



## Clinical trial results:

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

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2012-004476-19 |
| Trial protocol           | GB SE BE DE    |
| Global end of trial date | 19 May 2016    |

#### Results information

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

#### Trial information

##### Trial identification

|                       |              |
|-----------------------|--------------|
| Sponsor protocol code | PCYC-1117-CA |
|-----------------------|--------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01744691 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Pharmacyclics LLC.   |
| Sponsor organisation address | 995 East Arques Avenue, Sunnyvale, California, United States, 94085        |
| Public contact               | Clinical Trial information, Pharmacyclics LLC, 140 87740330, info@pcyc.com |
| Scientific contact           | Clinical Trial information, Pharmacyclics LLC, 140 87740330, info@pcyc.com |

Notes:

#### Paediatric regulatory details

|  |    |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

|  |                 |
|--|-----------------|
| Analysis stage                                       | Final           |
| Date of interim/final analysis                       | 09 January 2017 |
| Is this the analysis of the primary completion data? | No              |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 19 May 2016     |
| Was the trial ended prematurely?                     | No              |

Notes:

## General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

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

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United States: 84  |
| Country: Number of subjects enrolled | Australia: 7       |
| Country: Number of subjects enrolled | Belgium: 3         |
| Country: Number of subjects enrolled | Canada: 2          |
| Country: Number of subjects enrolled | Germany: 13        |
| Country: Number of subjects enrolled | New Zealand: 2     |
| Country: Number of subjects enrolled | Sweden: 8          |
| Country: Number of subjects enrolled | Turkey: 12         |
| Country: Number of subjects enrolled | United Kingdom: 14 |
| Worldwide total number of subjects   | 145                |
| EEA total number of subjects         | 38                 |

Notes:

### Subjects enrolled per age group

|   |   |
|---|---|
| In utero                                  | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |

|  |    |
|--|----|
| Newborns (0-27 days)                     | 0  |
| Infants and toddlers (28 days-23 months) | 0  |
| Children (2-11 years)                    | 0  |
| Adolescents (12-17 years)                | 0  |
| Adults (18-64 years)                     | 75 |
| From 65 to 84 years                      | 68 |
| 85 years and over                        | 2  |

## Subject disposition

### Recruitment

Recruitment details:

Key Inclusion Criteria:

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

Key Exclusion Criteria:

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

### Pre-assignment

Screening details:

One hundred forty-five subjects were enrolled and 144 subjects received at least 1 dose of PCI-32765 and constitute the all treated population and the safety analysis set.

### Period 1

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

### Arms

|           |           |
|-----------|-----------|
| Arm title | ibrutinib |
|-----------|-----------|

Arm description:

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

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

Dosage and administration details:

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

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

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Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: There was 1 additional subject enrolled who, however, did not receive any study medication and was excluded from all analyses.

## Baseline characteristics

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### Reporting groups

|                       |               |
|-----------------------|---------------|
| Reporting group title | overall study |
|-----------------------|---------------|

Reporting group description:

All subjects received PCI-32765 420 mg (3 x 140-mg capsules) orally once daily.

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| Reporting group values  | overall study | Total |  |
|-------------------------|---------------|-------|--|
| Number of subjects      | 144           | 144   |  |
| Age categorical         |               |       |  |
| Count of Participants   |               |       |  |
| Units: Subjects         |               |       |  |
| <=18 years              | 0             | 0     |  |
| Between 18 and 65 years | 75            | 75    |  |
| >=65 years              | 69            | 69    |  |
| Age continuous          |               |       |  |
| Units: years            |               |       |  |
| arithmetic mean         | 64.4          |       |  |
| standard deviation      | ± 9.9         | -     |  |
| Gender categorical      |               |       |  |
| Units: Subjects         |               |       |  |
| Female                  | 48            | 48    |  |
| Male                    | 96            | 96    |  |

## End points

### End points reporting groups

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

### Primary: Overall Response Rate

|  |                                      |
|--|--------------------------------------|
| End point title  | Overall Response Rate <sup>[1]</sup> |
| End point description:   |                                      |
| The primary objective of this study is to evaluate the efficacy of ibrutinib in terms of ORR according to an Independent Review Committee (IRC). ORR based upon IRC assessment is the proportion of responders in the all treated population. Responders were subjects who achieved partial response (PR) or better, ie, complete response (CR), complete response with incomplete marrow recovery (CRi), nodule partial response (nPR) or PR, per IWCLL 2008 criteria with the clarification for treatment-related lymphocytosis. |                                      |
| End point type   | Primary                              |
| End point timeframe:   |                                      |
| The median time on study for all treated participants is 33.3 (range 0.5 - 40.1) months  |                                      |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Response rate and 95% CI calculated based on normal approximation with Wilson's score method. However, as this has been a single arm study, no statistical analyses have been performed.

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

### Statistical analyses

No statistical analyses for this end point

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

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

|                             |                 |  |  |  |
|-----------------------------|-----------------|--|--|--|
| <b>End point values</b>     | ibrutinib       |  |  |  |
| Subject group type          | Reporting group |  |  |  |
| Number of subjects analysed | 144             |  |  |  |
| Units: Participants         | 144             |  |  |  |

### Statistical analyses

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No statistical analyses for this end point



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From first dose of PCI-32765 to within 30 days of last dose for each participant or until study closure

Adverse event reporting additional description:

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

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 17.0 |
|--------------------|------|

### Reporting groups

|                       |           |
|-----------------------|-----------|
| Reporting group title | PCI-32765 |
|-----------------------|-----------|

Reporting group description:

All subjects will receive PCI-32765 420 mg (3 x 140-mg capsules) orally once daily.

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

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

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

|   |                 |  |  |
|---|-----------------|--|--|
| Respiratory, thoracic and mediastinal disorders |                 |  |  |
| Pleural effusion                                |                 |  |  |
| subjects affected / exposed                     | 3 / 144 (2.08%) |  |  |
| occurrences causally related to treatment / all | 1 / 6           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Alveolitis allergic                             |                 |  |  |
| subjects affected / exposed                     | 1 / 144 (0.69%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Haemoptysis                                     |                 |  |  |
| subjects affected / exposed                     | 1 / 144 (0.69%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Haemothorax                                     |                 |  |  |
| subjects affected / exposed                     | 1 / 144 (0.69%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Interstitial lung disease                       |                 |  |  |
| subjects affected / exposed                     | 1 / 144 (0.69%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pneumonitis                                     |                 |  |  |
| subjects affected / exposed                     | 1 / 144 (0.69%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pulmonary embolism                              |                 |  |  |
| subjects affected / exposed                     | 1 / 144 (0.69%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pulmonary mass                                  |                 |  |  |
| subjects affected / exposed                     | 1 / 144 (0.69%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| Pulmonary oedema                                |                 |  |  |
| subjects affected / exposed                     | 1 / 144 (0.69%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Psychiatric disorders                           |                 |  |  |
| Psychotic disorder                              |                 |  |  |
| subjects affected / exposed                     | 1 / 144 (0.69%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Injury, poisoning and procedural complications  |                 |  |  |
| Subdural haematoma                              |                 |  |  |
| subjects affected / exposed                     | 3 / 144 (2.08%) |  |  |
| occurrences causally related to treatment / all | 2 / 3           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Alcohol poisoning                               |                 |  |  |
| subjects affected / exposed                     | 1 / 144 (0.69%) |  |  |
| occurrences causally related to treatment / all | 0 / 3           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Femoral neck fracture                           |                 |  |  |
| subjects affected / exposed                     | 1 / 144 (0.69%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Meniscus injury                                 |                 |  |  |
| subjects affected / exposed                     | 1 / 144 (0.69%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Muscle rupture                                  |                 |  |  |
| subjects affected / exposed                     | 1 / 144 (0.69%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Post procedural haematuria                      |                 |  |  |
| subjects affected / exposed                     | 1 / 144 (0.69%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

|  |                 |  |  |
|--|-----------------|--|--|
| Post procedural haemorrhage<br>subjects affected / exposed | 1 / 144 (0.69%) |  |  |
| occurrences causally related to<br>treatment / all         | 1 / 1           |  |  |
| deaths causally related to<br>treatment / all              | 0 / 0           |  |  |
| Traumatic haematoma<br>subjects affected / exposed         | 1 / 144 (0.69%) |  |  |
| occurrences causally related to<br>treatment / all         | 0 / 1           |  |  |
| deaths causally related to<br>treatment / all              | 0 / 0           |  |  |
| Cardiac disorders  |                 |  |  |
| Atrial fibrillation<br>subjects affected / exposed         | 8 / 144 (5.56%) |  |  |
| occurrences causally related to<br>treatment / all         | 3 / 11          |  |  |
| deaths causally related to<br>treatment / all              | 0 / 0           |  |  |
| Acute myocardial infarction<br>subjects affected / exposed | 2 / 144 (1.39%) |  |  |
| occurrences causally related to<br>treatment / all         | 0 / 2           |  |  |
| deaths causally related to<br>treatment / all              | 0 / 1           |  |  |
| Pericarditis<br>subjects affected / exposed                | 2 / 144 (1.39%) |  |  |
| occurrences causally related to<br>treatment / all         | 1 / 4           |  |  |
| deaths causally related to<br>treatment / all              | 0 / 0           |  |  |
| Cardiac failure<br>subjects affected / exposed             | 1 / 144 (0.69%) |  |  |
| occurrences causally related to<br>treatment / all         | 0 / 1           |  |  |
| deaths causally related to<br>treatment / all              | 0 / 1           |  |  |
| Myocardial infarction<br>subjects affected / exposed       | 1 / 144 (0.69%) |  |  |
| occurrences causally related to<br>treatment / all         | 1 / 1           |  |  |
| deaths causally related to<br>treatment / all              | 1 / 1           |  |  |
| Pericardial effusion<br>subjects affected / exposed        | 1 / 144 (0.69%) |  |  |
| occurrences causally related to<br>treatment / all         | 1 / 1           |  |  |
| deaths causally related to<br>treatment / all              | 0 / 0           |  |  |
| Sinus node dysfunction                                     |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 144 (0.69%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Nervous system disorders                        |                 |  |  |
| Syncope   |                 |  |  |
| subjects affected / exposed                     | 2 / 144 (1.39%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cerebrovascular accident                        |                 |  |  |
| subjects affected / exposed                     | 1 / 144 (0.69%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Critical illness polyneuropathy                 |                 |  |  |
| subjects affected / exposed                     | 1 / 144 (0.69%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Encephalopathy                                  |                 |  |  |
| subjects affected / exposed                     | 1 / 144 (0.69%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Haemorrhage intracranial                        |                 |  |  |
| subjects affected / exposed                     | 1 / 144 (0.69%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Blood and lymphatic system disorders            |                 |  |  |
| Anaemia   |                 |  |  |
| subjects affected / exposed                     | 4 / 144 (2.78%) |  |  |
| occurrences causally related to treatment / all | 1 / 5           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Febrile neutropenia                             |                 |  |  |
| subjects affected / exposed                     | 2 / 144 (1.39%) |  |  |
| occurrences causally related to treatment / all | 2 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Autoimmune haemolytic anaemia                   |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 144 (0.69%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Coagulopathy                                    |                 |  |  |
| subjects affected / exposed                     | 1 / 144 (0.69%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Haemolytic anaemia                              |                 |  |  |
| subjects affected / exposed                     | 1 / 144 (0.69%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Immune thrombocytopenic purpura                 |                 |  |  |
| subjects affected / exposed                     | 1 / 144 (0.69%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Iron deficiency anaemia                         |                 |  |  |
| subjects affected / exposed                     | 1 / 144 (0.69%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Spontaneous haematoma                           |                 |  |  |
| subjects affected / exposed                     | 1 / 144 (0.69%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Thrombocytopenia                                |                 |  |  |
| subjects affected / exposed                     | 1 / 144 (0.69%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Eye disorders                                   |                 |  |  |
| Iritis  |                 |  |  |
| subjects affected / exposed                     | 1 / 144 (0.69%) |  |  |
| occurrences causally related to treatment / all | 2 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Gastrointestinal disorders                      |                 |  |  |



|   |                 |  |  |  |
|---|-----------------|--|--|--|
| Colitis   |                 |  |  |  |
| subjects affected / exposed                     | 2 / 144 (1.39%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 2           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Diarrhoea                                       |                 |  |  |  |
| subjects affected / exposed                     | 2 / 144 (1.39%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Colitis ischaemic                               |                 |  |  |  |
| subjects affected / exposed                     | 1 / 144 (0.69%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Gastric ulcer haemorrhage                       |                 |  |  |  |
| subjects affected / exposed                     | 1 / 144 (0.69%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Gastritis                                       |                 |  |  |  |
| subjects affected / exposed                     | 1 / 144 (0.69%) |  |  |  |
| occurrences causally related to treatment / all | 2 / 2           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Intestinal obstruction                          |                 |  |  |  |
| subjects affected / exposed                     | 1 / 144 (0.69%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Oral mucosal blistering                         |                 |  |  |  |
| subjects affected / exposed                     | 1 / 144 (0.69%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Stomatitis                                      |                 |  |  |  |
| subjects affected / exposed                     | 1 / 144 (0.69%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Upper gastrointestinal haemorrhage              |                 |  |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 144 (0.69%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Vomiting  |                 |  |  |
| subjects affected / exposed                     | 1 / 144 (0.69%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hepatobiliary disorders                         |                 |  |  |
| Cholecystitis                                   |                 |  |  |
| subjects affected / exposed                     | 2 / 144 (1.39%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cholecystitis acute                             |                 |  |  |
| subjects affected / exposed                     | 1 / 144 (0.69%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hepatic function abnormal                       |                 |  |  |
| subjects affected / exposed                     | 1 / 144 (0.69%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Skin and subcutaneous tissue disorders          |                 |  |  |
| Livedo reticularis                              |                 |  |  |
| subjects affected / exposed                     | 1 / 144 (0.69%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Skin erosion                                    |                 |  |  |
| subjects affected / exposed                     | 1 / 144 (0.69%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Stevens-Johnson syndrome                        |                 |  |  |
| subjects affected / exposed                     | 1 / 144 (0.69%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Trichodysplasia spinulosa                       |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 144 (0.69%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Renal and urinary disorders                     |                 |  |  |
| Acute kidney injury                             |                 |  |  |
| subjects affected / exposed                     | 2 / 144 (1.39%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Renal failure                                   |                 |  |  |
| subjects affected / exposed                     | 2 / 144 (1.39%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Renal infarct                                   |                 |  |  |
| subjects affected / exposed                     | 1 / 144 (0.69%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 1 / 1           |  |  |
| Musculoskeletal and connective tissue disorders |                 |  |  |
| Arthritis                                       |                 |  |  |
| subjects affected / exposed                     | 2 / 144 (1.39%) |  |  |
| occurrences causally related to treatment / all | 2 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Myalgia   |                 |  |  |
| subjects affected / exposed                     | 2 / 144 (1.39%) |  |  |
| occurrences causally related to treatment / all | 2 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Osteoporosis                                    |                 |  |  |
| subjects affected / exposed                     | 2 / 144 (1.39%) |  |  |
| occurrences causally related to treatment / all | 1 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Arthralgia                                      |                 |  |  |
| subjects affected / exposed                     | 1 / 144 (0.69%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

|   |                   |  |  |  |
|---|-------------------|--|--|--|
| Chondromalacia                                  |                   |  |  |  |
| subjects affected / exposed                     | 1 / 144 (0.69%)   |  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| Dactylitis                                      |                   |  |  |  |
| subjects affected / exposed                     | 1 / 144 (0.69%)   |  |  |  |
| occurrences causally related to treatment / all | 1 / 1             |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| Muscular weakness                               |                   |  |  |  |
| subjects affected / exposed                     | 1 / 144 (0.69%)   |  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| Infections and infestations                     |                   |  |  |  |
| Pneumonia                                       |                   |  |  |  |
| subjects affected / exposed                     | 21 / 144 (14.58%) |  |  |  |
| occurrences causally related to treatment / all | 15 / 32           |  |  |  |
| deaths causally related to treatment / all      | 0 / 4             |  |  |  |
| Urinary tract infection                         |                   |  |  |  |
| subjects affected / exposed                     | 5 / 144 (3.47%)   |  |  |  |
| occurrences causally related to treatment / all | 1 / 5             |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| Cellulitis                                      |                   |  |  |  |
| subjects affected / exposed                     | 4 / 144 (2.78%)   |  |  |  |
| occurrences causally related to treatment / all | 1 / 4             |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| Bronchitis                                      |                   |  |  |  |
| subjects affected / exposed                     | 2 / 144 (1.39%)   |  |  |  |
| occurrences causally related to treatment / all | 1 / 2             |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| Pyelonephritis                                  |                   |  |  |  |
| subjects affected / exposed                     | 2 / 144 (1.39%)   |  |  |  |
| occurrences causally related to treatment / all | 1 / 2             |  |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |  |
| Sepsis  |                   |  |  |  |

|   |                 |  |  |  |
|---|-----------------|--|--|--|
| subjects affected / exposed                     | 2 / 144 (1.39%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |  |
| deaths causally related to treatment / all      | 0 / 2           |  |  |  |
| Septic shock                                    |                 |  |  |  |
| subjects affected / exposed                     | 2 / 144 (1.39%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 2           |  |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |  |
| Appendicitis                                    |                 |  |  |  |
| subjects affected / exposed                     | 1 / 144 (0.69%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Aspergillus infection                           |                 |  |  |  |
| subjects affected / exposed                     | 1 / 144 (0.69%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Atypical pneumonia                              |                 |  |  |  |
| subjects affected / exposed                     | 1 / 144 (0.69%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Bacteraemia                                     |                 |  |  |  |
| subjects affected / exposed                     | 1 / 144 (0.69%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Campylobacter gastroenteritis                   |                 |  |  |  |
| subjects affected / exposed                     | 1 / 144 (0.69%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Cystitis  |                 |  |  |  |
| subjects affected / exposed                     | 1 / 144 (0.69%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Empyema   |                 |  |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 144 (0.69%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Epiglottitis                                    |                 |  |  |
| subjects affected / exposed                     | 1 / 144 (0.69%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Gastroenteritis clostridial                     |                 |  |  |
| subjects affected / exposed                     | 1 / 144 (0.69%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Groin abscess                                   |                 |  |  |
| subjects affected / exposed                     | 1 / 144 (0.69%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Herpes simplex                                  |                 |  |  |
| subjects affected / exposed                     | 1 / 144 (0.69%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Influenza                                       |                 |  |  |
| subjects affected / exposed                     | 1 / 144 (0.69%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Lower respiratory tract infection viral         |                 |  |  |
| subjects affected / exposed                     | 1 / 144 (0.69%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Lung infection                                  |                 |  |  |
| subjects affected / exposed                     | 1 / 144 (0.69%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Lymphadenitis bacterial                         |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 144 (0.69%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Oropharyngeal candidiasis                       |                 |  |  |
| subjects affected / exposed                     | 1 / 144 (0.69%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pneumocystis jirovecii pneumonia                |                 |  |  |
| subjects affected / exposed                     | 1 / 144 (0.69%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Sinusitis fungal                                |                 |  |  |
| subjects affected / exposed                     | 1 / 144 (0.69%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Staphylococcal sepsis                           |                 |  |  |
| subjects affected / exposed                     | 1 / 144 (0.69%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Subcutaneous abscess                            |                 |  |  |
| subjects affected / exposed                     | 1 / 144 (0.69%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Varicella zoster virus infection                |                 |  |  |
| subjects affected / exposed                     | 1 / 144 (0.69%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Metabolism and nutrition disorders              |                 |  |  |
| Hypercalcaemia                                  |                 |  |  |
| subjects affected / exposed                     | 1 / 144 (0.69%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hyperkalaemia                                   |                 |  |  |

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

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

|   |                     |  |  |
|---|---------------------|--|--|
| <b>Non-serious adverse events</b>                                   | PCI-32765           |  |  |
| Total subjects affected by non-serious adverse events               |                     |  |  |
| subjects affected / exposed   | 144 / 144 (100.00%) |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                     |  |  |
| Basal cell carcinoma  |                     |  |  |
| subjects affected / exposed   | 11 / 144 (7.64%)    |  |  |
| occurrences (all)   | 11                  |  |  |
| Vascular disorders  |                     |  |  |
| Hypertension  |                     |  |  |
| subjects affected / exposed   | 39 / 144 (27.08%)   |  |  |
| occurrences (all)   | 51                  |  |  |
| General disorders and administration site conditions                |                     |  |  |
| Fatigue   |                     |  |  |
| subjects affected / exposed   | 53 / 144 (36.81%)   |  |  |
| occurrences (all)   | 61                  |  |  |
| Pyrexia   |                     |  |  |
| subjects affected / exposed   | 31 / 144 (21.53%)   |  |  |
| occurrences (all)   | 47                  |  |  |
| Oedema peripheral   |                     |  |  |



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

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

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

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

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

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

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported