



## 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.,<br>ClinicalTrialsEU@its.jnj.com |
| Scientific contact           | Clinical Registry Group, Janssen-Cilag International N.V.,<br>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:

| <b>Subjects enrolled per age group</b>    |    |
|---|----|
| 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<br>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<br>Units: years     |           |       |  |
| arithmetic mean                             | 60.9      |       |  |
| standard deviation                          | ± 11.83   | -     |  |
| Title for Gender<br>Units: subjects         |           |       |  |
| Female                                      | 43        | 43    |  |
| Male  | 67        | 67    |  |

## End points

### End points reporting groups

|  |           |
|--|-----------|
| Reporting group title  | Ibrutinib |
| Reporting group description:<br>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) <sup>[1]</sup> |
| End point description:<br>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:<br>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:<br>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) |           |

|                                  |                     |  |  |  |
|----------------------------------|---------------------|--|--|--|
| <b>End point values</b>          | 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)   |                                 |

|                                  |                  |  |  |  |
|----------------------------------|------------------|--|--|--|
| <b>End point values</b>          | 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)   |                       |

|                                  |                        |  |  |  |
|----------------------------------|------------------------|--|--|--|
| <b>End point values</b>          | 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)  |                  |

|                               |                    |  |  |  |
|-------------------------------|--------------------|--|--|--|
| <b>End point values</b>       | 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)

|                                  |                        |  |  |  |
|----------------------------------|------------------------|--|--|--|
| <b>End point values</b>          | 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)

|                               |                 |  |  |  |
|-------------------------------|-----------------|--|--|--|
| <b>End point values</b>       | 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 and 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:<br>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:<br>Pre-dose Day 1 of Cycles 1-3, post-dose Day 1 of Cycles 1, 2 at 1, 2, and 4 hours   |                                    |

|                                      |                    |  |  |  |
|--------------------------------------|--------------------|--|--|--|
| <b>End point values</b>              | Ibrutinib          |  |  |  |
| Subject group type                   | Reporting group    |  |  |  |
| Number of subjects analysed          | 110 <sup>[2]</sup> |  |  |  |
| 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:<br>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 (V <sub>ss</sub> ) is the apparent volume of distribution at steady-state which is estimated by $(D/AUC[0-\infty]) \cdot (AUMC[0-\infty]/AUC[0-\infty])$ 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:<br>Pre-dose Day 1 of Cycles 1-3, post-dose Day 1 of Cycles 1, 2 at 1, 2, and 4 hours   |  |

|                                      |                 |  |  |  |
|--------------------------------------|-----------------|--|--|--|
| <b>End point values</b>              | 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



## 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<br>Bacteraemia<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all | 2 / 110 (1.82%)<br>3 / 3<br>0 / 0 |  |  |
| Bacterial Sepsis<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                           | 1 / 110 (0.91%)<br>1 / 1<br>0 / 0 |  |  |
| Brain Abscess<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                              | 1 / 110 (0.91%)<br>1 / 1<br>0 / 0 |  |  |
| Bronchitis<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                                 | 1 / 110 (0.91%)<br>1 / 1<br>0 / 0 |  |  |
| Cellulitis<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                                 | 2 / 110 (1.82%)<br>2 / 2<br>0 / 0 |  |  |
| Emphysematous Cystitis<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                     | 1 / 110 (0.91%)<br>1 / 1<br>0 / 0 |  |  |
| Escherichia Bacteraemia<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                    | 1 / 110 (0.91%)<br>1 / 1<br>0 / 0 |  |  |
| Haematoma Infection<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                        | 1 / 110 (0.91%)<br>1 / 1<br>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           |  |  |
| <b>Pseudomonas Infection</b>                    |                 |  |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Pyelonephritis</b>                           |                 |  |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Sepsis</b>                                   |                 |  |  |
| subjects affected / exposed                     | 3 / 110 (2.73%) |  |  |
| occurrences causally related to treatment / all | 3 / 3           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Septic Shock</b>                             |                 |  |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Staphylococcal Abscess</b>                   |                 |  |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Urinary Tract Infection</b>                  |                 |  |  |
| subjects affected / exposed                     | 2 / 110 (1.82%) |  |  |
| occurrences causally related to treatment / all | 5 / 5           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Metabolism and nutrition disorders</b>       |                 |  |  |
| <b>Hypercalcaemia</b>                           |                 |  |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Hyperuricaemia</b>                           |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 110 (0.91%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Lactic Acidosis</b>                          |                 |  |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) |  |  |
| occurrences causally related to treatment / all | 2 / 2           |  |  |
| deaths causally related to treatment / all      | 1 / 1           |  |  |
| <b>Tumour Lysis Syndrome</b>                    |                 |  |  |
| 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 %

| <b>Non-serious adverse events</b>                            | Ibrutinib          |  |  |
|--|--------------------|--|--|
| <b>Total subjects affected by non-serious adverse events</b> |                    |  |  |
| subjects affected / exposed                                  | 105 / 110 (95.45%) |  |  |
| <b>Vascular disorders</b>                                    |                    |  |  |
| Hypertension   |                    |  |  |
| subjects affected / exposed                                  | 7 / 110 (6.36%)    |  |  |
| occurrences (all)  | 8                  |  |  |
| <b>General disorders and administration site conditions</b>  |                    |  |  |
| 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<br>occurrences (all)  | 24 / 110 (21.82%)<br>44   |  |  |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all)<br><br>Dyspnoea<br>subjects affected / exposed<br>occurrences (all)<br><br>Epistaxis<br>subjects affected / exposed<br>occurrences (all)<br><br>Oropharyngeal Pain<br>subjects affected / exposed<br>occurrences (all) | 39 / 110 (35.45%)<br>65<br><br>13 / 110 (11.82%)<br>17<br><br>8 / 110 (7.27%)<br>12<br><br>10 / 110 (9.09%)<br>14 |  |  |
| Psychiatric disorders<br>Depression<br>subjects affected / exposed<br>occurrences (all)<br><br>Insomnia<br>subjects affected / exposed<br>occurrences (all)   | 8 / 110 (7.27%)<br>9<br><br>14 / 110 (12.73%)<br>16   |  |  |
| Investigations<br>Blood Creatinine Increased<br>subjects affected / exposed<br>occurrences (all)<br><br>Platelet Count Decreased<br>subjects affected / exposed<br>occurrences (all)<br><br>White Blood Cell Count Decreased<br>subjects affected / exposed<br>occurrences (all)  | 10 / 110 (9.09%)<br>17<br><br>13 / 110 (11.82%)<br>26<br><br>6 / 110 (5.45%)<br>11                                |  |  |
| Injury, poisoning and procedural complications<br>Contusion<br>subjects affected / exposed<br>occurrences (all)   | 10 / 110 (9.09%)<br>13  |  |  |

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

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## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported