Clinical trial results:
An Open-label, Single arm, Multicenter Phase 2 Study of the Bruton's Tyrosine Kinase Inhibitor PCI-32765 (Ibrutinib) in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma with 17p Deletion (RESONATE™-17)

Summary

EudraCT number	2012-004476-19
Trial protocol	GB SE BE DE
Global end of trial date	

Results information

Result version number	v1
This version publication date	01 May 2016
First version publication date	01 May 2016

Trial information

Trial identification

Sponsor protocol code	PCYC-1117-CA

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01744691
WHO universal trial number (UTN)	-
Other trial identifiers	provider NLM_DES study id: S0003WPS

Notes:

Sponsors

Sponsor organisation name	Pharmacyclics LLC
Sponsor organisation address	999 E Arques Ave, Sunnyvale, United States, 94085
Public contact	Kristin Russell (CTM), Pharmacyclics LLC, 001 408-215-3508, krussell@pcyc.com
Scientific contact	Dr. Alvina Chu, Pharmacyclics LLC, 001 855-427-8846, medinfo@pcyc.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	Interim
Date of interim/final analysis	20 June 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 June 2014
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate the efficacy of ibrutinib in terms of ORR per IWCLL 2008 criteria in subjects with relapsed or refractory CLL/SLL with documented del17p, who received a minimum of 1 prior line of systemic treatment.

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki and ICH GCP.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 January 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 14
Country: Number of subjects enrolled	Germany: 13
Country: Number of subjects enrolled	Turkey: 11
Country: Number of subjects enrolled	United States: 84
Country: Number of subjects enrolled	Sweden: 8
Country: Number of subjects enrolled	Australia: 7
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	New Zealand: 2
Worldwide total number of subjects	144
EEA total number of subjects	38

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	75
From 65 to 84 years	67
85 years and over	2

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

One hundred forty-five subjects were enrolled and 144 subjects received at least 1 dose of Ibrutinib and constitute the all treated population and the safety analysis set.

Period 1

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

Arms

Arm title	Ibrutinib

Arm description:

All subjects who received at least one dose of Ibrutinib 420 mg (3 x 140-mg capsules) orally once daily.

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

Dosage and administration details:

All subjects received Ibrutinib 420 mg (3 x 140-mg capsules) orally once daily.

Number of subjects in period 1	Ibrutinib
Started	144
Completed	101
Not completed	43
Unacceptable toxicity, AE or death	18
Physician decision	4
Progressive Disease	18
Withdrawal of consent for treatment	3

Baseline characteristics

Reporting groups	
Reporting group title	Ibrutinib
Reporting group description:	
All subjects who received at least one dose of Ibrutinib 420 mg (3 x 140-mg capsules) orally once daily.	

Reporting group values	Ibrutinib	Total	
Number of subjects	144	144	
Age Categorical Units: Subjects			
<=18 years	0	0	
Between 18 and 65 years	75	75	
>=65 years	69	69	
Age Continuous Units: years			
arithmetic mean	64.4		
standard deviation	± 9.9	-	
Gender, Male/Female Units: Subjects			
Female	48	48	
Male	96	96	

End points

End points reporting groups

Reporting group title	Ibrutinib

Reporting group description:

All subjects who received at least one dose of Ibrutinib 420 mg (3 x 140-mg capsules) orally once daily.

Subject analysis set title	Ibrutinib
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All subjects who received at least one dose of ibrutinib 420 mg (3 x 140-mg capsules) orally once daily.

Primary: Overall Response Rate

End point title	Overall Response Rate[1]

End point description:

The primary objective of this study is to evaluate the efficacy of Ibrutinib in terms of ORR according to an Independent Review Committee (IRC). ORR based upon IRC assessment is the proportion of responders in the all treated population. Responders were subjects who achieved partial response (PR) or better, ie, complete response (CR), complete response with incomplete marrow recovery (CRi), nodule partial response (nPR) or PR, per IWCLL 2008 criteria with the clarification for treatment-related lymphocytosis.

End point type	Primary

End point timeframe:

The median time on study for all treated participants is 11.5 (range 0.5 - 16.6) months

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: Response rate and its 95% CI was calculated based on normal approximation with Wilson's score method.

End point values	Ibrutinib			
Subject group type	Subject analysis set			
Number of subjects analysed	144			
Units: % of participants with response by IRC				
number (confidence interval 95%)	63.9 (55.8 to 71.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Treatment Emergent Adverse Events (AEs)

End point title	Number of Participants With Treatment Emergent Adverse Events (AEs)

End point description:

Number of participants who had experienced at least one treatment emergent AE

End point type	Secondary

End point timeframe:

From first dose of Ibrutinib to within 30 days of last dose for each participant or until study closure

End point values	Ibrutinib			
Subject group type	Subject analysis set			
Number of subjects analysed	144			
Units: participants				
number (not applicable)	144			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From first dose of Ibrutinib to within 30 days of last dose	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.0
Reporting groups	
Reporting group title	Ibrutinib
Reporting group description: All subjects received Ibrutinib 420 mg (3 x 140-mg capsules) orally once daily.	

Serious adverse events	Ibrutinib		
Total subjects affected by serious adverse events			
subjects affected / exposed	58 / 144 (40.28%)		
number of deaths (all causes)	23		
number of deaths resulting from adverse events	2		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Chronic lymphocytic leukaemia			
subjects affected / exposed	3 / 144 (2.08%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 2		
Hodgkin's disease			
subjects affected / exposed	1 / 144 (0.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lymphoma transformation			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 144 (0.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Richter's syndrome			

subjects affected / exposed	4 / 144 (2.78%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 1			
Skin papilloma				
subjects affected / exposed	1 / 144 (0.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Arterial haemorrhage				
subjects affected / exposed	1 / 144 (0.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Fatigue				
subjects affected / exposed	1 / 144 (0.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
General physical health deterioration				
subjects affected / exposed	1 / 144 (0.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Localised oedema				
subjects affected / exposed	1 / 144 (0.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Oedema peripheral				
subjects affected / exposed	1 / 144 (0.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	3 / 144 (2.08%)			
occurrences causally related to treatment / all	3 / 7			
deaths causally related to treatment / all	0 / 0			

Respiratory, thoracic and mediastinal disorders			
Alveolitis allergic			
subjects affected / exposed	1 / 144 (0.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Haemoptysis			
subjects affected / exposed	1 / 144 (0.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Interstitial lung disease			
subjects affected / exposed	1 / 144 (0.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	3 / 144 (2.08%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Pneumonitis			
subjects affected / exposed	1 / 144 (0.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary oedema			
subjects affected / exposed	1 / 144 (0.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	1 / 144 (0.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Muscle rupture			

subjects affected / exposed	1 / 144 (0.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Post procedural haematuria			
subjects affected / exposed	1 / 144 (0.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Traumatic haematoma			
subjects affected / exposed	1 / 144 (0.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	2 / 144 (1.39%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Atrial fibrillation			
subjects affected / exposed	6 / 144 (4.17%)		
occurrences causally related to treatment / all	1 / 6		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			
subjects affected / exposed	1 / 144 (0.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Nervous system disorders			
Critical illness polyneuropathy			
subjects affected / exposed	1 / 144 (0.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	1 / 144 (0.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemorrhage intracranial			

subjects affected / exposed	1 / 144 (0.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 144 (2.08%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Autoimmune haemolytic anaemia			
subjects affected / exposed	1 / 144 (0.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Coagulopathy			
subjects affected / exposed	1 / 144 (0.69%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	2 / 144 (1.39%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Haemolytic anaemia			
subjects affected / exposed	1 / 144 (0.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune thrombocytopenic purpura			
subjects affected / exposed	1 / 144 (0.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Iron deficiency anaemia			
subjects affected / exposed	1 / 144 (0.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Thrombocytopenia			
subjects affected / exposed	1 / 144 (0.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Spontaneous haematoma			
subjects affected / exposed	1 / 144 (0.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Iritis			
subjects affected / exposed	1 / 144 (0.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	2 / 144 (1.39%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Anal fissure			
subjects affected / exposed	1 / 144 (0.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Colitis ischaemic			
subjects affected / exposed	1 / 144 (0.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 144 (0.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastric ulcer haemorrhage			
subjects affected / exposed	1 / 144 (0.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Gastritis				
subjects affected / exposed	1 / 144 (0.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Intestinal obstruction				
subjects affected / exposed	1 / 144 (0.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Oral mucosal blistering				
subjects affected / exposed	1 / 144 (0.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	1 / 144 (0.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Cholecystitis				
subjects affected / exposed	2 / 144 (1.39%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cholecystitis acute				
subjects affected / exposed	1 / 144 (0.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Skin erosion				
subjects affected / exposed	1 / 144 (0.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Stevens-Johnson syndrome				
subjects affected / exposed	1 / 144 (0.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Renal and urinary disorders			
Renal failure			
subjects affected / exposed	2 / 144 (1.39%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Renal infarct			
subjects affected / exposed	1 / 144 (0.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	2 / 144 (1.39%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Dactylitis			
subjects affected / exposed	1 / 144 (0.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Muscular weakness			
subjects affected / exposed	1 / 144 (0.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myalgia			
subjects affected / exposed	1 / 144 (0.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Osteoporosis			
subjects affected / exposed	1 / 144 (0.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Aspergillus infection			

subjects affected / exposed	1 / 144 (0.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bacteraemia				
subjects affected / exposed	1 / 144 (0.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Atypical pneumonia				
subjects affected / exposed	1 / 144 (0.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
subjects affected / exposed	2 / 144 (1.39%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Campylobacter gastroenteritis				
subjects affected / exposed	1 / 144 (0.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cystitis				
subjects affected / exposed	1 / 144 (0.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	3 / 144 (2.08%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis clostridial				
subjects affected / exposed	1 / 144 (0.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Groin abscess				

subjects affected / exposed	1 / 144 (0.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Herpes simplex				
subjects affected / exposed	1 / 144 (0.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Herpes zoster				
subjects affected / exposed	1 / 144 (0.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lobar pneumonia				
subjects affected / exposed	2 / 144 (1.39%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection viral				
subjects affected / exposed	1 / 144 (0.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lung infection				
subjects affected / exposed	1 / 144 (0.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Lymphadenitis bacterial				
subjects affected / exposed	1 / 144 (0.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Oropharyngeal candidiasis				
subjects affected / exposed	1 / 144 (0.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumocystis jirovecii pneumonia				

subjects affected / exposed	1 / 144 (0.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	17 / 144 (11.81%)			
occurrences causally related to treatment / all	12 / 26			
deaths causally related to treatment / all	0 / 4			
Pneumonia parainfluenzae viral				
subjects affected / exposed	1 / 144 (0.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	2 / 144 (1.39%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
Septic shock				
subjects affected / exposed	2 / 144 (1.39%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 1			
Sinusitis fungal				
subjects affected / exposed	1 / 144 (0.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	3 / 144 (2.08%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Hypercalcaemia				
subjects affected / exposed	1 / 144 (0.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hyperkalaemia				

subjects affected / exposed	1 / 144 (0.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	1 / 144 (0.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Ibrutinib		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	144 / 144 (100.00%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	28 / 144 (19.44%)		
occurrences (all)	34		
General disorders and administration site conditions			
Chills			
subjects affected / exposed	8 / 144 (5.56%)		
occurrences (all)	8		
Fatigue			
subjects affected / exposed	44 / 144 (30.56%)		
occurrences (all)	48		
Oedema peripheral			
subjects affected / exposed	21 / 144 (14.58%)		
occurrences (all)	27		
Pyrexia			
subjects affected / exposed	25 / 144 (17.36%)		
occurrences (all)	32		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	34 / 144 (23.61%)		
occurrences (all)	45		
Epistaxis			

subjects affected / exposed	10 / 144 (6.94%)		
occurrences (all)	11		
Dyspnoea			
subjects affected / exposed	16 / 144 (11.11%)		
occurrences (all)	21		
Nasal congestion			
subjects affected / exposed	9 / 144 (6.25%)		
occurrences (all)	12		
Oropharyngeal pain			
subjects affected / exposed	11 / 144 (7.64%)		
occurrences (all)	12		
Psychiatric disorders			
Depression			
subjects affected / exposed	10 / 144 (6.94%)		
occurrences (all)	10		
Insomnia			
subjects affected / exposed	11 / 144 (7.64%)		
occurrences (all)	11		
Investigations			
Weight decreased			
alternative assessment type: Non-systematic			
subjects affected / exposed	12 / 144 (8.33%)		
occurrences (all)	15		
Weight increased			
subjects affected / exposed	12 / 144 (8.33%)		
occurrences (all)	15		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	9 / 144 (6.25%)		
occurrences (all)	11		
Nervous system disorders			
Dizziness			
subjects affected / exposed	12 / 144 (8.33%)		
occurrences (all)	17		
Headache			

subjects affected / exposed	14 / 144 (9.72%)		
occurrences (all)	15		
Peripheral sensory neuropathy			
subjects affected / exposed	11 / 144 (7.64%)		
occurrences (all)	13		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	27 / 144 (18.75%)		
occurrences (all)	32		
Increased tendency to bruise			
subjects affected / exposed	20 / 144 (13.89%)		
occurrences (all)	22		
Neutropenia			
subjects affected / exposed	24 / 144 (16.67%)		
occurrences (all)	64		
Thrombocytopenia			
subjects affected / exposed	16 / 144 (11.11%)		
occurrences (all)	31		
Eye disorders			
Lacrimation increased			
subjects affected / exposed	9 / 144 (6.25%)		
occurrences (all)	11		
Vision blurred			
subjects affected / exposed	10 / 144 (6.94%)		
occurrences (all)	11		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	11 / 144 (7.64%)		
occurrences (all)	12		
Diarrhoea			
subjects affected / exposed	52 / 144 (36.11%)		
occurrences (all)	67		
Constipation			
alternative assessment type: Non-systematic			
subjects affected / exposed	17 / 144 (11.81%)		
occurrences (all)	17		

Dyspepsia			
subjects affected / exposed	15 / 144 (10.42%)		
occurrences (all)	22		
Nausea			
subjects affected / exposed	28 / 144 (19.44%)		
occurrences (all)	36		
Vomiting			
subjects affected / exposed	13 / 144 (9.03%)		
occurrences (all)	13		
Stomatitis			
subjects affected / exposed	9 / 144 (6.25%)		
occurrences (all)	12		
Skin and subcutaneous tissue disorders			
Night sweats			
subjects affected / exposed	15 / 144 (10.42%)		
occurrences (all)	18		
Pruritus			
subjects affected / exposed	8 / 144 (5.56%)		
occurrences (all)	8		
Rash			
subjects affected / exposed	9 / 144 (6.25%)		
occurrences (all)	10		
Rash erythematous			
subjects affected / exposed	10 / 144 (6.94%)		
occurrences (all)	12		
Skin lesion			
subjects affected / exposed	10 / 144 (6.94%)		
occurrences (all)	12		
Rash maculo-papular			
subjects affected / exposed	12 / 144 (8.33%)		
occurrences (all)	14		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	32 / 144 (22.22%)		
occurrences (all)	43		
Muscle spasms			

subjects affected / exposed	24 / 144 (16.67%)		
occurrences (all)	26		
Back pain			
subjects affected / exposed	18 / 144 (12.50%)		
occurrences (all)	22		
Pain in extremity			
subjects affected / exposed	11 / 144 (7.64%)		
occurrences (all)	17		
Myalgia			
subjects affected / exposed	15 / 144 (10.42%)		
occurrences (all)	15		
Infections and infestations			
Bronchitis			
subjects affected / exposed	9 / 144 (6.25%)		
occurrences (all)	10		
Sinusitis			
subjects affected / exposed	13 / 144 (9.03%)		
occurrences (all)	16		
Nasopharyngitis			
subjects affected / exposed	13 / 144 (9.03%)		
occurrences (all)	15		
Urinary tract infection			
subjects affected / exposed	17 / 144 (11.81%)		
occurrences (all)	20		
Upper respiratory tract infection			
subjects affected / exposed	15 / 144 (10.42%)		
occurrences (all)	16		
Metabolism and nutrition disorders			
Decreased appetite			
alternative assessment type: Non-systematic			
subjects affected / exposed	25 / 144 (17.36%)		
occurrences (all)	28		
Hyperuricaemia			
subjects affected / exposed	14 / 144 (9.72%)		
occurrences (all)	15		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 February 2013	• Changed the exclusion criteria governing number of prior lines of systemic therapy for CLL from 4 or more to 5 or more due to rapidity by which subjects with del17p CLL become relapsed or refractory to historical therapies. • Updated text for the management of ibrutinib with concomitant CYP3A4/5 inhibitors. • Updated text for the management of ibrutinib with concomitant anticoagulation therapy. Provided further clarification for restart of ibrutinib after anticoagulation therapy. • Provided guidance on perioperative holding of ibrutinib that was not previously available. • Clarified that ophthalmologic examination should be performed by an ophthalmologist. • Clarified that CT scans needed to be obtained for neck, chest, abdomen, and pelvis. • Except in the UK, PROs were no longer collected in the study.
16 December 2013	• Aligned the efficacy and safety populations to subjects who have received at least 1 dose of ibrutinib. • Delayed timing of the primary analysis to at least 12 months after the last subject's first dose of ibrutinib. Provided clarification that any updates to the timing of the primary or final analysis would be pre-specified in the SAP and would not warrant another protocol amendment as long as study conduct was not impacted. • Updated guideline for the use of concomitant QT-prolonging agents. • Updated guideline for concomitant use of anticoagulation and antiplatelet agents and included precautions for commonly used supplements such as fish oil and Vitamin E.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported