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

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

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

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

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

years)

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:

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.

End point type	Secondary

End point timeframe:

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.

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) Last evaluation (n=116)	44.96 (± 8.948) 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

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

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

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 cencorship rate. 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:

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

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

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

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

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			
Units: months				
arithmetic mean (standard deviation)				
Time to initial response	2.37 (± 1.045)			
Time to best response	3.62 (± 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

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

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.

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	1 / 120 (0.83%)		
occurrences (all)	1		
Hypogammaglobulinaemia			
subjects affected / exposed	4 / 120 (3.33%)		
occurrences (all)	4		
Reproductive system and breast disorders			
Benign Prostatic Hyperplasia			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	2		
Erectile Dysfunction			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	3		
Genital Erythema			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Genital Rash			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Haematospermia			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Oedema Genital			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Pelvic Pain			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Scrotal Swelling			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	1		
Scrotal Mass			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences (all)	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	1 / 120 (0.83%)			
occurrences (all)	1			
Depression				
subjects affected / exposed	4 / 120 (3.33%)			
occurrences (all)	4			
Hallucination, Auditory				
subjects affected / exposed	1 / 120 (0.83%)			
occurrences (all)	1			
Mental Status Changes				
subjects affected / exposed	1 / 120 (0.83%)			
occurrences (all)	1			
Insomnia				
subjects affected / exposed	10 / 120 (8.33%)			
occurrences (all)	10			
Investigations				
Activated Partial Thromboplastin Time Prolonged				
subjects affected / exposed	2 / 120 (1.67%)			
occurrences (all)	13			
Amylase Increased				
subjects affected / exposed	1 / 120 (0.83%)			
occurrences (all)	1			
Aspartate Aminotransferase Increased				
subjects affected / exposed	2 / 120 (1.67%)			
occurrences (all)	3			
Blood Albumin Decreased				
subjects affected / exposed	2 / 120 (1.67%)			
occurrences (all)	3			
Blood Alkaline Phosphatase Increased				
subjects affected / exposed	6 / 120 (5.00%)			
occurrences (all)	13			
Blood Bilirubin Increased				
subjects affected / exposed	5 / 120 (4.17%)			
occurrences (all)	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 occurrences (all)	1 / 120 (0.83%) 1		
Sinus Node Dysfunction subjects affected / exposed occurrences (all)	1 / 120 (0.83%) 1		
Sinus Tachycardia subjects affected / exposed occurrences (all)	1 / 120 (0.83%) 1		
Stress Cardiomyopathy subjects affected / exposed occurrences (all)	1 / 120 (0.83%) 1		
Supraventricular Tachycardia subjects affected / exposed occurrences (all)	1 / 120 (0.83%) 1		
Tachyarrhythmia subjects affected / exposed occurrences (all)	1 / 120 (0.83%) 1		
Tachycardia subjects affected / exposed occurrences (all)	8 / 120 (6.67%) 8		
Tricuspid Valve Disease subjects affected / exposed occurrences (all)	1 / 120 (0.83%) 1		
Ventricular Extrasystoles subjects affected / exposed occurrences (all)	1 / 120 (0.83%) 1		
Nervous system disorders Amnesia subjects affected / exposed occurrences (all)	2 / 120 (1.67%) 2		
Balance Disorder subjects affected / exposed occurrences (all)	2 / 120 (1.67%) 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 occurrences (all)	1 / 120 (0.83%) 1		
Rectal Haemorrhage subjects affected / exposed occurrences (all)	1 / 120 (0.83%) 1		
Stomatitis subjects affected / exposed occurrences (all)	15 / 120 (12.50%) 32		
Tongue Ulceration subjects affected / exposed occurrences (all)	1 / 120 (0.83%) 1		
Tooth Discolouration subjects affected / exposed occurrences (all)	1 / 120 (0.83%) 1		
Tooth Loss subjects affected / exposed occurrences (all)	1 / 120 (0.83%) 1		
Toothache subjects affected / exposed occurrences (all)	2 / 120 (1.67%) 2		
Vomiting subjects affected / exposed occurrences (all)	20 / 120 (16.67%) 29		
Hepatobiliary disorders			
Hepatic Failure subjects affected / exposed occurrences (all)	1 / 120 (0.83%) 1		
Hyperbilirubinaemia subjects affected / exposed occurrences (all)	1 / 120 (0.83%) 3		
Porcelain Gallbladder subjects affected / exposed occurrences (all)	1 / 120 (0.83%) 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 occurrences (all)	1 / 120 (0.83%) 1			
Skin Mass subjects affected / exposed occurrences (all)	4 / 120 (3.33%) 4			
Skin Lesion subjects affected / exposed occurrences (all)	7 / 120 (5.83%) 9			
Skin Ulcer subjects affected / exposed occurrences (all)	2 / 120 (1.67%) 3			
Skin Swelling subjects affected / exposed occurrences (all)	1 / 120 (0.83%) 1			
Urticaria subjects affected / exposed occurrences (all)	1 / 120 (0.83%) 1			
Renal and urinary disorders Bladder Irritation subjects affected / exposed occurrences (all)	1 / 120 (0.83%) 1			
Acute Kidney Injury subjects affected / exposed occurrences (all)	2 / 120 (1.67%) 2			
Dysuria subjects affected / exposed occurrences (all)	5 / 120 (4.17%) 5			
Haematuria subjects affected / exposed occurrences (all)	5 / 120 (4.17%) 5			
Hypertonic Bladder subjects affected / exposed occurrences (all)	1 / 120 (0.83%) 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: