Clinical trial results:
A Multicenter, Open-Label, Phase 2 Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor, Ibrutinib, in Subjects with Relapsed/Refractory Marginal Zone Lymphoma

Summary

EudraCT number	2013-003561-34
Trial protocol	BE DE GB
Global end of trial date	02 October 2017

Results information

Result version number	v2 (current)
This version publication date	12 December 2018
First version publication date	21 October 2017
Version creation reason	• New data added to full data set final analysis with last subject last visit 02 October 2017

Trial information

Trial identification

Sponsor protocol code	PCYC-1121-CA

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01980628
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pharmacyclics LLC
Sponsor organisation address	999 E Arques Ave, Sunnyvale, United States, 94085
Public contact	Thorsten Graef, Pharmacyclics LLC, +1 408) 215 2127, medinfo@pcyc.com
Scientific contact	Clinical Trial information, Pharmacyclics LLC, +1 408774 0330, 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	Final
Date of interim/final analysis	02 October 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 October 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of ibrutinib therapy in subjects with marginal zone lymphoma (MZL) using the overall response rate (ORR) as assessed by an Independent Review Committee (IRC)

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 Practice (GCP)

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 December 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 Kingdom: 4
Country: Number of subjects enrolled	United States: 44
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	France: 13
Country: Number of subjects enrolled	Germany: 1
Worldwide total number of subjects	63
EEA total number of subjects	19

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)	27
From 65 to 84 years	36

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a Phase 2, open-label, non-randomized, multicenter, monotherapy study assessing the safety and efficacy of ibrutinib in subjects with relapsed/refractory MZL. The study had a Simon's optimal design to test the null hypothesis that the ORR was ≤ 25%.

Pre-assignment

Screening details:

Histologically documented evidence of MZL including splenic, nodal, and extranodal MZL subtypes with at least 1 measurable lesion and a history of 1 or more prior lines of therapy including at least 1 CD20-directed regimen either as monotherapy or as CIT with disease progression or failure of response reported after the last therapy.

Period 1

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

Arms

Arm title	Overall Trial

Arm description:

Overall trial

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

Dosage and administration details:

Ibrutinib was provided as size-0, hard gelatin capsules each containing 140 mg of active drug for oral administration

Number of subjects in period 1	Overall Trial
Started	63
Completed	59
Not completed	4
Consent withdrawn by subject	4

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	63	63	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	27	27	
From 65-84 years	36	36	
85 years and over	0	0	
Age continuous Units: years			
median	66		
full range (min-max)	30 to 92	-	
Gender categorical Units: Subjects			
Female	27	27	
Male	36	36	

End points

End points reporting groups

Reporting group title	Overall Trial

Reporting group description:

Overall trial

Subject analysis set title	Efficacy analysis set
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

At baseline, 3 subjects in this study were reported with non-measurable disease by IRC assessment but with measurable disease per investigator assessment.

Primary: ORR

End point title	ORR[1]

End point description:

The primary endpoint of this study was ORR (defined as the proportion of subjects with evidence of disease at baseline having partial response [PR] or better) per IRC assessment. Secondary endpoints included DOR and PFS per IRC assessment, OS, and safety and PK evaluation. Exploratory endpoints included biomarker evaluation.

End point type	Primary

End point timeframe:

overall trial

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: This has been an open-label, uncontrolled Phase II study. No formal statistical analysis was therefore conducted.

End point values	Efficacy analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	60			
Units: percent				
number (confidence interval 95%)	48.3 (35.3 to 61.7)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug up to 30 days after the last dose of study drug

Adverse event reporting additional description:

Subjects who receieved at least one dose of study medication

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Serious adverse events	Overall trial		
Total subjects affected by serious adverse events			
subjects affected / exposed	28 / 63 (44.44%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lymphoma			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Marginal zone lymphoma			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			

subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Multiple organ dysfunction syndrome				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Non-cardiac chest pain				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Pneumothorax				
subjects affected / exposed	2 / 63 (3.17%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Eosinophilic pneumonia				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hypoxia				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				

subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonitis				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Ankle fracture				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Atrial fibrillation				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pericardial effusion				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Cerebral haemorrhage				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			

Cervical radiculopathy			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Autoimmune haemolytic anaemia			
subjects affected / exposed	2 / 63 (3.17%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Haemolytic anaemia			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Pancreatitis			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Stomatitis			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			

subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	5 / 63 (7.94%)		
occurrences causally related to treatment / all	5 / 6		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	2 / 63 (3.17%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	2 / 63 (3.17%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Escherichia sepsis			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infection			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Influenza			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Listeria sepsis			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Lung infection			

subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Parainfluenzae virus infection			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fluid overload			
subjects affected / exposed	1 / 63 (1.59%)		
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	Overall trial		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	63 / 63 (100.00%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	8 / 63 (12.70%)		
occurrences (all)	11		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	28 / 63 (44.44%)		
occurrences (all)	42		
Oedema peripheral			
subjects affected / exposed	15 / 63 (23.81%)		
occurrences (all)	26		
Pyrexia			

subjects affected / exposed	10 / 63 (15.87%)		
occurrences (all)	18		
Asthenia			
subjects affected / exposed	6 / 63 (9.52%)		
occurrences (all)	6		
Reproductive system and breast disorders			
Cough			
subjects affected / exposed	14 / 63 (22.22%)		
occurrences (all)	21		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	12 / 63 (19.05%)		
occurrences (all)	17		
Epistaxis			
subjects affected / exposed	8 / 63 (12.70%)		
occurrences (all)	12		
Nasal congestion			
subjects affected / exposed	5 / 63 (7.94%)		
occurrences (all)	6		
Oropharyngeal pain			
subjects affected / exposed	4 / 63 (6.35%)		
occurrences (all)	5		
Productive cough			
subjects affected / exposed	4 / 63 (6.35%)		
occurrences (all)	4		
Rhinorrhoea			
subjects affected / exposed	4 / 63 (6.35%)		
occurrences (all)	4		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	10 / 63 (15.87%)		
occurrences (all)	11		
Depression			
subjects affected / exposed	4 / 63 (6.35%)		
occurrences (all)	4		
Investigations			

Weight decreased subjects affected / exposed occurrences (all)	7 / 63 (11.11%) 8		
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	5 / 63 (7.94%) 8		
Blood creatine increased subjects affected / exposed occurrences (all)	4 / 63 (6.35%) 5		
Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all)	9 / 63 (14.29%) 11		
Contusion subjects affected / exposed occurrences (all)	6 / 63 (9.52%) 6		
Skin abrasion subjects affected / exposed occurrences (all)	6 / 63 (9.52%) 7		
Cardiac disorders Atrial fibrillation subjects affected / exposed occurrences (all)	4 / 63 (6.35%) 4		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	12 / 63 (19.05%) 18		
Headache subjects affected / exposed occurrences (all)	8 / 63 (12.70%) 20		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	21 / 63 (33.33%) 43		
Thrombocytopenia			

subjects affected / exposed	15 / 63 (23.81%)		
occurrences (all)	31		
Increased tendency to bruise			
subjects affected / exposed	12 / 63 (19.05%)		
occurrences (all)	15		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	27 / 63 (42.86%)		
occurrences (all)	51		
Nausea			
subjects affected / exposed	16 / 63 (25.40%)		
occurrences (all)	25		
Dyspepsia			
subjects affected / exposed	12 / 63 (19.05%)		
occurrences (all)	15		
Abdominal pain			
subjects affected / exposed	10 / 63 (15.87%)		
occurrences (all)	11		
Constipation			
subjects affected / exposed	9 / 63 (14.29%)		
occurrences (all)	11		
Abdominal pain upper			
subjects affected / exposed	8 / 63 (12.70%)		
occurrences (all)	8		
Stomatitis			
subjects affected / exposed	7 / 63 (11.11%)		
occurrences (all)	13		
Vomiting			
subjects affected / exposed	7 / 63 (11.11%)		
occurrences (all)	9		
Abdominal discomfort			
subjects affected / exposed	4 / 63 (6.35%)		
occurrences (all)	4		
Abdominal distension			
subjects affected / exposed	4 / 63 (6.35%)		
occurrences (all)	5		

Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	11 / 63 (17.46%)		
occurrences (all)	25		
Pruritus			
subjects affected / exposed	9 / 63 (14.29%)		
occurrences (all)	11		
Ecchymosis			
subjects affected / exposed	6 / 63 (9.52%)		
occurrences (all)	6		
Night sweats			
subjects affected / exposed	5 / 63 (7.94%)		
occurrences (all)	6		
Alopecia			
subjects affected / exposed	4 / 63 (6.35%)		
occurrences (all)	4		
Dry skin			
subjects affected / exposed	4 / 63 (6.35%)		
occurrences (all)	6		
Erythema			
subjects affected / exposed	4 / 63 (6.35%)		
occurrences (all)	4		
Rash erythematous			
subjects affected / exposed	4 / 63 (6.35%)		
occurrences (all)	5		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	5 / 63 (7.94%)		
occurrences (all)	5		
Endocrine disorders			
Vision blurred			
subjects affected / exposed	4 / 63 (6.35%)		
occurrences (all)	7		
Musculoskeletal and connective tissue disorders			
Arthralgia			

subjects affected / exposed	15 / 63 (23.81%)		
occurrences (all)	18		
Muscle spasms			
subjects affected / exposed	12 / 63 (19.05%)		
occurrences (all)	13		
Pain in extremity			
subjects affected / exposed	9 / 63 (14.29%)		
occurrences (all)	12		
Back pain			
subjects affected / exposed	6 / 63 (9.52%)		
occurrences (all)	6		
Musculoskeletal pain			
subjects affected / exposed	4 / 63 (6.35%)		
occurrences (all)	4		
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	13 / 63 (20.63%)		
occurrences (all)	18		
Sinusitis			
subjects affected / exposed	12 / 63 (19.05%)		
occurrences (all)	15		
Bronchitis			
subjects affected / exposed	7 / 63 (11.11%)		
occurrences (all)	8		
Urinary tract infection			
subjects affected / exposed	6 / 63 (9.52%)		
occurrences (all)	9		
Oral herpes			
subjects affected / exposed	5 / 63 (7.94%)		
occurrences (all)	5		
Conjunctivitis			
subjects affected / exposed	4 / 63 (6.35%)		
occurrences (all)	4		
Cystitis			
subjects affected / exposed	4 / 63 (6.35%)		
occurrences (all)	5		

Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	10 / 63 (15.87%)		
occurrences (all)	13		
Hyperglycaemia			
subjects affected / exposed	10 / 63 (15.87%)		
occurrences (all)	23		
Hyperuricaemia			
subjects affected / exposed	10 / 63 (15.87%)		
occurrences (all)	16		
Hypoalbuminaemia			
subjects affected / exposed	9 / 63 (14.29%)		
occurrences (all)	12		
Hypokalaemia			
subjects affected / exposed	8 / 63 (12.70%)		
occurrences (all)	12		
Hypocalcaemia			
subjects affected / exposed	6 / 63 (9.52%)		
occurrences (all)	12		
Hyponatraemia			
subjects affected / exposed	5 / 63 (7.94%)		
occurrences (all)	8		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 February 2014	Corrected language on ibrutinib dose as 560 mg (from 420 mg) orally once daily and removed requirement of dosing with meals. Clarified that analysis of primary endpoint was per independent review radiographic review for analysis of primary and secondary efficacy endpoints Updated/clarified eligibility criteria as it relates to prior treatments, prior therapies, exclusion of large cell transformation, the timing of PET scans, exclusionary concomitant medications and washout periods for strong CYP3A inhibitors. Clarified the language on specific study assessments (ie, tumor assessments, pre-treatment bone marrow aspirate and biopsy, biomarkers testing, long-term follow-up, discontinuation of treatment, and study withdrawal). Updated/added language for efficacy analysis, AE and SAE reporting requirements, and AEs of special interest.
07 October 2014	Revised the interim analysis for futility time point from 12 to 24 weeks post-enrollment of 19 subjects to align with anticipated response for an indolent disease, primary analysis time point from approximately 36 to 52 weeks after last patient Clarified specific protocol management and safety reporting procedures Updated information on ibrutinib to align with new version of Investigator's Brochure. Added guidelines regarding dose reductions, eye-related symptom assessment requirements and B-symptom assessment evaluations, and guidance on tumor flare assessments/ibrutinib dosing. Defined conventions for lesion measurement.
28 December 2015	Updated information on ibrutinib to align with new version of Investigator's Brochure. Clarified specific protocol management and safety reporting procedures Visit schedule changed from monthly to q12 weeks after 1 year of ibrutinib therapy Added language to permit concomitant administration of prednisone for <14 days at doses that do not exceed 100 mg/day of prednisone or equivalent for treatment of autoimmune cytopenias
05 February 2016	Update the synopsis to correct the inconsistencies between the body of the protocol and the synopsis Removed requirement for ECG to be performed in subjects who develop arrhythmic symptoms or new onset of dyspnea if clinically indicated

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported