / 120 (2.50%)		
occurrences (all)	3		
Hypoxia			
subjects affected / exposed	3 / 120 (2.50%)		
occurrences (all)	3		
Nasal Congestion			
subjects affected / exposed	10 / 120 (8.33%)		
occurrences (all)	12		
Nasal Inflammation			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	2		
Nasal Discomfort			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	2		
Nasal Mucosal Disorder			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Nasal Septum Perforation			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Nasal Septum Deviation			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Paranasal Sinus Discomfort			

subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Oropharyngeal Pain			
subjects affected / exposed	12 / 120 (10.00%)		
occurrences (all)	18		
Pharyngeal Erythema			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Pleural Effusion			
subjects affected / exposed	5 / 120 (4.17%)		
occurrences (all)	8		
Pneumothorax			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	2		
Productive Cough			
subjects affected / exposed	9 / 120 (7.50%)		
occurrences (all)	11		
Pulmonary Mass			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Pulmonary Oedema			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Respiratory Distress			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Respiratory Acidosis			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Respiratory Tract Congestion			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	2		
Respiratory Failure			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	3		
Rhinorrhoea			

subjects affected / exposed	9 / 120 (7.50%)		
occurrences (all)	10		
Sinus Congestion			
subjects affected / exposed	3 / 120 (2.50%)		
occurrences (all)	3		
Sleep Apnoea Syndrome			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Tachypnoea			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Tonsillar Hypertrophy			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Upper Respiratory Tract Congestion			
subjects affected / exposed	6 / 120 (5.00%)		
occurrences (all)	7		
Wheezing			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Upper-Airway Cough Syndrome			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Anxiety			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	2		
Confusional State			
subjects affected / exposed	5 / 120 (4.17%)		
occurrences (all)	6		
Delirium			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		

Depression Suicidal subjects affected / exposed occurrences (all)	1 / 120 (0.83%) 1		
Depression subjects affected / exposed occurrences (all)	4 / 120 (3.33%) 4		
Hallucination, Auditory subjects affected / exposed occurrences (all)	1 / 120 (0.83%) 1		
Mental Status Changes subjects affected / exposed occurrences (all)	1 / 120 (0.83%) 1		
Insomnia subjects affected / exposed occurrences (all)	10 / 120 (8.33%) 10		
Investigations			
Activated Partial Thromboplastin Time Prolonged subjects affected / exposed occurrences (all)	2 / 120 (1.67%) 13		
Amylase Increased subjects affected / exposed occurrences (all)	1 / 120 (0.83%) 1		
Aspartate Aminotransferase Increased subjects affected / exposed occurrences (all)	2 / 120 (1.67%) 3		
Blood Albumin Decreased subjects affected / exposed occurrences (all)	2 / 120 (1.67%) 3		
Blood Alkaline Phosphatase Increased subjects affected / exposed occurrences (all)	6 / 120 (5.00%) 13		
Blood Bilirubin Increased subjects affected / exposed occurrences (all)	5 / 120 (4.17%) 7		
Blood Chloride Decreased			

subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Blood Creatine Increased			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Blood Creatinine Increased			
subjects affected / exposed	11 / 120 (9.17%)		
occurrences (all)	22		
Blood Glucose Increased			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Blood Immunoglobulin G Decreased			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Blood Lactate Dehydrogenase Increased			
subjects affected / exposed	3 / 120 (2.50%)		
occurrences (all)	3		
Blood Pressure Decreased			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Blood Pressure Increased			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Blood Urea Increased			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Blood Uric Acid Increased			
subjects affected / exposed	4 / 120 (3.33%)		
occurrences (all)	5		
Carbon Dioxide Decreased			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Computerised Tomogram Thorax Abnormal			

subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Ejection Fraction Decreased			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Heart Rate Increased			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
International Normalised Ratio Increased			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	6		
Liver Function Test Abnormal			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Lymphocyte Count Increased			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	5		
Neutrophil Count Decreased			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	5		
Platelet Count Decreased			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	10		
Serum Ferritin Decreased			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Very Low Density Lipoprotein Increased			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Weight Decreased			
subjects affected / exposed	4 / 120 (3.33%)		
occurrences (all)	4		
Weight Increased			

subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	2		
White Blood Cell Count Decreased			
subjects affected / exposed	4 / 120 (3.33%)		
occurrences (all)	28		
White Blood Cell Count Increased			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Animal Bite			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	2		
Animal Scratch			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Ankle Fracture			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Arthropod Bite			
subjects affected / exposed	4 / 120 (3.33%)		
occurrences (all)	4		
Arthropod Sting			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Burns Second Degree			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Contusion			
subjects affected / exposed	18 / 120 (15.00%)		
occurrences (all)	25		
Excoriation			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Facial Bones Fracture			

subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Fall			
subjects affected / exposed	5 / 120 (4.17%)		
occurrences (all)	6		
Foot Fracture			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Haematuria Traumatic			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Laceration			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Ligament Rupture			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Ligament Sprain			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Meniscus Injury			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Periorbital Contusion			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Post Procedural Haemorrhage			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Procedural Pain			
subjects affected / exposed	3 / 120 (2.50%)		
occurrences (all)	3		
Skin Abrasion			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	6		
Sunburn			

subjects affected / exposed	3 / 120 (2.50%)		
occurrences (all)	3		
Thermal Burn			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Tibia Fracture			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Tooth Fracture			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Wound			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	2		
Wound Complication			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Cardiac disorders			
Angina Unstable			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Atrial Fibrillation			
subjects affected / exposed	11 / 120 (9.17%)		
occurrences (all)	18		
Atrial Flutter			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Cyanosis			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Bradycardia			
subjects affected / exposed	3 / 120 (2.50%)		
occurrences (all)	4		
Pericardial Effusion			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		

Sinus Bradycardia			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Sinus Node Dysfunction			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Sinus Tachycardia			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Stress Cardiomyopathy			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Supraventricular Tachycardia			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Tachyarrhythmia			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Tachycardia			
subjects affected / exposed	8 / 120 (6.67%)		
occurrences (all)	8		
Tricuspid Valve Disease			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Ventricular Extrasystoles			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Nervous system disorders			
Amnesia			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	2		
Balance Disorder			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	3		
Dementia			

subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Dizziness			
subjects affected / exposed	6 / 120 (5.00%)		
occurrences (all)	7		
Dizziness Exertional			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	2		
Dizziness Postural			
subjects affected / exposed	10 / 120 (8.33%)		
occurrences (all)	12		
Dysgeusia			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	3		
Dysarthria			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	12 / 120 (10.00%)		
occurrences (all)	15		
Hypersomnia			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Hypoaesthesia			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	2		
Memory Impairment			
subjects affected / exposed	3 / 120 (2.50%)		
occurrences (all)	3		
Muscle Contractions Involuntary			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	2		
Neuralgia			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	2		
Neuropathy Peripheral			

subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	2		
Paraesthesia			
subjects affected / exposed	5 / 120 (4.17%)		
occurrences (all)	7		
Peripheral Sensory Neuropathy			
subjects affected / exposed	6 / 120 (5.00%)		
occurrences (all)	6		
Post Herpetic Neuralgia			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Restless Legs Syndrome			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Sciatica			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Sinus Headache			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	2		
Speech Disorder			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Somnolence			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Syncope			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	2		
Tremor			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	2		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	27 / 120 (22.50%)		
occurrences (all)	48		

Bone Marrow Failure			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Coagulopathy			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Hypoglobulinaemia			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	2		
Leukocytosis			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	4		
Leukopenia			
subjects affected / exposed	6 / 120 (5.00%)		
occurrences (all)	17		
Leukostasis Syndrome			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Lymph Node Pain			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	2		
Lymphocytosis			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Neutropenia			
subjects affected / exposed	27 / 120 (22.50%)		
occurrences (all)	101		
Thrombocytopenia			
subjects affected / exposed	30 / 120 (25.00%)		
occurrences (all)	71		
Neutrophilia			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Thrombocytosis			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		

Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Cerumen Impaction			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	2		
Deafness Bilateral			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Ear Discomfort			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	2		
Ear Pain			
subjects affected / exposed	3 / 120 (2.50%)		
occurrences (all)	5		
Tinnitus			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Vertigo			
subjects affected / exposed	4 / 120 (3.33%)		
occurrences (all)	4		
Eye disorders			
Age-Related Macular Degeneration			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Cataract			
subjects affected / exposed	4 / 120 (3.33%)		
occurrences (all)	5		
Conjunctival Haemorrhage			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Dry Eye			
subjects affected / exposed	7 / 120 (5.83%)		
occurrences (all)	7		
Entropion			

subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Eye Haemorrhage			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Eye Pain			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Eye Pruritus			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Glaucoma			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	2		
Iridocyclitis			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Lacrimation Increased			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	2		
Keratitis			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Macular Degeneration			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Meibomian Gland Dysfunction			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Periorbital Oedema			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	2		
Photophobia			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Trichiasis			

subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	2		
Visual Acuity Reduced			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Vision Blurred			
subjects affected / exposed	10 / 120 (8.33%)		
occurrences (all)	10		
Visual Impairment			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	2		
Gastrointestinal disorders			
Abdominal Distension			
subjects affected / exposed	4 / 120 (3.33%)		
occurrences (all)	4		
Abdominal Pain			
subjects affected / exposed	10 / 120 (8.33%)		
occurrences (all)	10		
Abdominal Pain Lower			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	2		
Abdominal Pain Upper			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	2		
Aphthous Stomatitis			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	4		
Cheilitis			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	22 / 120 (18.33%)		
occurrences (all)	22		
Dental Caries			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		

Dental Discomfort			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	4		
Diarrhoea			
subjects affected / exposed	55 / 120 (45.83%)		
occurrences (all)	97		
Dry Mouth			
subjects affected / exposed	5 / 120 (4.17%)		
occurrences (all)	5		
Dyspepsia			
subjects affected / exposed	8 / 120 (6.67%)		
occurrences (all)	11		
Dysphagia			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	2		
Flatulence			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Eructation			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Food Poisoning			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Gastritis			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Gastritis Haemorrhagic			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Gastrooesophageal Reflux Disease			
subjects affected / exposed	6 / 120 (5.00%)		
occurrences (all)	6		
Gingival Pain			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		

Haemorrhoidal Haemorrhage			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Glossodynia			
subjects affected / exposed	4 / 120 (3.33%)		
occurrences (all)	4		
Haemorrhoids			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Ileus			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	2		
Impaired Gastric Emptying			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Inguinal Hernia			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	2		
Lip Pain			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Lip Swelling			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Loose Tooth			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Mouth Ulceration			
subjects affected / exposed	5 / 120 (4.17%)		
occurrences (all)	6		
Nausea			
subjects affected / exposed	25 / 120 (20.83%)		
occurrences (all)	44		
Oral Pain			
subjects affected / exposed	3 / 120 (2.50%)		
occurrences (all)	3		

Rectal Fissure			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Rectal Haemorrhage			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Stomatitis			
subjects affected / exposed	15 / 120 (12.50%)		
occurrences (all)	32		
Tongue Ulceration			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Tooth Discolouration			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Tooth Loss			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Toothache			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	2		
Vomiting			
subjects affected / exposed	20 / 120 (16.67%)		
occurrences (all)	29		
Hepatobiliary disorders			
Hepatic Failure			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Hyperbilirubinaemia			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	3		
Porcelain Gallbladder			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			

Acne			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	3		
Actinic Keratosis			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Alopecia			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	2		
Blister			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Capillaritis			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Dermal Cyst			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	2		
Decubitus Ulcer			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	2		
Dermatitis			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Dermatitis Acneiform			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	2		
Dermatitis Bullous			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Dry Skin			
subjects affected / exposed	6 / 120 (5.00%)		
occurrences (all)	8		
Dermatitis Contact			
subjects affected / exposed	3 / 120 (2.50%)		
occurrences (all)	3		

Ecchymosis			
subjects affected / exposed	3 / 120 (2.50%)		
occurrences (all)	4		
Erythema			
subjects affected / exposed	5 / 120 (4.17%)		
occurrences (all)	5		
Haemorrhage Subcutaneous			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Hair Disorder			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Hyperhidrosis			
subjects affected / exposed	4 / 120 (3.33%)		
occurrences (all)	6		
Ingrowing Nail			
subjects affected / exposed	3 / 120 (2.50%)		
occurrences (all)	4		
Lentigo			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Intertrigo			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Nail Bed Disorder			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Night Sweats			
subjects affected / exposed	6 / 120 (5.00%)		
occurrences (all)	6		
Nail Discolouration			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	2		
Pain of Skin			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	2		

Onychomadesis			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Petechiae			
subjects affected / exposed	7 / 120 (5.83%)		
occurrences (all)	9		
Pruritus			
subjects affected / exposed	10 / 120 (8.33%)		
occurrences (all)	11		
Pruritus Generalised			
subjects affected / exposed	3 / 120 (2.50%)		
occurrences (all)	3		
Purpura			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	9		
Rash			
subjects affected / exposed	23 / 120 (19.17%)		
occurrences (all)	44		
Rash Follicular			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Rash Generalised			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Rash Maculo-Papular			
subjects affected / exposed	3 / 120 (2.50%)		
occurrences (all)	3		
Rash Papular			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	5		
Rash Pruritic			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Skin Hyperpigmentation			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	2		

Skin Irritation			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Skin Mass			
subjects affected / exposed	4 / 120 (3.33%)		
occurrences (all)	4		
Skin Lesion			
subjects affected / exposed	7 / 120 (5.83%)		
occurrences (all)	9		
Skin Ulcer			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	3		
Skin Swelling			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Urticaria			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Renal and urinary disorders			
Bladder Irritation			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Acute Kidney Injury			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	2		
Dysuria			
subjects affected / exposed	5 / 120 (4.17%)		
occurrences (all)	5		
Haematuria			
subjects affected / exposed	5 / 120 (4.17%)		
occurrences (all)	5		
Hypertonic Bladder			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Nephrolithiasis			

subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	3		
Nocturia			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	2		
Pollakiuria			
subjects affected / exposed	3 / 120 (2.50%)		
occurrences (all)	3		
Renal Cyst			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Renal Failure			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	2		
Urinary Retention			
subjects affected / exposed	4 / 120 (3.33%)		
occurrences (all)	4		
Urinary Tract Obstruction			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Arthralgia			
subjects affected / exposed	20 / 120 (16.67%)		
occurrences (all)	36		
Back Pain			
subjects affected / exposed	15 / 120 (12.50%)		
occurrences (all)	17		
Bone Pain			

subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	2		
Flank Pain			
subjects affected / exposed	3 / 120 (2.50%)		
occurrences (all)	3		
Groin Pain			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	2		
Joint Effusion			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Joint Lock			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Joint Swelling			
subjects affected / exposed	4 / 120 (3.33%)		
occurrences (all)	7		
Limb Discomfort			
subjects affected / exposed	3 / 120 (2.50%)		
occurrences (all)	3		
Muscle Spasms			
subjects affected / exposed	27 / 120 (22.50%)		
occurrences (all)	40		
Muscle Tightness			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Muscular Weakness			
subjects affected / exposed	3 / 120 (2.50%)		
occurrences (all)	3		
Muscle Twitching			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Musculoskeletal Pain			
subjects affected / exposed	10 / 120 (8.33%)		
occurrences (all)	11		
Musculoskeletal Stiffness			

subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	2		
Myalgia			
subjects affected / exposed	17 / 120 (14.17%)		
occurrences (all)	22		
Myopathy			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Neck Pain			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Osteoarthritis			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	2		
Pain in Extremity			
subjects affected / exposed	11 / 120 (9.17%)		
occurrences (all)	12		
Pain in Jaw			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Vertebral Foraminal Stenosis			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Infections and infestations			
Acne Pustular			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Acute Sinusitis			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Anal Candidiasis			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Atypical Pneumonia			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		

Body Tinea			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Bronchitis			
subjects affected / exposed	8 / 120 (6.67%)		
occurrences (all)	11		
Cellulitis			
subjects affected / exposed	8 / 120 (6.67%)		
occurrences (all)	8		
Clostridium Difficile Colitis			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Clostridium Difficile Infection			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	2		
Conjunctivitis			
subjects affected / exposed	4 / 120 (3.33%)		
occurrences (all)	5		
Cystitis			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Device Related Infection			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Ear Infection			
subjects affected / exposed	4 / 120 (3.33%)		
occurrences (all)	4		
Folliculitis			
subjects affected / exposed	6 / 120 (5.00%)		
occurrences (all)	7		
Eye Infection			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	2		
Fungal Infection			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	2		

Fungal Skin Infection			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	2		
Gastroenteritis			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Gastroenteritis Viral			
subjects affected / exposed	3 / 120 (2.50%)		
occurrences (all)	4		
Genital Candidiasis			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Gingivitis			
subjects affected / exposed	3 / 120 (2.50%)		
occurrences (all)	3		
Haematoma Infection			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Herpes Zoster			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Hordeolum			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	2		
Localised Infection			
subjects affected / exposed	3 / 120 (2.50%)		
occurrences (all)	3		
Lower Respiratory Tract Infection			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	2		
Lung Infection			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	2		
Lyme Disease			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		

Nail Bed Infection			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	9 / 120 (7.50%)		
occurrences (all)	9		
Oral Candidiasis			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	2		
Oral Fungal Infection			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Oral Herpes			
subjects affected / exposed	4 / 120 (3.33%)		
occurrences (all)	5		
Osteomyelitis			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Otitis Media			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	3		
Paronychia			
subjects affected / exposed	3 / 120 (2.50%)		
occurrences (all)	5		
Peritonitis Bacterial			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Pharyngitis Streptococcal			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Pneumonia			
subjects affected / exposed	8 / 120 (6.67%)		
occurrences (all)	10		
Post Procedural Infection			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		

Rabies			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Respiratory Tract Infection			
subjects affected / exposed	3 / 120 (2.50%)		
occurrences (all)	3		
Respiratory Tract Infection Viral			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Rhinitis			
subjects affected / exposed	5 / 120 (4.17%)		
occurrences (all)	5		
Sepsis			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Sinusitis			
subjects affected / exposed	15 / 120 (12.50%)		
occurrences (all)	17		
Skin Infection			
subjects affected / exposed	3 / 120 (2.50%)		
occurrences (all)	3		
Staphylococcal Skin Infection			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Tooth Abscess			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Tooth Infection			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Upper Respiratory Tract Infection			
subjects affected / exposed	23 / 120 (19.17%)		
occurrences (all)	35		
Urinary Tract Infection			
subjects affected / exposed	12 / 120 (10.00%)		
occurrences (all)	12		

Urinary Tract Infection Fungal subjects affected / exposed occurrences (all)	1 / 120 (0.83%) 1		
Urosepsis subjects affected / exposed occurrences (all)	1 / 120 (0.83%) 1		
Urinary Tract Infection Bacterial subjects affected / exposed occurrences (all)	1 / 120 (0.83%) 1		
Viral Upper Respiratory Tract Infection subjects affected / exposed occurrences (all)	1 / 120 (0.83%) 1		
Vulvovaginal Candidiasis subjects affected / exposed occurrences (all)	1 / 120 (0.83%) 1		
Wound Infection subjects affected / exposed occurrences (all)	1 / 120 (0.83%) 1		
Metabolism and nutrition disorders			
Decreased Appetite subjects affected / exposed occurrences (all)	15 / 120 (12.50%) 20		
Dehydration subjects affected / exposed occurrences (all)	7 / 120 (5.83%) 7		
Gout subjects affected / exposed occurrences (all)	1 / 120 (0.83%) 1		
Hyperammonaemia subjects affected / exposed occurrences (all)	1 / 120 (0.83%) 1		
Hyperglycaemia subjects affected / exposed occurrences (all)	2 / 120 (1.67%) 3		
Hyperkalaemia			

subjects affected / exposed	4 / 120 (3.33%)		
occurrences (all)	8		
Hypernatraemia			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	5		
Hyperphosphataemia			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Hypertriglyceridaemia			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Hyperuricaemia			
subjects affected / exposed	5 / 120 (4.17%)		
occurrences (all)	6		
Hypoalbuminaemia			
subjects affected / exposed	7 / 120 (5.83%)		
occurrences (all)	18		
Hypocalcaemia			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	5		
Hypoglycaemia			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	3		
Hypokalaemia			
subjects affected / exposed	15 / 120 (12.50%)		
occurrences (all)	25		
Hypomagnesaemia			
subjects affected / exposed	10 / 120 (8.33%)		
occurrences (all)	13		
Hyponatraemia			
subjects affected / exposed	6 / 120 (5.00%)		
occurrences (all)	9		
Hypophosphataemia			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	3		
Lactic Acidosis			

subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Metabolic Acidosis			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 November 2012	This amendment was implemented primarily to modify exclusion criteria so as to exclude participants requiring anticoagulation with vitamin K antagonists (eg, phenprocoumon) and to specify that concomitant use of warfarin or a vitamin K antagonist was prohibited; clarify the management of ibrutinib when administered concomitantly with CYP3A4/5 inhibitors/inducers and anticoagulants; and to clarify the use of positron emission tomography (PET) scanning to confirm disease progression.
28 August 2013	This amendment was implemented primarily to update safety-related information and to revise operational aspects of the study. Specifically, the clinical cutoff for the primary analysis was changed from 6 months to approximately 1 year after the last subject was enrolled, and an interim database lock for analysis of pharmacokinetic data was specified to occur approximately 3 months after the scheduled pharmacokinetic sampling in Cycles 1 and 2; a requirement was added for reporting of other malignancies during all follow-up phases; additional guidance was added based on emerging data regarding concomitant use of CYP3A4/5 inhibitors, antiplatelet agents, anticoagulants, and agents known to cause QT prolongation.

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.

The single-arm study design that was used is typical for a Phase 2 oncology study. Within this context, there were no notable study limitations identified by the Sponsor.

Notes: