Clinical trial results:
An Open-label, Multicenter, Single-arm, Phase 2 Study of PCI-32765 (ibrutinib) in Subjects with Refractory Follicular Lymphoma

Summary

EudraCT number	2012-004097-26
Trial protocol	BE GB DE ES IT FR
Global end of trial date	18 May 2016

Results information

Result version number	v1 (current)
This version publication date	27 May 2017
First version publication date	27 May 2017

Trial information

Trial identification

Sponsor protocol code	PCI-32765FLR2002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01779791
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen-Cilag International N.V.
Sponsor organisation address	Turnhoutseweg 30, Beerse, Belgium, 2340
Public contact	Clinical Registry Group, Janssen-Cilag International N.V., ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group, Janssen-Cilag International N.V., 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	18 May 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 May 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study is to evaluate the overall response rate (ORR) of ibrutinib, as assessed by the Independent Review Committee (IRC), in subjects with Chemoimmunotherapy (CIT)-resistant follicular lymphoma (FL).

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 were based upon physical examinations, electrocardiograms, vital signs (temperature, heart rate, and blood pressure), and evaluation of changes to concomitant medications, and clinical laboratory parameters (hematology, serum chemistry, coagulation, hepatitis B and C screening, pregnancy test, serum immunoglobulin [IgG, IgM, IgA], and beta 2-microglobulin). Eastern Cooperative Oncology Group (ECOG) performance status grade was used to assess changes in the subject's daily living activities. Adverse events (AEs) were assessed throughout the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 March 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	Australia: 10
Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	France: 9
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Italy: 8
Country: Number of subjects enrolled	Poland: 5
Country: Number of subjects enrolled	Russian Federation: 7
Country: Number of subjects enrolled	United States: 50
Worldwide total number of subjects	110
EEA total number of subjects	43

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)	67
From 65 to 84 years	40
85 years and over	3

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 110 subjects were screened and assigned to Ibrutinib treatment group. All 110 subjects had discontinued the study by the clinical cut off date.

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:

Subjects self-administered 560 milligram (mg) oral Ibrutinib capsules (4*140 mg) once daily continuously until disease progression or unacceptable toxicity until study end (2 years after last subject enrolled).

Arm type	Experimental
Investigational medicinal product name	Ibrutinib
Investigational medicinal product code	JNJ-54179060
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects self-administered 560 mg oral Ibrutinib capsules (4*140 mg) once daily continuously until disease progression or unacceptable toxicity until study end (2 years after last subject enrolled).

Number of subjects in period 1	Ibrutinib
Started	110
Completed	0
Not completed	110
Consent withdrawn by subject	3
Physician decision	23
Death	4
Adverse event, serious non-fatal	7
Progressive disease	72
Lost to follow-up	1

Baseline characteristics

Reporting groups	
Reporting group title	Ibrutinib
Reporting group description:	
Subjects self-administered 560 milligram (mg) oral Ibrutinib capsules (4*140 mg) once daily continuously until disease progression or unacceptable toxicity until study end (2 years after last subject enrolled).	

Reporting group values	Ibrutinib	Total	
Number of subjects	110	110	
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	67	67	
From 65 to 84 years	40	40	
85 years and over	3	3	
Title for AgeContinuous Units: years			
arithmetic mean	60.9		
standard deviation	± 11.83	-	
Title for Gender Units: subjects			
Female	43	43	
Male	67	67	

End points

End points reporting groups

Reporting group title	Ibrutinib

Reporting group description:

Subjects self-administered 560 milligram (mg) oral Ibrutinib capsules (4*140 mg) once daily continuously until disease progression or unacceptable toxicity until study end (2 years after last subject enrolled).

Primary: Overall Response Rate (ORR)

End point title	Overall Response Rate (ORR)[1]

End point description:

ORR is defined as the percentage of subjects who achieved complete response or partial response (CR or PR), as assessed by the Independent Review Committee (IRC), according to the International Working Group (IWG) revised response criteria for malignant lymphoma. The primary efficacy analysis of ORR was conducted at approximately 24 months after enrollment of the last subject. Complete Response includes complete disappearance of all detectable evidence of disease and related symptoms. Partial Response includes greater than or equal to 50 percent decrease in the sum of the product of the diameters (SPD) of up to 6 of the largest dominant nodes or nodal masses. No increase was observed in size of nodes, liver, or spleen, 1 PET positive site of disease. The analysis was based on the all-treated population includes all subjects who received at least 1 dose of study drug.

End point type	Primary

End point timeframe:

Up to end of study (2 years after the last subject is enrolled).

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 is a single arm study, statistical comparison between arms is not in scope of this study.

End point values	Ibrutinib			
Subject group type	Reporting group			
Number of subjects analysed	110			
Units: Percentage of subjects				
number (confidence interval 95%)	20.9 (13.7 to 29.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)

End point description:

Duration of response is defined as the interval between the date of initial documentation of a response [complete response (CR) or partial response (PR)] and the date of first documented evidence of progressive disease (PD) (or relapse for subjects who experience CR during the study) or death, whichever occurs first. Subjects who are progression-free and alive, or have unknown status were censored at the last adequate disease assessment. Progressive disease or Relapsed Disease in most cases is the worsening, growth, or spread of the disease including abnormal lymph nodes, appearance of new nodal lesions/ extra nodal lesions, 50 percent increase from the nadir in the sum of the product of

the diameters (SPD) of any previously involved nodes. This may happen until death, serious debility, or organ failure occurs. DOR was analyzed for subjects who achieved a CR or PR. Here, value 99999 indicates that the data is not estimable.

End point type	Secondary

End point timeframe:

Every 12 weeks during the first 96 weeks, followed by every 24 weeks thereafter until disease progression (up to 2 years after the last subject was enrolled)

End point values	Ibrutinib			
Subject group type	Reporting group			
Number of subjects analysed	23			
Units: Months				
median (confidence interval 95%)	19.4 (8.3 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival (PFS)

End point title	Progression-free survival (PFS)

End point description:

PFS is defined as the interval between the date of first dose of study drug and the date of first confirmed documented evidence of PD (or relapse for subjects who experience CR during the study) or death, whichever comes first. Subjects who were progression-free and alive, or had unknown status were censored at the last adequate disease assessment. The all-treated population included all subjects who received at least 1 dose of study drug (Ibrutinib).

End point type	Secondary

End point timeframe:

Up to progressive disease, death, lost to follow-up, withdrawal of consent, or study end (up to 2 years after the last subject is enrolled)

End point values	Ibrutinib			
Subject group type	Reporting group			
Number of subjects analysed	110			
Units: Months				
median (confidence interval 95%)	4.6 (2.8 to 5.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

OS is defined as the interval between the date of the first dose of study drug and the date of the subject's death from any cause. If the subject is alive at the time of the cut-off, it was censored at the last known alive date (the last date among visit date, adverse event start and end dates, treatment date, disease assessment date, and survival follow up date, and if available, survival sweep date, etc.). The all-treated population included all subjects who received at least 1 dose of study drug (Ibrutinib). Here, value 99999 indicates that data is not estimable because more than 50 percent of subjects were censored for this outcome measure.

End point type	Secondary

End point timeframe:

Up to death, lost to follow-up, withdrawal of consent, or study end (up to 2 years after the last subject is enrolled)

End point values	Ibrutinib			
Subject group type	Reporting group			
Number of subjects analysed	110			
Units: Months				
median (confidence interval 95%)	99999 (99999 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response

End point title	Time to Response

End point description:

Time to response (or best response) is defined as the interval between the date of first dose and the date of initial documentation of a response (or best response). Time to Response was analyzed for subjects who achieved a CR or PR.

End point type	Secondary

End point timeframe:

Every 12 weeks during the first 96 weeks, followed by every 24 weeks thereafter until disease progression (up to 2 years after the last subject is enrolled)

End point values	Ibrutinib			
Subject group type	Reporting group			
Number of subjects analysed	23			
Units: Months				
median (full range (min-max))				
Time to Initial Response	5.65 (2.6 to 13.8)			
Time to Best Response	8.34 (2.7 to 19.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Progressive Diseases on Prior Last Line of Treatment

End point title	Time to Progressive Diseases on Prior Last Line of Treatment

End point description:

Time to PD on last line of treatment was defined as the interval between prior last line of treatment start date and the date of PD/relapse on prior last line of treatment. Time to PD was defined as first dose date of ibrutinib to the first documented PD or death due to PD whichever came first. The all-treated population included all subjects who received at least 1 dose of study drug (Ibrutinib).

End point type	Secondary

End point timeframe:

Up to progressive disease, death, lost to follow-up, withdrawal of consent, or study end (up to 2 years after the last patient is enrolled)

End point values	Ibrutinib			
Subject group type	Reporting group			
Number of subjects analysed	110			
Units: months				
median (full range (min-max))	7.4 (1 to 32)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Next Treatment on Last Prior Line of Therapy

End point title	Time to Next Treatment on Last Prior Line of Therapy

End point description:

Time to next treatment on last prior line of therapy was the time from the first dose of the previous antineoplastic therapy to the time of the first ibrutinib dose in the study. The all-treated population included all subjects who received at least 1 dose of study drug (Ibrutinib).

End point type	Secondary

End point timeframe:

Time from the first dose of the previous antineoplastic therapy to the time of the first ibrutinib dose during study period (up to 2 years after the last patient is enrolled)

End point values	Ibrutinib			
Subject group type	Reporting group			
Number of subjects analysed	110			
Units: months				
median (confidence interval 95%)	16.03 (10.71 to 19.12)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Resolution of Lymphoma-Related B Symptoms

End point title	Percentage of Subjects With Resolution of Lymphoma-Related B Symptoms

End point description:

For subjects who have reported symptoms at baseline and had at least one time point of assessment post baseline (before start of subsequent therapy), percentage of subjects who have no symptoms reported at least one post baseline time point (before start of subsequent therapy) were summarized. The All-treated population was defined as all subjects who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Day 1 of every cycle during the first 12 months, thereafter every other cycle (up to 2 years after the last patient is enrolled)

End point values	Ibrutinib			
Subject group type	Reporting group			
Number of subjects analysed	110			
Units: Percentage of Subjects				
number (not applicable)				
Postbaseline	23.6			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Identified With Blood Biomarkers That Alter B-Cell Receptor Signaling or Activate Alternative Signaling Pathways

End point title	Number of Subjects Identified With Blood Biomarkers That Alter B-Cell Receptor Signaling or Activate Alternative Signaling Pathways

End point description:

Number of subjects with T-cell subset and chemokine/cytokine analyses were categorized as responders (CR an PR) and non-responders (SD and PD). T-cell subsets in peripheral blood were assessed via flow cytometry for 57 subjects with available samples. Cytokine/chemokine analysis was performed on samples from 50 subjects, using Somalogic’s Somascan Assay. The analysis was based on the all treated population includes all subjects who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Baseline, Day 1 of Cycles 1-3, and time of disease progression, or at end-of treatment visit for participants who discontinue treatment without disease progression

End point values	Ibrutinib			
Subject group type	Reporting group			
Number of subjects analysed	110			
Units: Subjects				
number (not applicable)				
T cell subsets (n=57): Responders	14			
T cell subsets (n=57): Non Responders	43			
Cytokine/Chemokine analysis (n=50): Responders	21			
Cytokine/Chemokine analysis (n=50): Non Responders	29			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration at 24 hour (C24h) after administration of PCI-32765

End point title	Plasma Concentration at 24 hour (C24h) after administration of PCI- 32765

End point description:

The (C24h) is the Plasma Concentration at 24 hour observed after administration of PCI-32765 at steady state. This population included all-treated subjects with at least 1 post treatment pharmacokinetic sample.

End point type	Secondary

End point timeframe:

24 hours post-dose on Day 1 of Cycle 4

End point values	Ibrutinib			
Subject group type	Reporting group			
Number of subjects analysed	107			
Units: nanogram per milliliter (ng/mL)				
arithmetic mean (standard deviation)	5.77 (± 3.56)			

Statistical analyses

No statistical analyses for this end point

Secondary: Oral Plasma Clearance of PCI-32765

End point title	Oral Plasma Clearance of PCI-32765

End point description:

The Oral plasma Clearance (CL/F) is the clearance based on oral bioavailability. This population included all-treated subjects with at least 1 post treatment pharmacokinetic sample.

End point type	Secondary

End point timeframe:

Pre-dose Day 1 of Cycles 1-3, post-dose Day 1 of Cycles 1, 2 at 1, 2, and 4 hours

End point values	Ibrutinib			
Subject group type	Reporting group			
Number of subjects analysed	110[2]			
Units: Liter per hour (L/h)				
arithmetic mean (standard deviation)	1100 (± 99999)			

Notes:

[2] - Here 99999 indicates that no standard deviation was reported as mean was considered fixed parameter.

Statistical analyses

No statistical analyses for this end point

Secondary: Oral Volume of Distribution at Steady State of PCI-32765

End point title	Oral Volume of Distribution at Steady State of PCI-32765

End point description:

Volume of distribution is defined as the theoretical volume in which the total amount of drug would need to be uniformly distributed to produce the desired blood concentration of a drug. Steady state volume of distribution (Vss) is the apparent volume of distribution at steady-state which is estimated by (D/AUC[0-infinity])*(AUMC[0-infinity])/AUC[0-infinity]) where D is the dose of study drug, AUMC(0-infinity) is the area under the first moment curve extrapolated to infinity and AUC(0-infinity) is the area under the plasma concentration-time curve from time zero to infinite time. This population included all-treated subjects with at least 1 post treatment pharmacokinetic sample.

End point type	Secondary

End point timeframe:

Pre-dose Day 1 of Cycles 1-3, post-dose Day 1 of Cycles 1, 2 at 1, 2, and 4 hours

End point values	Ibrutinib			
Subject group type	Reporting group			
Number of subjects analysed	110			
Units: Liter (L)				
arithmetic mean (standard deviation)	10553 (± 3882)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Plasma Concentration-Time Curve From Time Zero to 24 Hours (AUC[0-24]) of PCI-32765

End point title	Area Under the Plasma Concentration-Time Curve From Time Zero to 24 Hours (AUC[0-24]) of PCI-32765

End point description:

The AUC (0-24) is the area under the plasma concentration-time curve from time zero to 24 hours at steady state. This population included all-treated subjects with at least 1 post treatment Pharmacokinetic sample.

End point type	Secondary

End point timeframe:

Predose, 1, 2, and 4 hours postdose on Day 1 of Cycle 4

End point values	Ibrutinib			
Subject group type	Reporting group			
Number of subjects analysed	107			
Units: nanogram* hour per milliliter (ng*h/mL)				
arithmetic mean (standard deviation)	539 (± 360)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Adverse Events

End point title	Number of Subjects With Adverse Events

End point description:

An AE is any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. The safety population included all subjects who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Up to 30 days after the last dose of study medication

End point values	Ibrutinib			
Subject group type	Reporting group			
Number of subjects analysed	110			
Units: Subjects	107			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to 30 days after the last dose of study medication	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups	
Reporting group title	Ibrutinib

Reporting group description:

Subjects self-administered 560 milligram (mg) oral Ibrutinib capsules (4*140 mg) once daily continuously until disease progression or unacceptable toxicity until study end (2 years after last subject enrolled).

Serious adverse events	Ibrutinib		
Total subjects affected by serious adverse events			
subjects affected / exposed	53 / 110 (48.18%)		
number of deaths (all causes)	38		
number of deaths resulting from adverse events	5		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute Myeloid Leukaemia			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Basal Cell Carcinoma			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Invasive Ductal Breast Carcinoma			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Malignant Melanoma			

subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Metastases to Meninges			
subjects affected / exposed	1 / 110 (0.91%)		
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 / 110 (0.91%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Embolism			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Inferior Vena Cava Syndrome			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest Pain			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Fatigue			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General Physical Health Deterioration			
subjects affected / exposed	2 / 110 (1.82%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	1 / 1		

Multi-Organ Failure				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Oedema Peripheral				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	7 / 110 (6.36%)			
occurrences causally related to treatment / all	9 / 9			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
Benign Prostatic Hyperplasia				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Dyspnoea				
subjects affected / exposed	2 / 110 (1.82%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Hypoxia				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pleural Effusion				
subjects affected / exposed	4 / 110 (3.64%)			
occurrences causally related to treatment / all	6 / 6			
deaths causally related to treatment / all	0 / 0			
Pneumonitis				

subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary Embolism				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Alcohol Abuse				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Alcohol Withdrawal Syndrome				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				
Weight Decreased				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Femoral Neck Fracture				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Head Injury				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hip Fracture				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Lumbar Vertebral Fracture				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Post Procedural Haemorrhage				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Subdural Haematoma				
subjects affected / exposed	2 / 110 (1.82%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Acute Myocardial Infarction				
subjects affected / exposed	2 / 110 (1.82%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Atrial Fibrillation				
subjects affected / exposed	3 / 110 (2.73%)			
occurrences causally related to treatment / all	4 / 4			
deaths causally related to treatment / all	0 / 0			
Palpitations				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pericardial Effusion				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Sinus Tachycardia				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				

Cerebral Haemorrhage				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebral Infarction				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal Cord Compression				
subjects affected / exposed	1 / 110 (0.91%)			
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	1 / 110 (0.91%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Febrile Neutropenia				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Iron Deficiency Anaemia				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Lymphadenopathy				
subjects affected / exposed	2 / 110 (1.82%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Spleen Disorder				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Eye disorders				

Macular Fibrosis			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	3 / 110 (2.73%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Internal Hernia			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal Perforation			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	1 / 1		
Small Intestinal Obstruction			
subjects affected / exposed	2 / 110 (1.82%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Volvulus			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Bile Duct Obstruction			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Cholelithiasis				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatic Failure				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	1 / 1			
Hepatosplenomegaly				
subjects affected / exposed	1 / 110 (0.91%)			
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 / 110 (1.82%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Renal Failure				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary Tract Obstruction				
subjects affected / exposed	2 / 110 (1.82%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Monarthritis				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Muscular Weakness				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Infections and infestations			
Bacteraemia			
subjects affected / exposed	2 / 110 (1.82%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Bacterial Sepsis			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Brain Abscess			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	2 / 110 (1.82%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Emphysematous Cystitis			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Escherichia Bacteraemia			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Haematoma Infection			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Herpes Zoster Disseminated			

subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Lower Respiratory Tract Infection				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Lung Abscess				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Lymph Node Abscess				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Meningitis Bacterial				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Neutropenic Sepsis				
subjects affected / exposed	2 / 110 (1.82%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	1 / 1			
Peritonitis				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumocystis Jirovecii Pneumonia				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				

subjects affected / exposed	7 / 110 (6.36%)			
occurrences causally related to treatment / all	8 / 8			
deaths causally related to treatment / all	1 / 1			
Pseudomonas Infection				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	3 / 110 (2.73%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Septic Shock				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Staphylococcal Abscess				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary Tract Infection				
subjects affected / exposed	2 / 110 (1.82%)			
occurrences causally related to treatment / all	5 / 5			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Hypercalcaemia				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hyperuricaemia				

subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Lactic Acidosis			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	1 / 1		
Tumour Lysis Syndrome			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	1 / 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	105 / 110 (95.45%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	7 / 110 (6.36%)		
occurrences (all)	8		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	14 / 110 (12.73%)		
occurrences (all)	14		
Chills			
subjects affected / exposed	11 / 110 (10.00%)		
occurrences (all)	13		
Fatigue			
subjects affected / exposed	44 / 110 (40.00%)		
occurrences (all)	77		
Oedema Peripheral			
subjects affected / exposed	31 / 110 (28.18%)		
occurrences (all)	36		
Pyrexia			

subjects affected / exposed	24 / 110 (21.82%)		
occurrences (all)	44		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	39 / 110 (35.45%)		
occurrences (all)	65		
Dyspnoea			
subjects affected / exposed	13 / 110 (11.82%)		
occurrences (all)	17		
Epistaxis			
subjects affected / exposed	8 / 110 (7.27%)		
occurrences (all)	12		
Oropharyngeal Pain			
subjects affected / exposed	10 / 110 (9.09%)		
occurrences (all)	14		
Psychiatric disorders			
Depression			
subjects affected / exposed	8 / 110 (7.27%)		
occurrences (all)	9		
Insomnia			
subjects affected / exposed	14 / 110 (12.73%)		
occurrences (all)	16		
Investigations			
Blood Creatinine Increased			
subjects affected / exposed	10 / 110 (9.09%)		
occurrences (all)	17		
Platelet Count Decreased			
subjects affected / exposed	13 / 110 (11.82%)		
occurrences (all)	26		
White Blood Cell Count Decreased			
subjects affected / exposed	6 / 110 (5.45%)		
occurrences (all)	11		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	10 / 110 (9.09%)		
occurrences (all)	13		

Fall subjects affected / exposed occurrences (all)	6 / 110 (5.45%) 7		
Cardiac disorders Atrial Fibrillation subjects affected / exposed occurrences (all)	8 / 110 (7.27%) 9		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all)	12 / 110 (10.91%) 14 19 / 110 (17.27%) 26		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all)	24 / 110 (21.82%) 62 16 / 110 (14.55%) 28 21 / 110 (19.09%) 40		
Eye disorders Dry Eye subjects affected / exposed occurrences (all) Lacrimation Increased subjects affected / exposed occurrences (all) Vision Blurred subjects affected / exposed occurrences (all)	6 / 110 (5.45%) 7 7 / 110 (6.36%) 7 6 / 110 (5.45%) 7		
Gastrointestinal disorders Abdominal Pain			

subjects affected / exposed	12 / 110 (10.91%)		
occurrences (all)	13		
Abdominal Pain Upper			
subjects affected / exposed	10 / 110 (9.09%)		
occurrences (all)	10		
Constipation			
subjects affected / exposed	14 / 110 (12.73%)		
occurrences (all)	15		
Diarrhoea			
subjects affected / exposed	55 / 110 (50.00%)		
occurrences (all)	115		
Dry Mouth			
subjects affected / exposed	11 / 110 (10.00%)		
occurrences (all)	14		
Dyspepsia			
subjects affected / exposed	8 / 110 (7.27%)		
occurrences (all)	9		
Nausea			
subjects affected / exposed	32 / 110 (29.09%)		
occurrences (all)	44		
Stomatitis			
subjects affected / exposed	6 / 110 (5.45%)		
occurrences (all)	8		
Vomiting			
subjects affected / exposed	15 / 110 (13.64%)		
occurrences (all)	17		
Skin and subcutaneous tissue disorders			
Dry Skin			
subjects affected / exposed	10 / 110 (9.09%)		
occurrences (all)	11		
Pruritus			
subjects affected / exposed	13 / 110 (11.82%)		
occurrences (all)	15		
Rash			
subjects affected / exposed	18 / 110 (16.36%)		
occurrences (all)	24		

Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	9 / 110 (8.18%)		
occurrences (all)	10		
Back Pain			
subjects affected / exposed	14 / 110 (12.73%)		
occurrences (all)	18		
Muscle Spasms			
subjects affected / exposed	35 / 110 (31.82%)		
occurrences (all)	76		
Myalgia			
subjects affected / exposed	11 / 110 (10.00%)		
occurrences (all)	15		
Pain in Extremity			
subjects affected / exposed	11 / 110 (10.00%)		
occurrences (all)	13		
Infections and infestations			
Bronchitis			
subjects affected / exposed	11 / 110 (10.00%)		
occurrences (all)	14		
Conjunctivitis			
subjects affected / exposed	9 / 110 (8.18%)		
occurrences (all)	18		
Nasopharyngitis			
subjects affected / exposed	6 / 110 (5.45%)		
occurrences (all)	9		
Sinusitis			
subjects affected / exposed	11 / 110 (10.00%)		
occurrences (all)	14		
Upper Respiratory Tract Infection			
subjects affected / exposed	19 / 110 (17.27%)		
occurrences (all)	31		
Urinary Tract Infection			
subjects affected / exposed	7 / 110 (6.36%)		
occurrences (all)	18		
Metabolism and nutrition disorders			

Decreased Appetite			
subjects affected / exposed	16 / 110 (14.55%)		
occurrences (all)	19		
Hypokalaemia			
subjects affected / exposed	14 / 110 (12.73%)		
occurrences (all)	37		
Hypomagnesaemia			
subjects affected / exposed	9 / 110 (8.18%)		
occurrences (all)	11		
Hyponatraemia			
subjects affected / exposed	10 / 110 (9.09%)		
occurrences (all)	12		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 September 2012	The global amendment INT-1 included clarification to the mechanism of action of ibrutinib. Additional safety data were added. Clarification regarding collection of tissue specimen for biomarker analysis was added. Other malignant diseases were observed in subjects who were treated with ibrutinib; it was unclear whether or not these events were attributable to ibrutinib. Therefore, other malignancies occurring in subjects treated in this study were reported and collected on the electronic case report form (eCRF). Guidance and clarification for the administration of cytochrome P450 (CYP) 3A4/5 subtype inhibitors/inducers during ibrutinib administration was provided. QT prolongation was not expected with ibrutinib; the precaution for concomitant use of ibrutinib and medications known to cause QT prolongation was simplified. Instructions for concomitant use of ibrutinib and antiplatelet agents, anticoagulants, supplements such as fish oil and vitamin E preparations were updated. Actual increase for the maximum plasma concentration and the area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration in ibrutinib exposure when administered in combination with ketoconazole was updated. Additional pharmacokinetic (PK) samples were requested from subjects who received a strong or moderate cytochrome P450 (CYP) 3A4/5 inhibitor while receiving treatment with ibrutinib. Additional details for the Hepatitis B and C samples collected at screening and instructions for documentation of any additional laboratory testing performed in relation to an adverse event(s) (AE) were added. Interim analysis was removed.
31 January 2014	The global amendment INT-2 addressed the novel situation of delayed responses that had been observed after progressive disease (PD). In addition, this amendment addressed the situation of subjects with borderline disease progression and the management and evaluation of subjects with radiological evidence of PD. Language was added to allow for continuation of ibrutinib in subjects with radiological evidence of PD who were clinically stable or improving or exhibiting signs of tumor flare without confirmation of PD by positron emission tomography (PET) or biopsy, had no signs of impending organ compromise, and who were not experiencing significant toxicity. In addition, resumption of ibrutinib was permitted if a delayed response was observed after ibrutinib had been discontinued for PD. Additional new safety information (rashes and infection) based on studies conducted with ibrutinib and the incidence for treatment discontinuations in the monotherapy and combination therapy safety population was added.
18 December 2014	The global amendment INT-3 included the following changes: The clinical cutoff was extended to 15 months after the last subject enrolled to ensure that response data was fully captured for the study. PET scans performed at maximal tumor reduction could include response assessments at 12 months. Instructions for PET assessment for those subjects who had been on the study more than 48 weeks without a PET scan were added. Potential risks associated with ibrutinib were updated based on the 2014 investigator's brochure (IB) (version 8.0) and new risks (cytopenias, diarrhea) were added. The definition of a major hemorrhagic bleeding event was broadened to include any bleeding event that was grade 3 or higher (including all hemorrhagic events requiring a transfusion of red blood cells), was considered a serious AE, or any central nervous system hemorrhage/hematoma. Atrial fibrillation and atrial flutter have been reported in subjects treated with ibrutinib, particularly in subjects with cardiac risk factors, acute infections, and a previous history of atrial fibrillation. Instructions were added to periodically monitor subjects clinically for atrial fibrillation. Precautions for concomitant use of ibrutinib with CYP3A inhibitors, CYP3A inducers, P-glycoprotein (P-gp) substrates, QT prolonging agents, agents and anticoagulants were revised.

16 November 2015	The global amendment INT-5 included the following changes: Subjects continued to experience a partial or complete response to treatment with ibrutinib; therefore, the clinical cutoff was further extended to 24 months to allow for maturation of the data on the duration of response (DOR). Expanded disease evaluation to include screening, every 12 weeks (+/- 7 days) for the first 96 weeks, and then every 24 weeks (+/-) 14 days) thereafter until disease progression or the clinical cutoff. For subjects who had disease evaluations greater than 3 months prior to clinical cutoff, a final disease evaluation was to be performed at the last cycle visit prior to clinical cutoff.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported