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	19 May 2016

Results information

Result version number	v2 (current)
This version publication date	28 June 2017
First version publication date	01 May 2016
Version creation reason	

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)	-

Notes:

Sponsors

Sponsor organisation name	Pharmacyclics LLC.
Sponsor organisation address	995 East Arques Avenue, Sunnyvale, California, United States, 94085
Public contact	Clinical Trial information, Pharmacyclics LLC, 140 87740330, info@pcyc.com
Scientific contact	Clinical Trial information, Pharmacyclics LLC, 140 87740330, info@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	Final
Date of interim/final analysis	09 January 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 May 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

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

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 84
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	Germany: 13
Country: Number of subjects enrolled	New Zealand: 2
Country: Number of subjects enrolled	Sweden: 8
Country: Number of subjects enrolled	Turkey: 12
Country: Number of subjects enrolled	United Kingdom: 14
Worldwide total number of subjects	145
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 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	75
From 65 to 84 years	68
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Key Inclusion Criteria:

•Documentation of del (17p13.1)
•Must have relapsed or refractory CLL/SLL after receiving at least 1 prior line of systemic therapy.
•Measurable nodal disease by computed tomography (CT)
Key Exclusion Criteria:

•History or current evidence of Richter's transformation or prolymphocytic leukemia
•Prior hematologic st

Pre-assignment

Screening details:

One hundred forty-five subjects were enrolled and 144 subjects received at least 1 dose of PCI-32765 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	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	ibrutinib

Arm description:

All subjects will receive ibrutnib 420 mg (3 x 140-mg capsules) orally once daily.

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:

All subjects will receive ibrutinib 420 mg (3 x 140-mg capsules) orally once daily.

Number of subjects in period 1[1]	ibrutinib
Started	144
Completed	101
Not completed	43
Unacceptable toxicity, AE or death	18
Consent withdrawn by subject	3
Physician decision	4
Progressive Disease	18

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: There was 1 additional subject enrolled who, however, did not receive any study medication and was excluded from all analyses.

Baseline characteristics

Reporting groups	
Reporting group title	overall study
Reporting group description:	
All subjects received PCI-32765 420 mg (3 x 140-mg capsules) orally once daily.	

Reporting group values	overall study	Total	
Number of subjects	144	144	
Age categorical			
Count of Participants			
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 categorical			
Units: Subjects			
Female	48	48	
Male	96	96	

End points

End points reporting groups

Reporting group title	ibrutinib
Reporting group description:	
All subjects will receive ibrutnib 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 33.3 (range 0.5 - 40.1) 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 95% CI calculated based on normal approximation with Wilsons`s score method. However, as this has been a single arm study, no statistical analyses have been performed.

End point values	ibrutinib			
Subject group type	Reporting group			
Number of subjects analysed	144			
Units: % of participants with response by PI				
number (confidence interval 95%)	77.8 (70.3 to 83.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Treatment Emergent Adverse Events (AEs) [Time Frame: From first dose of PCI-32765 to within 30 days of last dose for each participant or until study closure]

End point title	Number of Participants With Treatment Emergent Adverse Events (AEs) [Time Frame: From first dose of PCI-32765 to within 30 days of last dose for each participant or until study closure]
End point description:	
Participants who received at least 1 dose of PCI-32765 and constitute the all treated population.	
End point type	Secondary
End point timeframe:	
From first dose of PCI-32765 to within 30 days of last dose for each participant or until study closure	

End point values	ibrutinib			
Subject group type	Reporting group			
Number of subjects analysed	144			
Units: Participants	144			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From first dose of PCI-32765 to within 30 days of last dose for each participant or until study closure	
Adverse event reporting additional description:	
Number of participants who had experienced at least one treatment emergent AE	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups	
Reporting group title	PCI-32765
Reporting group description:	
All subjects will receive PCI-32765 420 mg (3 x 140-mg capsules) orally once daily.	

Serious adverse events	PCI-32765		
Total subjects affected by serious adverse events			
subjects affected / exposed	76 / 144 (52.78%)		
number of deaths (all causes)	19		
number of deaths resulting from adverse events	2		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Richter's syndrome			
subjects affected / exposed	6 / 144 (4.17%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 2		
Chronic lymphocytic leukaemia			
subjects affected / exposed	5 / 144 (3.47%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 2		
Basal cell carcinoma			
subjects affected / exposed	2 / 144 (1.39%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hodgkin's disease			

subjects affected / exposed	2 / 144 (1.39%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
B-cell small lymphocytic lymphoma				
subjects affected / exposed	1 / 144 (0.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Lymphoma transformation				
subjects affected / exposed	1 / 144 (0.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
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			
Squamous cell carcinoma of skin				
subjects affected / exposed	1 / 144 (0.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vulval cancer stage 0				
subjects affected / exposed	1 / 144 (0.69%)			
occurrences causally related to treatment / all	0 / 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			
Hypertension				
subjects affected / exposed	1 / 144 (0.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Orthostatic hypotension				

subjects affected / exposed	1 / 144 (0.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	3 / 144 (2.08%)		
occurrences causally related to treatment / all	3 / 7		
deaths causally related to treatment / all	0 / 0		
Fatigue			
subjects affected / exposed	2 / 144 (1.39%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Asthenia			
subjects affected / exposed	1 / 144 (0.69%)		
occurrences causally related to treatment / all	0 / 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		
Reproductive system and breast disorders			
Prostatomegaly			
subjects affected / exposed	1 / 144 (0.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	3 / 144 (2.08%)		
occurrences causally related to treatment / all	1 / 6		
deaths causally related to treatment / all	0 / 0		
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		
Haemothorax			
subjects affected / exposed	1 / 144 (0.69%)		
occurrences causally related to treatment / all	0 / 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		
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 embolism			
subjects affected / exposed	1 / 144 (0.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary mass			
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			
Psychiatric disorders				
Psychotic disorder				
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				
Subdural haematoma				
subjects affected / exposed	3 / 144 (2.08%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Alcohol poisoning				
subjects affected / exposed	1 / 144 (0.69%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
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			
Meniscus injury				
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			

Post procedural haemorrhage			
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			
Atrial fibrillation			
subjects affected / exposed	8 / 144 (5.56%)		
occurrences causally related to treatment / all	3 / 11		
deaths causally related to treatment / all	0 / 0		
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		
Pericarditis			
subjects affected / exposed	2 / 144 (1.39%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
subjects affected / exposed	1 / 144 (0.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
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		
Pericardial effusion			
subjects affected / exposed	1 / 144 (0.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Sinus node dysfunction			

subjects affected / exposed	1 / 144 (0.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Syncope			
subjects affected / exposed	2 / 144 (1.39%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cerebrovascular accident			
subjects affected / exposed	1 / 144 (0.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
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		
Encephalopathy			
subjects affected / exposed	1 / 144 (0.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
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			
subjects affected / exposed	4 / 144 (2.78%)		
occurrences causally related to treatment / all	1 / 5		
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		
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			
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			
Spontaneous haematoma				
subjects affected / exposed	1 / 144 (0.69%)			
occurrences causally related to treatment / all	0 / 2			
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			
Eye disorders				
Iritis				
subjects affected / exposed	1 / 144 (0.69%)			
occurrences causally related to treatment / all	2 / 2			
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		
Diarrhoea			
subjects affected / exposed	2 / 144 (1.39%)		
occurrences causally related to treatment / all	0 / 2		
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		
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	2 / 2		
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		
Stomatitis			
subjects affected / exposed	1 / 144 (0.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Upper gastrointestinal haemorrhage			

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			
Hepatic function abnormal				
subjects affected / exposed	1 / 144 (0.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Skin and subcutaneous tissue disorders				
Livedo reticularis				
subjects affected / exposed	1 / 144 (0.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
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			
Trichodysplasia spinulosa				

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			
Acute kidney injury			
subjects affected / exposed	2 / 144 (1.39%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
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		
Myalgia			
subjects affected / exposed	2 / 144 (1.39%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Osteoporosis			
subjects affected / exposed	2 / 144 (1.39%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Arthralgia			
subjects affected / exposed	1 / 144 (0.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Chondromalacia				
subjects affected / exposed	1 / 144 (0.69%)			
occurrences causally related to treatment / all	0 / 1			
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			
Infections and infestations				
Pneumonia				
subjects affected / exposed	21 / 144 (14.58%)			
occurrences causally related to treatment / all	15 / 32			
deaths causally related to treatment / all	0 / 4			
Urinary tract infection				
subjects affected / exposed	5 / 144 (3.47%)			
occurrences causally related to treatment / all	1 / 5			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	4 / 144 (2.78%)			
occurrences causally related to treatment / all	1 / 4			
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			
Pyelonephritis				
subjects affected / exposed	2 / 144 (1.39%)			
occurrences causally related to treatment / all	1 / 2			
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			
Appendicitis				
subjects affected / exposed	1 / 144 (0.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
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			
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			
Bacteraemia				
subjects affected / exposed	1 / 144 (0.69%)			
occurrences causally related to treatment / all	0 / 1			
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			
Empyema				

subjects affected / exposed	1 / 144 (0.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Epiglottitis				
subjects affected / exposed	1 / 144 (0.69%)			
occurrences causally related to treatment / all	0 / 1			
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			
Influenza				
subjects affected / exposed	1 / 144 (0.69%)			
occurrences causally related to treatment / all	0 / 1			
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			
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			
Staphylococcal sepsis				
subjects affected / exposed	1 / 144 (0.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Subcutaneous abscess				
subjects affected / exposed	1 / 144 (0.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Varicella zoster virus infection				
subjects affected / exposed	1 / 144 (0.69%)			
occurrences causally related to treatment / all	0 / 1			
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		
Hypomagnesaemia			
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	PCI-32765		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	144 / 144 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	11 / 144 (7.64%)		
occurrences (all)	11		
Vascular disorders			
Hypertension			
subjects affected / exposed	39 / 144 (27.08%)		
occurrences (all)	51		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	53 / 144 (36.81%)		
occurrences (all)	61		
Pyrexia			
subjects affected / exposed	31 / 144 (21.53%)		
occurrences (all)	47		
Oedema peripheral			

subjects affected / exposed	27 / 144 (18.75%)		
occurrences (all)	36		
Chills			
subjects affected / exposed	9 / 144 (6.25%)		
occurrences (all)	9		
Peripheral swelling			
subjects affected / exposed	9 / 144 (6.25%)		
occurrences (all)	11		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	46 / 144 (31.94%)		
occurrences (all)	71		
Dyspnoea			
subjects affected / exposed	18 / 144 (12.50%)		
occurrences (all)	28		
Oropharyngeal pain			
subjects affected / exposed	13 / 144 (9.03%)		
occurrences (all)	16		
Epistaxis			
subjects affected / exposed	12 / 144 (8.33%)		
occurrences (all)	14		
Nasal congestion			
subjects affected / exposed	10 / 144 (6.94%)		
occurrences (all)	16		
Productive cough			
subjects affected / exposed	10 / 144 (6.94%)		
occurrences (all)	13		
Rhinorrhoea			
subjects affected / exposed	8 / 144 (5.56%)		
occurrences (all)	10		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	12 / 144 (8.33%)		
occurrences (all)	13		
Depression			

subjects affected / exposed	10 / 144 (6.94%)		
occurrences (all)	10		
Anxiety			
subjects affected / exposed	8 / 144 (5.56%)		
occurrences (all)	8		
Investigations			
Weight increased			
subjects affected / exposed	20 / 144 (13.89%)		
occurrences (all)	27		
Weight decreased			
subjects affected / exposed	16 / 144 (11.11%)		
occurrences (all)	20		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	10 / 144 (6.94%)		
occurrences (all)	15		
Fall			
subjects affected / exposed	8 / 144 (5.56%)		
occurrences (all)	9		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	9 / 144 (6.25%)		
occurrences (all)	9		
Nervous system disorders			
Headache			
subjects affected / exposed	18 / 144 (12.50%)		
occurrences (all)	20		
Dizziness			
subjects affected / exposed	14 / 144 (9.72%)		
occurrences (all)	22		
Peripheral sensory neuropathy			
subjects affected / exposed	12 / 144 (8.33%)		
occurrences (all)	19		
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	32 / 144 (22.22%)		
occurrences (all)	42		
Neutropenia			
subjects affected / exposed	29 / 144 (20.14%)		
occurrences (all)	76		
Increased tendency to bruise			
subjects affected / exposed	23 / 144 (15.97%)		
occurrences (all)	25		
Thrombocytopenia			
subjects affected / exposed	21 / 144 (14.58%)		
occurrences (all)	43		
Spontaneous haematoma			
subjects affected / exposed	8 / 144 (5.56%)		
occurrences (all)	16		
Eye disorders			
Vision blurred			
subjects affected / exposed	16 / 144 (11.11%)		
occurrences (all)	20		
Visual acuity reduced			
subjects affected / exposed	12 / 144 (8.33%)		
occurrences (all)	13		
Dry eye			
subjects affected / exposed	11 / 144 (7.64%)		
occurrences (all)	11		
Lacrimation increased			
subjects affected / exposed	11 / 144 (7.64%)		
occurrences (all)	17		
Eye irritation			
subjects affected / exposed	8 / 144 (5.56%)		
occurrences (all)	10		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	61 / 144 (42.36%)		
occurrences (all)	89		
Nausea			

subjects affected / exposed	34 / 144 (23.61%)		
occurrences (all)	45		
Constipation			
subjects affected / exposed	21 / 144 (14.58%)		
occurrences (all)	23		
Dyspepsia			
subjects affected / exposed	18 / 144 (12.50%)		
occurrences (all)	25		
Vomiting			
subjects affected / exposed	16 / 144 (11.11%)		
occurrences (all)	18		
Abdominal pain			
subjects affected / exposed	14 / 144 (9.72%)		
occurrences (all)	15		
Stomatitis			
subjects affected / exposed	11 / 144 (7.64%)		
occurrences (all)	18		
Abdominal pain upper			
subjects affected / exposed	8 / 144 (5.56%)		
occurrences (all)	8		
Gastrooesophageal reflux disease			
subjects affected / exposed	8 / 144 (5.56%)		
occurrences (all)	9		
Skin and subcutaneous tissue disorders			
Night sweats			
subjects affected / exposed	23 / 144 (15.97%)		
occurrences (all)	27		
Rash maculo-papular			
subjects affected / exposed	13 / 144 (9.03%)		
occurrences (all)	16		
Rash erythematous			
subjects affected / exposed	12 / 144 (8.33%)		
occurrences (all)	14		
Rash			
subjects affected / exposed	11 / 144 (7.64%)		
occurrences (all)	13		

Skin lesion			
subjects affected / exposed	11 / 144 (7.64%)		
occurrences (all)	13		
Pruritus			
subjects affected / exposed	9 / 144 (6.25%)		
occurrences (all)	9		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	9 / 144 (6.25%)		
occurrences (all)	11		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	41 / 144 (28.47%)		
occurrences (all)	57		
Muscle spasms			
subjects affected / exposed	28 / 144 (19.44%)		
occurrences (all)	31		
Back pain			
subjects affected / exposed	23 / 144 (15.97%)		
occurrences (all)	27		
Myalgia			
subjects affected / exposed	17 / 144 (11.81%)		
occurrences (all)	19		
Pain in extremity			
subjects affected / exposed	15 / 144 (10.42%)		
occurrences (all)	25		
Musculoskeletal pain			
subjects affected / exposed	8 / 144 (5.56%)		
occurrences (all)	9		
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	30 / 144 (20.83%)		
occurrences (all)	38		
Urinary tract infection			
subjects affected / exposed	28 / 144 (19.44%)		
occurrences (all)	47		

Pneumonia subjects affected / exposed occurrences (all)	13 / 144 (9.03%) 16		
Nasopharyngitis subjects affected / exposed occurrences (all)	18 / 144 (12.50%) 29		
Sinusitis subjects affected / exposed occurrences (all)	16 / 144 (11.11%) 21		
Bronchitis subjects affected / exposed occurrences (all)	13 / 144 (9.03%) 16		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	28 / 144 (19.44%) 32		
Hyperuricaemia subjects affected / exposed occurrences (all)	18 / 144 (12.50%) 22		
Hyponatraemia subjects affected / exposed occurrences (all)	10 / 144 (6.94%) 11		
Hypokalaemia subjects affected / exposed occurrences (all)	9 / 144 (6.25%) 13		
Hyperglycaemia subjects affected / exposed occurrences (all)	8 / 144 (5.56%) 10		

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 systematic 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 futher clarification for restart of ibrutinib after anticoagulation therapy. Provided guidance on perioperative holding of ibrutinib that was not previously available Clarified that opthalmologic examination should be performed by an ophtalmologist. 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 ibrtinib.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