



## Clinical trial results:

### A Study of IPI-145 and Ofatumumab in Patients With Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Previously Enrolled in Study IPI-145-07 Duvelisib (IPI-145)

#### Summary

|                          |                               |
|--------------------------|-------------------------------|
| EudraCT number           | 2013-003639-31                |
| Trial protocol           | IT HU ES GB BE AT DE FR LV GR |
| Global end of trial date | 12 June 2020                  |

#### Results information

|                                |                                                                                                                        |
|--------------------------------|------------------------------------------------------------------------------------------------------------------------|
| Result version number          | v2 (current)                                                                                                           |
| This version publication date  | 06 October 2023                                                                                                        |
| First version publication date | 08 June 2023                                                                                                           |
| Version creation reason        | <ul style="list-style-type: none"><li>• Correction of full data set</li></ul> Results contact information has changed. |

#### Trial information

##### Trial identification

|                       |            |
|-----------------------|------------|
| Sponsor protocol code | IPI-145-12 |
|-----------------------|------------|

##### Additional study identifiers

|                                    |                 |
|------------------------------------|-----------------|
| ISRCTN number                      | -               |
| ClinicalTrials.gov id (NCT number) | NCT02049515     |
| WHO universal trial number (UTN)   | U1111-1138-8603 |

Notes:

#### Sponsors

|                              |                                                                                       |
|------------------------------|---------------------------------------------------------------------------------------|
| Sponsor organisation name    | Secura Bio, Inc.                                                                      |
| Sponsor organisation address | 1995 Village Center Circle, Suite 128, Las Vegas, NV, United States, 89134            |
| Public contact               | Beth Gregory, PharmD, MBA, Secura Bio, Inc., +1 702 -254-0011, bgregory@securabio.com |
| Scientific contact           | Beth Gregory, PharmD, MBA, Secura Bio, Inc., +1 702 -254-0011, bgregory@securabio.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                       | 12 June 2020 |
| Is this the analysis of the primary completion data? | No           |
| Global end of trial reached?                         | Yes          |
| Global end of trial date                             | 12 June 2020 |
| Was the trial ended prematurely?                     | No           |

Notes:

## General information about the trial

Main objective of the trial:

A Phase 3 (extension) clinical trial to examine the efficacy of IPI-145 (duvelisib) monotherapy or ofatumumab monotherapy in participants with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma who experienced disease progression after treatment with IPI-145 or ofatumumab in study IPI-145-07 (2013-002405-61).

Protection of trial subjects:

This study was conducted in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which the study was conducted.

Background therapy: -

Evidence for comparator: -

|                                                           |                  |
|-----------------------------------------------------------|------------------|
| Actual start date of recruitment                          | 20 December 2013 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | No               |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                   |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Austria: 9        |
| Country: Number of subjects enrolled | France: 11        |
| Country: Number of subjects enrolled | Australia: 7      |
| Country: Number of subjects enrolled | New Zealand: 4    |
| Country: Number of subjects enrolled | United States: 11 |
| Country: Number of subjects enrolled | Germany: 2        |
| Country: Number of subjects enrolled | Italy: 13         |
| Country: Number of subjects enrolled | Spain: 11         |
| Country: Number of subjects enrolled | Belgium: 8        |
| Country: Number of subjects enrolled | Hungary: 15       |
| Country: Number of subjects enrolled | United Kingdom: 8 |
| Worldwide total number of subjects   | 99                |
| EEA total number of subjects         | 69                |

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)                      | 38 |
| From 65 to 84 years                       | 59 |
| 85 years and over                         | 2  |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

All participants previously enrolled in study IPI-145-07 (2013-002405-61) who experienced radiologically confirmed disease progression while on treatment in that study were eligible to participate in this study.

### 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

|                              |         |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes     |
| <b>Arm title</b>             | IPI-145 |

Arm description:

IPI-145 was administered orally and supplied as 5 milligram (mg) and 25 mg formulated capsules.

|                                        |                                     |
|----------------------------------------|-------------------------------------|
| Arm type                               | Experimental                        |
| Investigational medicinal product name | IPI-145                             |
| Investigational medicinal product code |                                     |
| Other name                             | Duvelisib, Copiktra, PI3K Inhibitor |
| Pharmaceutical forms                   | Capsule                             |
| Routes of administration               | Oral use                            |

Dosage and administration details:

Doses of 5, 10, 15, and 25 mg were administered orally.

|                  |            |
|------------------|------------|
| <b>Arm title</b> | Ofatumumab |
|------------------|------------|

Arm description:

Ofatumumab was administered as an intravenous (IV) infusion and was supplied in single-use vials at two strengths, 100 mg/5 millilitres (mL) and 1000 mg/50 mL.

|                                        |                                       |
|----------------------------------------|---------------------------------------|
| Arm type                               | Active comparator                     |
| Investigational medicinal product name | Ofatumumab                            |
| Investigational medicinal product code |                                       |
| Other name                             | Arzerra                               |
| Pharmaceutical forms                   | Concentrate for solution for infusion |
| Routes of administration               | Intravenous use                       |

Dosage and administration details:

Doses of 300 and 2000 mg were administered IV.

| Number of subjects in period 1         | IPI-145 | Ofatumumab |
|----------------------------------------|---------|------------|
| Started                                | 90      | 9          |
| Received at Least 1 Dose of Study Drug | 90      | 9          |
| Completed                              | 0       | 3          |
| Not completed                          | 90      | 6          |

|                                               |    |   |
|-----------------------------------------------|----|---|
| Treatment Interruption >42 Days               | 1  | - |
| Consent withdrawn by subject                  | 3  | - |
| Physician decision                            | 5  | 1 |
| Clinical Deterioration                        | 1  | - |
| Adverse event, non-fatal                      | 46 | 2 |
| Death                                         | 6  | - |
| Need Treatment for Metastatic Melanoma        | 1  | - |
| Suspected and Unconfirmed Disease Progression | 1  | - |
| Protocol-specified Disease Progression        | 23 | 2 |
| Termination of the Study by Sponsor           | 2  | - |
| Protocol deviation                            | 1  | 1 |

## Baseline characteristics

### Reporting groups

|                                                                                                                                                                                                 |            |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|
| Reporting group title                                                                                                                                                                           | IPI-145    |
| Reporting group description:<br>IPI-145 was administered orally and supplied as 5 milligram (mg) and 25 mg formulated capsules.                                                                 |            |
| Reporting group title                                                                                                                                                                           | Ofatumumab |
| Reporting group description:<br>Ofatumumab was administered as an intravenous (IV) infusion and was supplied in single-use vials at two strengths, 100 mg/5 millilitres (mL) and 1000 mg/50 mL. |            |

| Reporting group values                                                                        | IPI-145 | Ofatumumab | Total |
|-----------------------------------------------------------------------------------------------|---------|------------|-------|
| Number of subjects                                                                            | 90      | 9          | 99    |
| Age categorical<br>Units: Subjects                                                            |         |            |       |
| In utero                                                                                      | 0       | 0          | 0     |
| Preterm newborn infants<br>(gestational age < 37 wks)                                         | 0       | 0          | 0     |
| Newborns (0-27 days)                                                                          | 0       | 0          | 0     |
| Infants and toddlers (28 days-23<br>months)                                                   | 0       | 0          | 0     |
| Children (2-11 years)                                                                         | 0       | 0          | 0     |
| Adolescents (12-17 years)                                                                     | 0       | 0          | 0     |
| Adults (18-64 years)                                                                          | 35      | 3          | 38    |
| From 65-84 years                                                                              | 53      | 6          | 59    |
| 85 years and over                                                                             | 2       | 0          | 2     |
| Gender categorical<br>Units: Subjects                                                         |         |            |       |
| Female                                                                                        | 33      | 4          | 37    |
| Male                                                                                          | 57      | 5          | 62    |
| Race (National Institutes of<br>Health/Office of Management and<br>Budget)<br>Units: Subjects |         |            |       |
| American Indian or Alaska Native                                                              | 0       | 0          | 0     |
| Asian                                                                                         | 0       | 0          | 0     |
| Native Hawaiian or Other Pacific<br>Islander                                                  | 0       | 0          | 0     |
| Black or African American                                                                     | 0       | 0          | 0     |
| White                                                                                         | 82      | 9          | 91    |
| More than one race                                                                            | 0       | 0          | 0     |
| Unknown or Not Reported                                                                       | 8       | 0          | 8     |

## End points

### End points reporting groups

|                                                                                                                                                                                                 |                          |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------|
| Reporting group title                                                                                                                                                                           | IPI-145                  |
| Reporting group description:<br>IPI-145 was administered orally and supplied as 5 milligram (mg) and 25 mg formulated capsules.                                                                 |                          |
| Reporting group title                                                                                                                                                                           | Ofatumumab               |
| Reporting group description:<br>Ofatumumab was administered as an intravenous (IV) infusion and was supplied in single-use vials at two strengths, 100 mg/5 millilitres (mL) and 1000 mg/50 mL. |                          |
| Subject analysis set title                                                                                                                                                                      | All-treated Analysis Set |
| Subject analysis set type                                                                                                                                                                       | Intention-to-treat       |
| Subject analysis set description:<br>All participants who received any amount of study drug (IPI-145 or ofatumumab).                                                                            |                          |

### Primary: Overall Response Rate (ORR)

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                            |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Overall Response Rate (ORR) <sup>[1]</sup> |
| End point description:<br>ORR was defined as the percentage of participants with a best response (per investigator assessment) of complete response (CR), CR with incomplete marrow recovery (CRi), partial response (PR), or PR with lymphocytosis (PRwL), according to the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) or revised International Working Group Response (IWG) Criteria, with modification for treatment-related lymphocytosis. The 95% confidence interval was calculated using exact binomial method. Select IWCLL criteria for tumour load assessed by computed tomography (CT): CR/CRi (CLL only), lymphadenopathy (none >1.5 centimetres [cm]), hepatomegaly/splenomegaly (none); PR, lymphadenopathy/hepatomegaly/splenomegaly (decrease ≥50%); PRwL, lymphadenopathy only (decrease ≥50%). Select IWG criteria for tumour load assessed by CT: CR, lymphadenopathy/hepatomegaly/splenomegaly (normal size); PR, lymphadenopathy/hepatomegaly/splenomegaly (decrease ≥50%); PRwL, lymphadenopathy only (decrease ≥50%). |                                            |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Primary                                    |
| End point timeframe:<br>Until progressive disease (PD), death, or other anticancer therapy is initiated (up to 4.5 years)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                            |
| Notes:<br>[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.<br>Justification: Only descriptive statistics (median plus confidence interval) are reported for ORR.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                            |

| End point values                  | IPI-145             | Ofatumumab       |  |  |
|-----------------------------------|---------------------|------------------|--|--|
| Subject group type                | Reporting group     | Reporting group  |  |  |
| Number of subjects analysed       | 90 <sup>[2]</sup>   | 9 <sup>[3]</sup> |  |  |
| Units: percentage of participants |                     |                  |  |  |
| number (confidence interval 95%)  | 76.7 (66.6 to 84.9) | 0 (0 to 0)       |  |  |

Notes:

[2] - All-treated Analysis Set

[3] - All-treated Analysis Set

### Statistical analyses

No statistical analyses for this end point

### Secondary: Duration of Response (DOR)

|                 |                            |
|-----------------|----------------------------|
| End point title | Duration of Response (DOR) |
|-----------------|----------------------------|

**End point description:**

DOR was defined as the time from the first documentation of response per investigator assessment to either PD or death due to any cause. DOR was evaluated using the Kaplan-Meier method based on all treated participants with a documentation of response (that is, CR, CRi, PR, or PRwL) as determined by investigator assessment. Select IWCLL criteria for tumour load assessed by CT: CR/CRi (CLL only), lymphadenopathy (none >1.5 cm), hepatomegaly/splenomegaly (none); PR, lymphadenopathy/hepatomegaly/splenomegaly (decrease  $\geq 50\%$ ); PRwL, lymphadenopathy only (decrease  $\geq 50\%$ ). Select IWG criteria for tumour load assessed by CT: CR, lymphadenopathy/hepatomegaly/splenomegaly (normal size); PR, lymphadenopathy/hepatomegaly/splenomegaly (decrease  $\geq 50\%$ ); PRwL, lymphadenopathy only (decrease  $\geq 50\%$ ).

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

**End point timeframe:**

From the first documentation of response to the first documentation of PD or death due to any cause (up to 4.5 years)

| End point values                 | IPI-145             | Ofatumumab       |  |  |
|----------------------------------|---------------------|------------------|--|--|
| Subject group type               | Reporting group     | Reporting group  |  |  |
| Number of subjects analysed      | 90 <sup>[4]</sup>   | 0 <sup>[5]</sup> |  |  |
| Units: months                    |                     |                  |  |  |
| median (confidence interval 95%) | 14.9 (8.55 to 18.6) | ( to )           |  |  |

Notes:

[4] - All-treated Analysis Set

[5] - DOR was determined only for treated participants with documentation of response.

**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 was defined as the time from the first dose of study treatment to the first documentation of either investigator-assessed PD or death resulting from any cause. PFS was determined using the Kaplan-Meier method based on all treated participants with a documentation of response (that is, CR, CRi, PR, or PRwL) as determined by investigator assessment.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

**End point timeframe:**

From the first dose of study treatment to the first documentation of PD or death from any cause (up to 4.5 years)

| End point values                 | IPI-145             | Ofatumumab       |  |  |
|----------------------------------|---------------------|------------------|--|--|
| Subject group type               | Reporting group     | Reporting group  |  |  |
| Number of subjects analysed      | 90 <sup>[6]</sup>   | 0 <sup>[7]</sup> |  |  |
| Units: month                     |                     |                  |  |  |
| median (confidence interval 95%) | 15.3 (12.2 to 20.6) | ( to )           |  |  |

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Notes:

[6] - All-treated Analysis Set

[7] - PFS was determined only for treated participants with documentation of response.

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### **Statistical analyses**

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

4.5 years

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 16.1 |
|--------------------|------|

### Reporting groups

|                       |         |
|-----------------------|---------|
| Reporting group title | IPI-145 |
|-----------------------|---------|

Reporting group description:

IPI-145 was administered orally and supplied as 5 mg and 25 mg formulated capsules.

|                       |            |
|-----------------------|------------|
| Reporting group title | Ofatumumab |
|-----------------------|------------|

Reporting group description:

Ofatumumab was administered as an IV infusion and was supplied in single-use vials at two strengths, 100 mg/5 mL and 1000 mg/50 mL.

| Serious adverse events                                              | IPI-145          | Ofatumumab     |  |
|---------------------------------------------------------------------|------------------|----------------|--|
| Total subjects affected by serious adverse events                   |                  |                |  |
| subjects affected / exposed                                         | 68 / 90 (75.56%) | 4 / 9 (44.44%) |  |
| number of deaths (all causes)                                       | 20               | 2              |  |
| number of deaths resulting from adverse events                      |                  |                |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                  |                |  |
| Basosquamous carcinoma                                              |                  |                |  |
| subjects affected / exposed                                         | 1 / 90 (1.11%)   | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all                     | 0 / 1            | 0 / 0          |  |
| deaths causally related to treatment / all                          | 0 / 0            | 0 / 0          |  |
| Malignant melanoma                                                  |                  |                |  |
| subjects affected / exposed                                         | 1 / 90 (1.11%)   | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all                     | 0 / 1            | 0 / 0          |  |
| deaths causally related to treatment / all                          | 0 / 0            | 0 / 0          |  |
| Squamous cell carcinoma                                             |                  |                |  |
| subjects affected / exposed                                         | 1 / 90 (1.11%)   | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all                     | 0 / 1            | 0 / 0          |  |
| deaths causally related to treatment / all                          | 0 / 0            | 0 / 0          |  |
| Squamous cell carcinoma of skin                                     |                  |                |  |

|                                                      |                |               |  |
|------------------------------------------------------|----------------|---------------|--|
| subjects affected / exposed                          | 1 / 90 (1.11%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0         |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0         |  |
| Vascular disorders                                   |                |               |  |
| Aortic dissection                                    |                |               |  |
| subjects affected / exposed                          | 1 / 90 (1.11%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0         |  |
| deaths causally related to treatment / all           | 0 / 1          | 0 / 0         |  |
| Arterial rupture                                     |                |               |  |
| subjects affected / exposed                          | 1 / 90 (1.11%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0         |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0         |  |
| Vena cava thrombosis                                 |                |               |  |
| subjects affected / exposed                          | 1 / 90 (1.11%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0         |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0         |  |
| General disorders and administration site conditions |                |               |  |
| Pyrexia                                              |                |               |  |
| subjects affected / exposed                          | 3 / 90 (3.33%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 5          | 0 / 0         |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0         |  |
| Disease progression                                  |                |               |  |
| subjects affected / exposed                          | 2 / 90 (2.22%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 2          | 0 / 0         |  |
| deaths causally related to treatment / all           | 0 / 2          | 0 / 0         |  |
| General physical health deterioration                |                |               |  |
| subjects affected / exposed                          | 2 / 90 (2.22%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 2          | 0 / 0         |  |
| deaths causally related to treatment / all           | 0 / 2          | 0 / 0         |  |
| Drug intolerance                                     |                |               |  |
| subjects affected / exposed                          | 1 / 90 (1.11%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0         |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0         |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| Multi-organ failure                             |                |                |  |
| subjects affected / exposed                     | 1 / 90 (1.11%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0          |  |
| Oedema                                          |                |                |  |
| subjects affected / exposed                     | 0 / 90 (0.00%) | 1 / 9 (11.11%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Respiratory, thoracic and mediastinal disorders |                |                |  |
| Respiratory failure                             |                |                |  |
| subjects affected / exposed                     | 2 / 90 (2.22%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0          |  |
| Interstitial lung disease                       |                |                |  |
| subjects affected / exposed                     | 1 / 90 (1.11%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Lung infiltration                               |                |                |  |
| subjects affected / exposed                     | 1 / 90 (1.11%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0          |  |
| Pleural effusion                                |                |                |  |
| subjects affected / exposed                     | 1 / 90 (1.11%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Pneumonitis                                     |                |                |  |
| subjects affected / exposed                     | 1 / 90 (1.11%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Investigations                                  |                |                |  |
| Transaminases increased                         |                |                |  |
| subjects affected / exposed                     | 1 / 90 (1.11%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

|                                                                |                |                |  |
|----------------------------------------------------------------|----------------|----------------|--|
| Neutrophil count decreased<br>subjects affected / exposed      | 0 / 90 (0.00%) | 1 / 9 (11.11%) |  |
| occurrences causally related to<br>treatment / all             | 0 / 0          | 0 / 1          |  |
| deaths causally related to<br>treatment / all                  | 0 / 0          | 0 / 0          |  |
| Injury, poisoning and procedural<br>complications              |                |                |  |
| Subdural haematoma<br>subjects affected / exposed              | 1 / 90 (1.11%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to<br>treatment / all             | 0 / 1          | 0 / 0          |  |
| deaths causally related to<br>treatment / all                  | 0 / 0          | 0 / 0          |  |
| Toxicity to various agents<br>subjects affected / exposed      | 1 / 90 (1.11%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to<br>treatment / all             | 0 / 1          | 0 / 0          |  |
| deaths causally related to<br>treatment / all                  | 0 / 0          | 0 / 0          |  |
| Humerus fracture<br>subjects affected / exposed                | 0 / 90 (0.00%) | 1 / 9 (11.11%) |  |
| occurrences causally related to<br>treatment / all             | 0 / 0          | 0 / 1          |  |
| deaths causally related to<br>treatment / all                  | 0 / 0          | 0 / 0          |  |
| Cardiac disorders                                              |                |                |  |
| Acute myocardial infarction<br>subjects affected / exposed     | 1 / 90 (1.11%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to<br>treatment / all             | 0 / 1          | 0 / 0          |  |
| deaths causally related to<br>treatment / all                  | 0 / 0          | 0 / 0          |  |
| Atrioventricular block complete<br>subjects affected / exposed | 1 / 90 (1.11%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to<br>treatment / all             | 0 / 1          | 0 / 0          |  |
| deaths causally related to<br>treatment / all                  | 0 / 0          | 0 / 0          |  |
| Cardiac failure<br>subjects affected / exposed                 | 1 / 90 (1.11%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to<br>treatment / all             | 0 / 1          | 0 / 0          |  |
| deaths causally related to<br>treatment / all                  | 0 / 1          | 0 / 0          |  |
| Cardiac failure chronic<br>subjects affected / exposed         | 1 / 90 (1.11%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to<br>treatment / all             | 0 / 2          | 0 / 0          |  |
| deaths causally related to<br>treatment / all                  | 0 / 0          | 0 / 0          |  |

|                                                 |                |               |  |
|-------------------------------------------------|----------------|---------------|--|
| Nervous system disorders                        |                |               |  |
| Cerebral ischaemia                              |                |               |  |
| subjects affected / exposed                     | 1 / 90 (1.11%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         |  |
| Cerebrovascular accident                        |                |               |  |
| subjects affected / exposed                     | 1 / 90 (1.11%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         |  |
| Dizziness                                       |                |               |  |
| subjects affected / exposed                     | 1 / 90 (1.11%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         |  |
| Encephalitis                                    |                |               |  |
| subjects affected / exposed                     | 1 / 90 (1.11%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         |  |
| Mental impairment                               |                |               |  |
| subjects affected / exposed                     | 1 / 90 (1.11%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         |  |
| Muscle contractions involuntary                 |                |               |  |
| subjects affected / exposed                     | 1 / 90 (1.11%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         |  |
| Blood and lymphatic system disorders            |                |               |  |
| Febrile neutropenia                             |                |               |  |
| subjects affected / exposed                     | 3 / 90 (3.33%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3          | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         |  |
| Neutropenia                                     |                |               |  |
| subjects affected / exposed                     | 2 / 90 (2.22%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3          | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         |  |

|                                                 |                  |                |  |
|-------------------------------------------------|------------------|----------------|--|
| Pancytopenia                                    |                  |                |  |
| subjects affected / exposed                     | 2 / 90 (2.22%)   | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          |  |
| Anaemia                                         |                  |                |  |
| subjects affected / exposed                     | 1 / 90 (1.11%)   | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          |  |
| Haemolytic anaemia                              |                  |                |  |
| subjects affected / exposed                     | 1 / 90 (1.11%)   | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          |  |
| Thrombocytopenia                                |                  |                |  |
| subjects affected / exposed                     | 1 / 90 (1.11%)   | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          |  |
| Gastrointestinal disorders                      |                  |                |  |
| Diarrhoea                                       |                  |                |  |
| subjects affected / exposed                     | 16 / 90 (17.78%) | 1 / 9 (11.11%) |  |
| occurrences causally related to treatment / all | 0 / 17           | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          |  |
| Colitis                                         |                  |                |  |
| subjects affected / exposed                     | 8 / 90 (8.89%)   | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 8            | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          |  |
| Oesophagitis                                    |                  |                |  |
| subjects affected / exposed                     | 2 / 90 (2.22%)   | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          |  |
| Abdominal pain                                  |                  |                |  |
| subjects affected / exposed                     | 1 / 90 (1.11%)   | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0          |  |
| Colitis ischaemic                               |                  |                |  |

|                                                 |                |               |  |
|-------------------------------------------------|----------------|---------------|--|
| subjects affected / exposed                     | 1 / 90 (1.11%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         |  |
| Enterocolitis                                   |                |               |  |
| subjects affected / exposed                     | 1 / 90 (1.11%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         |  |
| Gastritis                                       |                |               |  |
| subjects affected / exposed                     | 1 / 90 (1.11%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         |  |
| Large intestinal ulcer                          |                |               |  |
| subjects affected / exposed                     | 1 / 90 (1.11%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         |  |
| Mouth ulceration                                |                |               |  |
| subjects affected / exposed                     | 1 / 90 (1.11%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         |  |
| Vomiting                                        |                |               |  |
| subjects affected / exposed                     | 1 / 90 (1.11%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         |  |
| Skin and subcutaneous tissue disorders          |                |               |  |
| Rash maculo-papular                             |                |               |  |
| subjects affected / exposed                     | 2 / 90 (2.22%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         |  |
| Actinic keratosis                               |                |               |  |
| subjects affected / exposed                     | 1 / 90 (1.11%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         |  |
| Dermatitis                                      |                |               |  |

|                                                 |                |               |  |
|-------------------------------------------------|----------------|---------------|--|
| subjects affected / exposed                     | 1 / 90 (1.11%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         |  |
| Pityriasis lichenoides et varioliformis acuta   |                |               |  |
| subjects affected / exposed                     | 1 / 90 (1.11%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         |  |
| Pityriasis rubra pilaris                        |                |               |  |
| subjects affected / exposed                     | 1 / 90 (1.11%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         |  |
| Psoriasis                                       |                |               |  |
| subjects affected / exposed                     | 1 / 90 (1.11%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         |  |
| Rash                                            |                |               |  |
| subjects affected / exposed                     | 1 / 90 (1.11%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         |  |
| Toxic skin eruption                             |                |               |  |
| subjects affected / exposed                     | 1 / 90 (1.11%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         |  |
| Renal and urinary disorders                     |                |               |  |
| Renal failure acute                             |                |               |  |
| subjects affected / exposed                     | 4 / 90 (4.44%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 4          | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         |  |
| Azotaemia                                       |                |               |  |
| subjects affected / exposed                     | 1 / 90 (1.11%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         |  |
| Dysuria                                         |                |               |  |

|                                                 |                  |               |  |
|-------------------------------------------------|------------------|---------------|--|
| subjects affected / exposed                     | 1 / 90 (1.11%)   | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0         |  |
| Pollakiuria                                     |                  |               |  |
| subjects affected / exposed                     | 1 / 90 (1.11%)   | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0         |  |
| Renal impairment                                |                  |               |  |
| subjects affected / exposed                     | 1 / 90 (1.11%)   | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0         |  |
| Endocrine disorders                             |                  |               |  |
| Hypopituitarism                                 |                  |               |  |
| subjects affected / exposed                     | 1 / 90 (1.11%)   | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0         |  |
| Musculoskeletal and connective tissue disorders |                  |               |  |
| Back pain                                       |                  |               |  |
| subjects affected / exposed                     | 1 / 90 (1.11%)   | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0         |  |
| Flank pain                                      |                  |               |  |
| subjects affected / exposed                     | 1 / 90 (1.11%)   | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0         |  |
| Osteoarthritis                                  |                  |               |  |
| subjects affected / exposed                     | 1 / 90 (1.11%)   | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0         |  |
| Infections and infestations                     |                  |               |  |
| Pneumonia                                       |                  |               |  |
| subjects affected / exposed                     | 13 / 90 (14.44%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 14           | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0         |  |

|                                                 |                |               |  |
|-------------------------------------------------|----------------|---------------|--|
| Sepsis                                          |                |               |  |
| subjects affected / exposed                     | 4 / 90 (4.44%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 4          | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0         |  |
| Pneumocystis jirovecii pneumonia                |                |               |  |
| subjects affected / exposed                     | 3 / 90 (3.33%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3          | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0         |  |
| Pseudomonal sepsis                              |                |               |  |
| subjects affected / exposed                     | 3 / 90 (3.33%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3          | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         |  |
| Bronchitis                                      |                |               |  |
| subjects affected / exposed                     | 2 / 90 (2.22%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         |  |
| Urinary tract infection                         |                |               |  |
| subjects affected / exposed                     | 2 / 90 (2.22%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         |  |
| Campylobacter gastroenteritis                   |                |               |  |
| subjects affected / exposed                     | 1 / 90 (1.11%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         |  |
| Campylobacter infection                         |                |               |  |
| subjects affected / exposed                     | 1 / 90 (1.11%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         |  |
| Device related infection                        |                |               |  |
| subjects affected / exposed                     | 1 / 90 (1.11%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         |  |
| Enterococcal bacteraemia                        |                |               |  |

|                                                 |                |               |  |
|-------------------------------------------------|----------------|---------------|--|
| subjects affected / exposed                     | 1 / 90 (1.11%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         |  |
| H1N1 influenza                                  |                |               |  |
| subjects affected / exposed                     | 1 / 90 (1.11%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         |  |
| Influenza                                       |                |               |  |
| subjects affected / exposed                     | 1 / 90 (1.11%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         |  |
| Laryngitis                                      |                |               |  |
| subjects affected / exposed                     | 1 / 90 (1.11%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         |  |
| Lung infection                                  |                |               |  |
| subjects affected / exposed                     | 1 / 90 (1.11%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         |  |
| Mucosal infection                               |                |               |  |
| subjects affected / exposed                     | 1 / 90 (1.11%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         |  |
| Nasopharyngitis                                 |                |               |  |
| subjects affected / exposed                     | 1 / 90 (1.11%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         |  |
| Pneumonia cytomegaloviral                       |                |               |  |
| subjects affected / exposed                     | 1 / 90 (1.11%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         |  |
| Pneumonia haemophilus                           |                |               |  |

|                                                 |                |               |  |
|-------------------------------------------------|----------------|---------------|--|
| subjects affected / exposed                     | 1 / 90 (1.11%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         |  |
| Pneumonia pneumococcal                          |                |               |  |
| subjects affected / exposed                     | 1 / 90 (1.11%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         |  |
| Pneumonia pseudomonas aeruginosa                |                |               |  |
| subjects affected / exposed                     | 1 / 90 (1.11%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         |  |
| Respiratory tract infection                     |                |               |  |
| subjects affected / exposed                     | 1 / 90 (1.11%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         |  |
| Salmonellosis                                   |                |               |  |
| subjects affected / exposed                     | 1 / 90 (1.11%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         |  |
| Staphylococcal bacteraemia                      |                |               |  |
| subjects affected / exposed                     | 1 / 90 (1.11%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         |  |
| Staphylococcal skin infection                   |                |               |  |
| subjects affected / exposed                     | 1 / 90 (1.11%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         |  |
| Urosepsis                                       |                |               |  |
| subjects affected / exposed                     | 1 / 90 (1.11%) | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0         |  |

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

| <b>Non-serious adverse events</b>                     | <b>IPI-145</b>   | <b>Ofatumumab</b> |  |
|-------------------------------------------------------|------------------|-------------------|--|
| Total subjects affected by non-serious adverse events |                  |                   |  |
| subjects affected / exposed                           | 80 / 90 (88.89%) | 8 / 9 (88.89%)    |  |
| Vascular disorders                                    |                  |                   |  |
| Hypertension                                          |                  |                   |  |
| subjects affected / exposed                           | 2 / 90 (2.22%)   | 1 / 9 (11.11%)    |  |
| occurrences (all)                                     | 2                | 1                 |  |
| General disorders and administration site conditions  |                  |                   |  |
| Pyrexia                                               |                  |                   |  |
| subjects affected / exposed                           | 21 / 90 (23.33%) | 0 / 9 (0.00%)     |  |
| occurrences (all)                                     | 33               | 0                 |  |
| Asthenia                                              |                  |                   |  |
| subjects affected / exposed                           | 11 / 90 (12.22%) | 0 / 9 (0.00%)     |  |
| occurrences (all)                                     | 14               | 0                 |  |
| Oedema peripheral                                     |                  |                   |  |
| subjects affected / exposed                           | 6 / 90 (6.67%)   | 0 / 9 (0.00%)     |  |
| occurrences (all)                                     | 8                | 0                 |  |
| Non-cardiac chest pain                                |                  |                   |  |
| subjects affected / exposed                           | 1 / 90 (1.11%)   | 1 / 9 (11.11%)    |  |
| occurrences (all)                                     | 1                | 1                 |  |
| Immune system disorders                               |                  |                   |  |
| Hypersensitivity                                      |                  |                   |  |
| subjects affected / exposed                           | 0 / 90 (0.00%)   | 1 / 9 (11.11%)    |  |
| occurrences (all)                                     | 0                | 2                 |  |
| Reproductive system and breast disorders              |                  |                   |  |
| Vaginal haemorrhage                                   |                  |                   |  |
| subjects affected / exposed <sup>[1]</sup>            | 0 / 33 (0.00%)   | 1 / 4 (25.00%)    |  |
| occurrences (all)                                     | 0                | 1                 |  |
| Vulvovaginal pruritus                                 |                  |                   |  |
| subjects affected / exposed <sup>[2]</sup>            | 0 / 33 (0.00%)   | 1 / 4 (25.00%)    |  |
| occurrences (all)                                     | 0                | 1                 |  |
| Respiratory, thoracic and mediastinal disorders       |                  |                   |  |

|                                                                                                                                 |                        |                     |  |
|---------------------------------------------------------------------------------------------------------------------------------|------------------------|---------------------|--|
| Cough<br>subjects affected / exposed<br>occurrences (all)                                                                       | 15 / 90 (16.67%)<br>20 | 0 / 9 (0.00%)<br>0  |  |
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all)                                                                    | 3 / 90 (3.33%)<br>3    | 1 / 9 (11.11%)<br>3 |  |
| Psychiatric disorders<br>Anxiety<br>subjects affected / exposed<br>occurrences (all)                                            | 1 / 90 (1.11%)<br>1    | 1 / 9 (11.11%)<br>1 |  |
| Investigations<br>Lipase increased<br>subjects affected / exposed<br>occurrences (all)                                          | 9 / 90 (10.00%)<br>13  | 0 / 9 (0.00%)<br>0  |  |
| Weight decreased<br>subjects affected / exposed<br>occurrences (all)                                                            | 7 / 90 (7.78%)<br>7    | 0 / 9 (0.00%)<br>0  |  |
| Injury, poisoning and procedural complications<br>Infusion related reaction<br>subjects affected / exposed<br>occurrences (all) | 0 / 90 (0.00%)<br>0    | 3 / 9 (33.33%)<br>3 |  |
| Cardiac disorders<br>Cardiac disorder<br>subjects affected / exposed<br>occurrences (all)                                       | 0 / 90 (0.00%)<br>0    | 1 / 9 (11.11%)<br>1 |  |
| Tachycardia<br>subjects affected / exposed<br>occurrences (all)                                                                 | 0 / 90 (0.00%)<br>0    | 1 / 9 (11.11%)<br>1 |  |
| Nervous system disorders<br>Headache<br>subjects affected / exposed<br>occurrences (all)                                        | 7 / 90 (7.78%)<br>7    | 0 / 9 (0.00%)<br>0  |  |
| Blood and lymphatic system disorders<br>Neutropenia<br>subjects affected / exposed<br>occurrences (all)                         | 23 / 90 (25.56%)<br>41 | 1 / 9 (11.11%)<br>2 |  |
| Anaemia                                                                                                                         |                        |                     |  |

|                                  |                  |                |  |
|----------------------------------|------------------|----------------|--|
| subjects affected / exposed      | 8 / 90 (8.89%)   | 2 / 9 (22.22%) |  |
| occurrences (all)                | 13               | 7              |  |
| Thrombocytopenia                 |                  |                |  |
| subjects affected / exposed      | 9 / 90 (10.00%)  | 1 / 9 (11.11%) |  |
| occurrences (all)                | 11               | 2              |  |
| Ear and labyrinth disorders      |                  |                |  |
| Vertigo                          |                  |                |  |
| subjects affected / exposed      | 2 / 90 (2.22%)   | 1 / 9 (11.11%) |  |
| occurrences (all)                | 2                | 1              |  |
| Gastrointestinal disorders       |                  |                |  |
| Diarrhoea                        |                  |                |  |
| subjects affected / exposed      | 43 / 90 (47.78%) | 0 / 9 (0.00%)  |  |
| occurrences (all)                | 92               | 0              |  |
| Abdominal pain                   |                  |                |  |
| subjects affected / exposed      | 9 / 90 (10.00%)  | 0 / 9 (0.00%)  |  |
| occurrences (all)                | 10               | 0              |  |
| Nausea                           |                  |                |  |
| subjects affected / exposed      | 10 / 90 (11.11%) | 1 / 9 (11.11%) |  |
| occurrences (all)                | 10               | 1              |  |
| Vomiting                         |                  |                |  |
| subjects affected / exposed      | 10 / 90 (11.11%) | 0 / 9 (0.00%)  |  |
| occurrences (all)                | 10               | 0              |  |
| Abdominal pain upper             |                  |                |  |
| subjects affected / exposed      | 7 / 90 (7.78%)   | 0 / 9 (0.00%)  |  |
| occurrences (all)                | 8                | 0              |  |
| Colitis                          |                  |                |  |
| subjects affected / exposed      | 6 / 90 (6.67%)   | 0 / 9 (0.00%)  |  |
| occurrences (all)                | 7                | 0              |  |
| Dyspepsia                        |                  |                |  |
| subjects affected / exposed      | 5 / 90 (5.56%)   | 0 / 9 (0.00%)  |  |
| occurrences (all)                | 6                | 0              |  |
| Constipation                     |                  |                |  |
| subjects affected / exposed      | 5 / 90 (5.56%)   | 0 / 9 (0.00%)  |  |
| occurrences (all)                | 5                | 0              |  |
| Gastrooesophageal reflux disease |                  |                |  |

|                                                                                                                      |                        |                     |  |
|----------------------------------------------------------------------------------------------------------------------|------------------------|---------------------|--|
| subjects affected / exposed<br>occurrences (all)                                                                     | 3 / 90 (3.33%)<br>3    | 1 / 9 (11.11%)<br>1 |  |
| Oesophagitis<br>subjects affected / exposed<br>occurrences (all)                                                     | 1 / 90 (1.11%)<br>2    | 1 / 9 (11.11%)<br>1 |  |
| Stomatitis<br>subjects affected / exposed<br>occurrences (all)                                                       | 1 / 90 (1.11%)<br>1    | 1 / 9 (11.11%)<br>1 |  |
| Skin and subcutaneous tissue disorders<br>Rash<br>subjects affected / exposed<br>occurrences (all)                   | 21 / 90 (23.33%)<br>24 | 0 / 9 (0.00%)<br>0  |  |
| Skin lesion<br>subjects affected / exposed<br>occurrences (all)                                                      | 3 / 90 (3.33%)<br>3    | 1 / 9 (11.11%)<br>1 |  |
| Urticaria<br>subjects affected / exposed<br>occurrences (all)                                                        | 0 / 90 (0.00%)<br>0    | 1 / 9 (11.11%)<br>1 |  |
| Musculoskeletal and connective tissue disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all)    | 9 / 90 (10.00%)<br>10  | 0 / 9 (0.00%)<br>0  |  |
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all)                                                | 5 / 90 (5.56%)<br>5    | 1 / 9 (11.11%)<br>1 |  |
| Infections and infestations<br>Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 7 / 90 (7.78%)<br>9    | 0 / 9 (0.00%)<br>0  |  |
| Bronchitis<br>subjects affected / exposed<br>occurrences (all)                                                       | 8 / 90 (8.89%)<br>8    | 0 / 9 (0.00%)<br>0  |  |
| Respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)                                      | 5 / 90 (5.56%)<br>6    | 0 / 9 (0.00%)<br>0  |  |
| Urinary tract infection                                                                                              |                        |                     |  |

|                                                                        |                        |                     |  |
|------------------------------------------------------------------------|------------------------|---------------------|--|
| subjects affected / exposed<br>occurrences (all)                       | 6 / 90 (6.67%)<br>6    | 1 / 9 (11.11%)<br>1 |  |
| Fungal infection<br>subjects affected / exposed<br>occurrences (all)   | 0 / 90 (0.00%)<br>0    | 1 / 9 (11.11%)<br>1 |  |
| Metabolism and nutrition disorders                                     |                        |                     |  |
| Decreased appetite<br>subjects affected / exposed<br>occurrences (all) | 11 / 90 (12.22%)<br>13 | 0 / 9 (0.00%)<br>0  |  |
| Hypokalaemia<br>subjects affected / exposed<br>occurrences (all)       | 7 / 90 (7.78%)<br>8    | 1 / 9 (11.11%)<br>1 |  |
| Hyperuricaemia<br>subjects affected / exposed<br>occurrences (all)     | 2 / 90 (2.22%)<br>2    | 1 / 9 (11.11%)<br>1 |  |
| Metabolic acidosis<br>subjects affected / exposed<br>occurrences (all) | 0 / 90 (0.00%)<br>0    | 1 / 9 (11.11%)<br>1 |  |

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: This adverse event only affected female/male participants.

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: This adverse event only affected female/male participants.

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date          | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|---------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 02 April 2014 | <ul style="list-style-type: none"><li>• Increased complete blood count frequency to every 2 months from Baseline through Cycle 24.</li><li>• Treatment modification guidelines updated with clinical data from Study IPI-145-02, including safety, efficacy, pharmacokinetic (PK), and pharmacodynamic data as of 28 October 2014; in response to PK/pharmacodynamic findings from that study, dose reduction levels changed to 15 mg twice daily (BID) for Level -1, 10 mg BID for Level -2, and 5 mg BID for Level -3 (new level), and text added to clarify that participants with a history of cytomegalovirus or Epstein-Barr virus infection and/or who enter the study while receiving antiviral prophylaxis should be monitored for reactivation via serology or viral load detection per institutional guidelines while on study treatment.</li><li>• Detail added for Grade 3 or higher nonhematologic toxicity (infections, hepatic events, gastrointestinal events, skin rash, cardiac events).</li><li>• In response to safety findings from Study IPI-145-07 (2013-002405-61): Detail added for Grade 2 or higher nonhematologic toxicity (new pulmonary symptoms).</li><li>• Changed criteria for discontinuation of participants due to treatment-related toxicities from &lt;25 mg once-daily dose to &lt;15 mg BID.</li><li>• In response to regulatory agency feedback, added guidance to withhold ofatumumab until return to ≤Grade 1 or Baseline level for Grade 3 thrombocytopenia associated with ≥Grade 2 hemorrhage to align with duvelisib treatment modifications.</li><li>• Added new Photosafety section.</li></ul> |
| 02 March 2015 | <ul style="list-style-type: none"><li>• Revised treatment interruption/hold/modification guidelines to recommend treatment interruption for all events of QT interval corrected with Fridericia's method prolongation ≥Grade 3 (≥500 milliseconds).</li><li>• Added clarifying text to response criteria definitions for both chronic lymphocytic leukemia and small lymphocytic lymphoma, specifically, language defining progressive disease.</li></ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| 24 March 2016 | <ul style="list-style-type: none"><li>• To permit continued access to duvelisib beyond 24 months for participants demonstrating evidence of clinical benefit after 1 year of treatment, added text indicating that these participants were permitted to receive duvelisib monotherapy until PD, unacceptable toxicity, participant withdrawal, or start of alternate therapy (amended from the last version of the protocol, in which participants could receive treatment for only up to 2 years).</li><li>• Clarified that ofatumumab was to be given for a maximum of 7 cycles and that there would be no follow-up after 2 years (Cycle 24).</li><li>• Changed the frequency of clinic visits after Cycle 18 to once every 3 cycles (previously every 2 cycles).</li></ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported