



## Clinical trial results: A Phase 2 Study of IPI-145 in Subjects with Refractory Indolent Non-Hodgkin Lymphoma Summary

|                          |                      |
|--------------------------|----------------------|
| EudraCT number           | 2013-004008-20       |
| Trial protocol           | GB IT HU CZ ES BE BG |
| Global end of trial date | 18 November 2020     |

### Results information

|                                |  |
|--------------------------------|--|
| Result version number          | v2 (current)   |
| This version publication date  | 30 September 2023  |
| First version publication date | 13 August 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-145-06 |
|-----------------------|------------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01882803 |
| WHO universal trial number (UTN)   | -           |

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                       | 18 November 2020 |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 18 November 2020 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

The main objective of this trial was to evaluate the therapeutic effect of duvelisib (IPI-145) administered to participants diagnosed with indolent non-Hodgkin lymphoma (defined as follicular lymphoma, marginal zone lymphoma [splenic, nodal and extranodal], or small lymphocytic lymphoma) whose disease was refractory to rituximab and to either chemotherapy or radioimmunotherapy.

Protection of trial subjects:

This study was conducted in accordance with 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 a study is conducted.

Background therapy: -

Evidence for comparator: -

|   |              |
|---|--------------|
| Actual start date of recruitment                          | 17 June 2013 |
| Long term follow-up planned                               | No           |
| Independent data monitoring committee (IDMC) involvement? | Yes          |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | France: 6          |
| Country: Number of subjects enrolled | Canada: 9          |
| Country: Number of subjects enrolled | United States: 46  |
| Country: Number of subjects enrolled | Italy: 21          |
| Country: Number of subjects enrolled | Czechia: 9         |
| Country: Number of subjects enrolled | Bulgaria: 5        |
| Country: Number of subjects enrolled | Spain: 2           |
| Country: Number of subjects enrolled | Belarus: 10        |
| Country: Number of subjects enrolled | Belgium: 2         |
| Country: Number of subjects enrolled | Georgia: 1         |
| Country: Number of subjects enrolled | Hungary: 7         |
| Country: Number of subjects enrolled | United Kingdom: 11 |
| Worldwide total number of subjects   | 129                |
| EEA total number of subjects         | 52                 |

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)                      | 64 |
| From 65 to 84 years                       | 62 |
| 85 years and over                         | 3  |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

This multicenter, multinational study enrolled participants at 56 medical clinics across 12 countries.

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Overall Study (overall period) |
| Is this the baseline period? | Yes                            |
| Allocation method            | Not applicable                 |
| Blinding used                | Not blinded                    |

### Arms

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

Arm description:

Participants received a dose of 25 milligrams (mg) duvelisib twice daily (BID) over the course of 28-day treatment cycles until disease progression or unacceptable toxicity.

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

Dosage and administration details:

Duvelisib was administered orally as a capsule.

| Number of subjects in period 1         | Duvelisib |
|--|-----------|
| Started                                | 129       |
| Received at Least 1 Dose of Study drug | 129       |
| Completed                              | 0         |
| Not completed                          | 129       |
| Consent withdrawn by subject           | 9         |
| Physician decision                     | 3         |
| Disease progression                    | 1         |
| Death                                  | 68        |
| Follow-up completed                    | 39        |
| Lost to follow-up                      | 3         |
| Study terminated by the Sponsor        | 6         |

## Baseline characteristics

### Reporting groups

|                       |               |
|-----------------------|---------------|
| Reporting group title | Overall Study |
|-----------------------|---------------|

Reporting group description:

Full Analysis Set: all participants who received at least 1 dose of duvelisib.

| Reporting group values  | Overall Study | Total |  |
|---|---------------|-------|--|
| Number of subjects  | 129           | 129   |  |
| Age categorical   |               |       |  |
| Units: Subjects   |               |       |  |
| ≤18 years   | 0             | 0     |  |
| Between 18 and 64 years   | 64            | 64    |  |
| ≥65 years   | 65            | 65    |  |
| Age continuous  |               |       |  |
| Units: years  |               |       |  |
| arithmetic mean   | 63.6          |       |  |
| standard deviation  | ± 11.69       | -     |  |
| Gender categorical  |               |       |  |
| Units: Subjects   |               |       |  |
| Female  | 41            | 41    |  |
| Male  | 88            | 88    |  |
| Ethnicity   |               |       |  |
| National Institutes of Health/Office of Management and Budget (NIH/OMB) |               |       |  |
| Units: Subjects   |               |       |  |
| Hispanic or Latino  | 3             | 3     |  |
| Not Hispanic or Latino  | 118           | 118   |  |
| Unknown or Not Reported   | 8             | 8     |  |
| Race  |               |       |  |
| Units: Subjects   |               |       |  |
| American Indian or Alaskan Native                                       | 1             | 1     |  |
| Asian   | 1             | 1     |  |
| Black or African American   | 6             | 6     |  |
| Native Hawaiian or other Pacific Islander                               | 0             | 0     |  |
| White   | 116           | 116   |  |
| Other   | 1             | 1     |  |
| Unknown   | 2             | 2     |  |
| Missing   | 2             | 2     |  |
| Region of Enrollment  |               |       |  |
| Units: Subjects   |               |       |  |
| Hungary   | 7             | 7     |  |
| United States   | 46            | 46    |  |
| Czechia   | 9             | 9     |  |
| United Kingdom  | 11            | 11    |  |
| Belarus   | 10            | 10    |  |
| Spain   | 2             | 2     |  |
| Canada  | 9             | 9     |  |
| Belgium   | 2             | 2     |  |

|          |    |    |  |
|----------|----|----|--|
| Italy    | 21 | 21 |  |
| Georgia  | 1  | 1  |  |
| France   | 6  | 6  |  |
| Bulgaria | 5  | 5  |  |

## End points

### End points reporting groups

|   |                      |
|---|----------------------|
| Reporting group title   | Duvelisib            |
| Reporting group description:<br>Participants received a dose of 25 milligrams (mg) duvelisib twice daily (BID) over the course of 28-day treatment cycles until disease progression or unacceptable toxicity.               |                      |
| Subject analysis set title  | IPI-656              |
| Subject analysis set type   | Sub-group analysis   |
| Subject analysis set description:<br>Participants who received at least 1 dose of duvelisib and with at least 1 adequate post-baseline blood sample for measuring concentrations of the main duvelisib metabolite, IPI-656. |                      |
| Subject analysis set title  | Full Analysis Set    |
| Subject analysis set type   | Full analysis        |
| Subject analysis set description:<br>All participants who received at least 1 dose of duvelisib.  |                      |
| Subject analysis set title  | Pharmacokinetics Set |
| Subject analysis set type   | Sub-group analysis   |
| Subject analysis set description:<br>All participants who received at least 1 dose of duvelisib and with at least 1 adequate post-baseline blood sample.  |                      |

### Primary: Overall Response Rate (ORR)

|   |  |
|---|--|
| End point title   | Overall Response Rate (ORR) <sup>[1]</sup> |
| End point description:<br>ORR, defined as the total percentage of participants who had a best overall response of either complete response (CR) or partial response (PR), was evaluated locally (investigator's assessment) according to the revised International Working Group (IWG) Response Criteria for Malignant Lymphoma. ORR is reported with a 2-sided 95% exact confidence interval. ORR was tested against the null ( $\leq 30\%$ ) by 1-sided exact binomial test at 0.025 level. The p-value ( $\leq 0.0001$ ) was calculated by 1-sided exact binomial test with the null hypothesis that $ORR \leq 30\%$ . |  |
| End point type  | Primary                                    |
| End point timeframe:<br>Every 8-16 weeks while on treatment with duvelisib for up to 72 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: Statistical analysis (p-value) located under 'End point description'.

| End point values                 | Duvelisib           |  |  |  |
|----------------------------------|---------------------|--|--|--|
| Subject group type               | Reporting group     |  |  |  |
| Number of subjects analysed      | 129 <sup>[2]</sup>  |  |  |  |
| Units: percent                   |                     |  |  |  |
| number (confidence interval 95%) | 59.7 (50.7 to 68.2) |  |  |  |

Notes:

[2] - Full Analysis Set

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants With Treatment-emergent Adverse Events (TEAEs)

|                 |   |
|-----------------|---|
| End point title | Number of Participants With Treatment-emergent Adverse Events (TEAEs) |
|-----------------|---|

End point description:

An adverse event was defined as any untoward medical occurrence in a participant who received study drug without regard to possibility of causal relationship. A TEAE was defined as any adverse event that emerged or worsened in the period from the first dose of study treatment to 30 days after the last dose of study treatment. A summary of serious and all other non-serious adverse events regardless of causality is located in the Reported Adverse Events module.

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

End point timeframe:

Every 2-8 weeks for up to 73 months

|                             |                    |  |  |  |
|-----------------------------|--------------------|--|--|--|
| <b>End point values</b>     | Duvelisib          |  |  |  |
| Subject group type          | Reporting group    |  |  |  |
| Number of subjects analysed | 129 <sup>[3]</sup> |  |  |  |
| Units: Participant          | 128                |  |  |  |

Notes:

[3] - Full 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, defined as the time from the first documentation of response to either progressive disease (PD) or death due to any cause, was evaluated locally (investigator's assessment) according to the revised IWG Response Criteria for Malignant Lymphoma.

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

End point timeframe:

Every 8-16 weeks for up to 72 months

|                                  |                       |  |  |  |
|----------------------------------|-----------------------|--|--|--|
| <b>End point values</b>          | Duvelisib             |  |  |  |
| Subject group type               | Reporting group       |  |  |  |
| Number of subjects analysed      | 129 <sup>[4]</sup>    |  |  |  |
| Units: month                     |                       |  |  |  |
| median (confidence interval 95%) | 10.16 (8.78 to 13.61) |  |  |  |

Notes:

[4] - Full Analysis Set

## 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, 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, was evaluated locally (investigator's assessment) according to the revised IWG Response Criteria for Malignant Lymphoma.

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

End point timeframe:

Every 8-16 weeks for up to 72 months

| End point values                 | Duvelisib            |  |  |  |
|----------------------------------|----------------------|--|--|--|
| Subject group type               | Reporting group      |  |  |  |
| Number of subjects analysed      | 129 <sup>[5]</sup>   |  |  |  |
| Units: month                     |                      |  |  |  |
| median (confidence interval 95%) | 9.57 (8.35 to 11.70) |  |  |  |

Notes:

[5] - Full Analysis Set

### Statistical analyses

No statistical analyses for this end point

### Secondary: Overall Survival (OS)

|                 |                       |
|-----------------|-----------------------|
| End point title | Overall Survival (OS) |
|-----------------|-----------------------|

End point description:

OS, defined as the time from the first dose of study treatment to the date of death, was evaluated locally (investigator's assessment) according to the revised IWG Response Criteria for Malignant Lymphoma.

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

End point timeframe:

Every 16 weeks for up to 72 months

| End point values                 | Duvelisib              |  |  |  |
|----------------------------------|------------------------|--|--|--|
| Subject group type               | Reporting group        |  |  |  |
| Number of subjects analysed      | 129 <sup>[6]</sup>     |  |  |  |
| Units: month                     |                        |  |  |  |
| median (confidence interval 95%) | 28.96 (21.37 to 37.02) |  |  |  |

Notes:

[6] - Full Analysis Set

### Statistical analyses

No statistical analyses for this end point

## Secondary: Plasma Concentration of Duvelisib and IPI-656

|                 |   |
|-----------------|---|
| End point title | Plasma Concentration of Duvelisib and IPI-656 |
|-----------------|---|

End point description:

The serum concentration of duvelisib and its main metabolite, IPI-656, are reported for Day 15 of Cycle 1 (C1D15) and Day 1 of Cycle 2 (C2D1) and Day 1 of Cycle 3 (C3D1). Results are reported in nanograms/millilitre (ng/mL).

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

End point timeframe:

Every 4 weeks for 12 weeks (C1D15: predose, 1 and 4 hours post dose; C2D1 and C3D1: anytime during study visit)

| End point values              | Duvelisib          | IPI-656              |  |  |
|-------------------------------|--------------------|----------------------|--|--|
| Subject group type            | Reporting group    | Subject analysis set |  |  |
| Number of subjects analysed   | 129 <sup>[7]</sup> | 129 <sup>[8]</sup>   |  |  |
| Units: ng/mL                  |                    |                      |  |  |
| median (full range (min-max)) |                    |                      |  |  |
| C1D15 Predose                 | 414 (19 to 4590)   | 648 (116 to 6010)    |  |  |
| C1D15 1 hour post dose        | 1175 (206 to 6820) | 641 (160 to 5920)    |  |  |
| C1D15 4 hours post dose       | 852 (233 to 5170)  | 714 (230 to 6020)    |  |  |
| C2D1                          | 631 (0000 to 4180) | 704 (0000 to 10200)  |  |  |
| C3D1                          | 696 (0000 to 3540) | 664 (0000 to 6850)   |  |  |

Notes:

[7] - Pharmacokinetics Set; N = 117, 118, 129, 129, 110

0000 = lower limit of quantification

[8] - Pharmacokinetics Set; N = 117, 118, 118, 117, 110

0000 = lower limit of quantification

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to Response (TTR)

|                 |                        |
|-----------------|------------------------|
| End point title | Time to Response (TTR) |
|-----------------|------------------------|

End point description:

TTR, defined as the time from the first dose of study treatment to the first documentation of response, was evaluated by an independent, third-party panel of radiologists and oncologists (Independent Review Committee [IRC]) according to the revised IWG Response Criteria for Malignant Lymphoma.

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

End point timeframe:

First dose to first documentation of complete or partial response (up to 6 months)

|                                       |                     |  |  |  |
|---------------------------------------|---------------------|--|--|--|
| <b>End point values</b>               | Duvelisib           |  |  |  |
| Subject group type                    | Reporting group     |  |  |  |
| Number of subjects analysed           | 59 <sup>[9]</sup>   |  |  |  |
| Units: month                          |                     |  |  |  |
| median (inter-quartile range (Q1-Q3)) | 1.87 (1.71 to 3.65) |  |  |  |

Notes:

[9] - Participants in the FAS who were responders (CR or PR) per IRC.

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

73 months

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

### Dictionary used

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

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

### Reporting groups

|                       |           |
|-----------------------|-----------|
| Reporting group title | Duvelisib |
|-----------------------|-----------|

Reporting group description:

Participants received a dose of 25 mg duvelisib BID over the course of 28-day treatment cycles until disease progression or unacceptable toxicity.

| Serious adverse events  | Duvelisib         |  |  |
|---|-------------------|--|--|
| Total subjects affected by serious adverse events                   |                   |  |  |
| subjects affected / exposed   | 83 / 129 (64.34%) |  |  |
| number of deaths (all causes)                                       | 68                |  |  |
| number of deaths resulting from adverse events                      | 18                |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                   |  |  |
| Squamous cell carcinoma of skin                                     |                   |  |  |
| subjects affected / exposed   | 3 / 129 (2.33%)   |  |  |
| occurrences causally related to treatment / all                     | 0 / 3             |  |  |
| deaths causally related to treatment / all                          | 0 / 0             |  |  |
| Acute myeloid leukaemia   |                   |  |  |
| subjects affected / exposed   | 1 / 129 (0.78%)   |  |  |
| occurrences causally related to treatment / all                     | 0 / 1             |  |  |
| deaths causally related to treatment / all                          | 0 / 0             |  |  |
| Malignant melanoma  |                   |  |  |
| subjects affected / exposed   | 1 / 129 (0.78%)   |  |  |
| occurrences causally related to treatment / all                     | 0 / 1             |  |  |
| deaths causally related to treatment / all                          | 0 / 0             |  |  |
| Myelodysplastic syndrome  |                   |  |  |
| subjects affected / exposed   | 1 / 129 (0.78%)   |  |  |
| occurrences causally related to treatment / all                     | 0 / 1             |  |  |
| deaths causally related to treatment / all                          | 0 / 0             |  |  |

|  |                 |  |  |
|--|-----------------|--|--|
| Neuroendocrine carcinoma of the skin                 |                 |  |  |
| subjects affected / exposed                          | 1 / 129 (0.78%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Non-small cell lung cancer                           |                 |  |  |
| subjects affected / exposed                          | 1 / 129 (0.78%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Squamous cell carcinoma                              |                 |  |  |
| subjects affected / exposed                          | 1 / 129 (0.78%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Vascular disorders                                   |                 |  |  |
| Deep vein thrombosis                                 |                 |  |  |
| subjects affected / exposed                          | 1 / 129 (0.78%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Embolism   |                 |  |  |
| subjects affected / exposed                          | 1 / 129 (0.78%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Peripheral embolism                                  |                 |  |  |
| subjects affected / exposed                          | 1 / 129 (0.78%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Superior vena cava syndrome                          |                 |  |  |
| subjects affected / exposed                          | 1 / 129 (0.78%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| General disorders and administration site conditions |                 |  |  |
| Disease progression                                  |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 9 / 129 (6.98%) |  |  |
| occurrences causally related to treatment / all | 0 / 9           |  |  |
| deaths causally related to treatment / all      | 0 / 9           |  |  |
| Pyrexia   |                 |  |  |
| subjects affected / exposed                     | 4 / 129 (3.10%) |  |  |
| occurrences causally related to treatment / all | 0 / 4           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| General physical health deterioration           |                 |  |  |
| subjects affected / exposed                     | 2 / 129 (1.55%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Fatigue   |                 |  |  |
| subjects affected / exposed                     | 1 / 129 (0.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Respiratory, thoracic and mediastinal disorders |                 |  |  |
| Pneumonitis                                     |                 |  |  |
| subjects affected / exposed                     | 4 / 129 (3.10%) |  |  |
| occurrences causally related to treatment / all | 0 / 4           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Pleural effusion                                |                 |  |  |
| subjects affected / exposed                     | 3 / 129 (2.33%) |  |  |
| occurrences causally related to treatment / all | 0 / 3           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Respiratory failure                             |                 |  |  |
| subjects affected / exposed                     | 2 / 129 (1.55%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Chronic obstructive pulmonary disease           |                 |  |  |
| subjects affected / exposed                     | 1 / 129 (0.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Dyspnoea  |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 129 (0.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Respiratory disorder                            |                 |  |  |
| subjects affected / exposed                     | 1 / 129 (0.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Investigations                                  |                 |  |  |
| Alanine aminotransferase increased              |                 |  |  |
| subjects affected / exposed                     | 1 / 129 (0.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Amylase increased                               |                 |  |  |
| subjects affected / exposed                     | 1 / 129 (0.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Blood creatinine increased                      |                 |  |  |
| subjects affected / exposed                     | 1 / 129 (0.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Lipase increased                                |                 |  |  |
| subjects affected / exposed                     | 1 / 129 (0.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Injury, poisoning and procedural complications  |                 |  |  |
| Infusion related reaction                       |                 |  |  |
| subjects affected / exposed                     | 1 / 129 (0.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Spinal compression fracture                     |                 |  |  |
| subjects affected / exposed                     | 1 / 129 (0.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| Traumatic fracture                              |                 |  |  |
| subjects affected / exposed                     | 1 / 129 (0.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cardiac disorders                               |                 |  |  |
| Atrial fibrillation                             |                 |  |  |
| subjects affected / exposed                     | 2 / 129 (1.55%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cardiac failure                                 |                 |  |  |
| subjects affected / exposed                     | 1 / 129 (0.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cardiac failure congestive                      |                 |  |  |
| subjects affected / exposed                     | 1 / 129 (0.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Cardio-respiratory arrest                       |                 |  |  |
| subjects affected / exposed                     | 1 / 129 (0.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Coronary artery occlusion                       |                 |  |  |
| subjects affected / exposed                     | 1 / 129 (0.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pericarditis                                    |                 |  |  |
| subjects affected / exposed                     | 1 / 129 (0.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Nervous system disorders                        |                 |  |  |
| Transient ischaemic attack                      |                 |  |  |
| subjects affected / exposed                     | 1 / 129 (0.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |



|   |                  |  |  |
|---|------------------|--|--|
| Blood and lymphatic system disorders            |                  |  |  |
| Febrile neutropenia                             |                  |  |  |
| subjects affected / exposed                     | 9 / 129 (6.98%)  |  |  |
| occurrences causally related to treatment / all | 0 / 9            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pancytopenia                                    |                  |  |  |
| subjects affected / exposed                     | 4 / 129 (3.10%)  |  |  |
| occurrences causally related to treatment / all | 0 / 4            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Anaemia   |                  |  |  |
| subjects affected / exposed                     | 2 / 129 (1.55%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Lymphadenopathy                                 |                  |  |  |
| subjects affected / exposed                     | 1 / 129 (0.78%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Thrombocytopenia                                |                  |  |  |
| subjects affected / exposed                     | 2 / 129 (1.55%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Eye disorders                                   |                  |  |  |
| Glaucoma  |                  |  |  |
| subjects affected / exposed                     | 1 / 129 (0.78%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Gastrointestinal disorders                      |                  |  |  |
| Diarrhoea                                       |                  |  |  |
| subjects affected / exposed                     | 10 / 129 (7.75%) |  |  |
| occurrences causally related to treatment / all | 0 / 10           |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Colitis   |                  |  |  |

|   |                 |  |  |  |
|---|-----------------|--|--|--|
| subjects affected / exposed                     | 6 / 129 (4.65%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 6           |  |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |  |
| Enterocolitis                                   |                 |  |  |  |
| subjects affected / exposed                     | 2 / 129 (1.55%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Vomiting  |                 |  |  |  |
| subjects affected / exposed                     | 2 / 129 (1.55%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Abdominal mass                                  |                 |  |  |  |
| subjects affected / exposed                     | 1 / 129 (0.78%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Abdominal pain                                  |                 |  |  |  |
| subjects affected / exposed                     | 2 / 129 (1.55%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Duodenitis                                      |                 |  |  |  |
| subjects affected / exposed                     | 1 / 129 (0.78%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Nausea  |                 |  |  |  |
| subjects affected / exposed                     | 1 / 129 (0.78%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Oesophagitis                                    |                 |  |  |  |
| subjects affected / exposed                     | 1 / 129 (0.78%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Pancreatitis acute                              |                 |  |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 129 (0.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Small intestinal haemorrhage                    |                 |  |  |
| subjects affected / exposed                     | 1 / 129 (0.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hepatobiliary disorders                         |                 |  |  |
| Cholecystitis                                   |                 |  |  |
| subjects affected / exposed                     | 1 / 129 (0.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hyperbilirubinaemia                             |                 |  |  |
| subjects affected / exposed                     | 1 / 129 (0.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Skin and subcutaneous tissue disorders          |                 |  |  |
| Rash  |                 |  |  |
| subjects affected / exposed                     | 3 / 129 (2.33%) |  |  |
| occurrences causally related to treatment / all | 0 / 3           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Rash generalised                                |                 |  |  |
| subjects affected / exposed                     | 2 / 129 (1.55%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Dermatitis allergic                             |                 |  |  |
| subjects affected / exposed                     | 1 / 129 (0.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Dermatitis exfoliative                          |                 |  |  |
| subjects affected / exposed                     | 1 / 129 (0.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Drug reaction with eosinophilia and             |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| systemic symptoms                               |                 |  |  |
| subjects affected / exposed                     | 1 / 129 (0.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Toxic epidermal necrolysis                      |                 |  |  |
| subjects affected / exposed                     | 1 / 129 (0.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Renal and urinary disorders                     |                 |  |  |
| Renal failure acute                             |                 |  |  |
| subjects affected / exposed                     | 4 / 129 (3.10%) |  |  |
| occurrences causally related to treatment / all | 0 / 4           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Renal failure                                   |                 |  |  |
| subjects affected / exposed                     | 2 / 129 (1.55%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Musculoskeletal and connective tissue disorders |                 |  |  |
| Rhabdomyolysis                                  |                 |  |  |
| subjects affected / exposed                     | 1 / 129 (0.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Infections and infestations                     |                 |  |  |
| Pneumonia                                       |                 |  |  |
| subjects affected / exposed                     | 7 / 129 (5.43%) |  |  |
| occurrences causally related to treatment / all | 0 / 7           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Bronchopneumonia                                |                 |  |  |
| subjects affected / exposed                     | 4 / 129 (3.10%) |  |  |
| occurrences causally related to treatment / all | 0 / 4           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cellulitis                                      |                 |  |  |

|   |                 |  |  |  |
|---|-----------------|--|--|--|
| subjects affected / exposed                     | 3 / 129 (2.33%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 3           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Lower respiratory tract infection               |                 |  |  |  |
| subjects affected / exposed                     | 2 / 129 (1.55%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Oral candidiasis                                |                 |  |  |  |
| subjects affected / exposed                     | 2 / 129 (1.55%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Pneumonia pseudomonas aeruginosa                |                 |  |  |  |
| subjects affected / exposed                     | 2 / 129 (1.55%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Bronchitis                                      |                 |  |  |  |
| subjects affected / exposed                     | 1 / 129 (0.78%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Bronchopulmonary aspergillosis                  |                 |  |  |  |
| subjects affected / exposed                     | 1 / 129 (0.78%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Campylobacter gastroenteritis                   |                 |  |  |  |
| subjects affected / exposed                     | 1 / 129 (0.78%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Campylobacter infection                         |                 |  |  |  |
| subjects affected / exposed                     | 1 / 129 (0.78%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Clostridium difficile colitis                   |                 |  |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 129 (0.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cystitis pseudomonal                            |                 |  |  |
| subjects affected / exposed                     | 1 / 129 (0.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Diverticulitis                                  |                 |  |  |
| subjects affected / exposed                     | 1 / 129 (0.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Enteritis infectious                            |                 |  |  |
| subjects affected / exposed                     | 1 / 129 (0.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Escherichia sepsis                              |                 |  |  |
| subjects affected / exposed                     | 1 / 129 (0.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Gastroenteritis                                 |                 |  |  |
| subjects affected / exposed                     | 1 / 129 (0.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Infective myositis                              |                 |  |  |
| subjects affected / exposed                     | 1 / 129 (0.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Influenza                                       |                 |  |  |
| subjects affected / exposed                     | 1 / 129 (0.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Klebsiella sepsis                               |                 |  |  |

|   |                 |  |  |  |
|---|-----------------|--|--|--|
| subjects affected / exposed                     | 1 / 129 (0.78%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Neutropenic sepsis                              |                 |  |  |  |
| subjects affected / exposed                     | 1 / 129 (0.78%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Oropharyngeal candidiasis                       |                 |  |  |  |
| subjects affected / exposed                     | 1 / 129 (0.78%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Pneumocystis jirovecii pneumonia                |                 |  |  |  |
| subjects affected / exposed                     | 1 / 129 (0.78%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Pneumonia cytomegaloviral                       |                 |  |  |  |
| subjects affected / exposed                     | 1 / 129 (0.78%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Pneumonia moraxella                             |                 |  |  |  |
| subjects affected / exposed                     | 1 / 129 (0.78%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Pseudomembranous colitis                        |                 |  |  |  |
| subjects affected / exposed                     | 1 / 129 (0.78%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Pseudomonal bacteraemia                         |                 |  |  |  |
| subjects affected / exposed                     | 1 / 129 (0.78%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Pseudomonal sepsis                              |                 |  |  |  |

|   |                 |  |  |  |
|---|-----------------|--|--|--|
| subjects affected / exposed                     | 1 / 129 (0.78%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Pyelonephritis acute                            |                 |  |  |  |
| subjects affected / exposed                     | 1 / 129 (0.78%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Scrotal infection                               |                 |  |  |  |
| subjects affected / exposed <sup>[1]</sup>      | 1 / 88 (1.14%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |  |
| Sepsis  |                 |  |  |  |
| subjects affected / exposed                     | 1 / 129 (0.78%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Sepsis syndrome                                 |                 |  |  |  |
| subjects affected / exposed                     | 1 / 129 (0.78%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |  |
| Septic shock                                    |                 |  |  |  |
| subjects affected / exposed                     | 1 / 129 (0.78%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |  |
| Urinary tract infection                         |                 |  |  |  |
| subjects affected / exposed                     | 1 / 129 (0.78%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Viral infection                                 |                 |  |  |  |
| subjects affected / exposed                     | 1 / 129 (0.78%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |  |
| Vulval cellulitis                               |                 |  |  |  |



|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed <sup>[2]</sup>      | 1 / 41 (2.44%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Metabolism and nutrition disorders              |                 |  |  |
| Hypercalcaemia                                  |                 |  |  |
| subjects affected / exposed                     | 2 / 129 (1.55%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hypokalaemia                                    |                 |  |  |
| subjects affected / exposed                     | 2 / 129 (1.55%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hyperkalaemia                                   |                 |  |  |
| subjects affected / exposed                     | 1 / 129 (0.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hypoglycaemia                                   |                 |  |  |
| subjects affected / exposed                     | 1 / 129 (0.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hyponatraemia                                   |                 |  |  |
| subjects affected / exposed                     | 1 / 129 (0.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

Notes:

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

Justification: This adverse event only affected male participants.

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

Justification: This adverse event only affected female participants.

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

|   |                    |  |  |
|---|--------------------|--|--|
| <b>Non-serious adverse events</b>                     | Duvelisib          |  |  |
| Total subjects affected by non-serious adverse events |                    |  |  |
| subjects affected / exposed                           | 122 / 129 (94.57%) |  |  |
| Investigations  |                    |  |  |

|                                       |                   |  |  |
|---------------------------------------|-------------------|--|--|
| Alanine aminotransferase increased    |                   |  |  |
| subjects affected / exposed           | 17 / 129 (13.18%) |  |  |
| occurrences (all)                     | 39                |  |  |
| Aspartate aminotransferase increased  |                   |  |  |
| subjects affected / exposed           | 13 / 129 (10.08%) |  |  |
| occurrences (all)                     | 27                |  |  |
| Weight decreased                      |                   |  |  |
| subjects affected / exposed           | 13 / 129 (10.08%) |  |  |
| occurrences (all)                     | 17                |  |  |
| Lipase increased                      |                   |  |  |
| subjects affected / exposed           | 12 / 129 (9.30%)  |  |  |
| occurrences (all)                     | 23                |  |  |
| Blood creatinine increased            |                   |  |  |
| subjects affected / exposed           | 8 / 129 (6.20%)   |  |  |
| occurrences (all)                     | 9                 |  |  |
| Blood alkaline phosphatase increased  |                   |  |  |
| subjects affected / exposed           | 7 / 129 (5.43%)   |  |  |
| occurrences (all)                     | 9                 |  |  |
| Blood lactate dehydrogenase increased |                   |  |  |
| subjects affected / exposed           | 7 / 129 (5.43%)   |  |  |
| occurrences (all)                     | 7                 |  |  |
| Neutrophil count decreased            |                   |  |  |
| subjects affected / exposed           | 7 / 129 (5.43%)   |  |  |
| occurrences (all)                     | 17                |  |  |
| Vascular disorders                    |                   |  |  |
| Hypertension                          |                   |  |  |
| subjects affected / exposed           | 7 / 129 (5.43%)   |  |  |
| occurrences (all)                     | 7                 |  |  |
| Hypotension                           |                   |  |  |
| subjects affected / exposed           | 7 / 129 (5.43%)   |  |  |
| occurrences (all)                     | 8                 |  |  |
| Nervous system disorders              |                   |  |  |
| Headache                              |                   |  |  |
| subjects affected / exposed           | 21 / 129 (16.28%) |  |  |
| occurrences (all)                     | 25                |  |  |
| Dizziness                             |                   |  |  |

|   |                      |  |  |
|---|----------------------|--|--|
| subjects affected / exposed<br>occurrences (all)        | 7 / 129 (5.43%)<br>7 |  |  |
| Blood and lymphatic system disorders                    |                      |  |  |
| Anaemia   |                      |  |  |
| subjects affected / exposed                             | 36 / 129 (27.91%)    |  |  |
| occurrences (all)                                       | 78                   |  |  |
| Neutropenia   |                      |  |  |
| subjects affected / exposed                             | 37 / 129 (28.68%)    |  |  |
| occurrences (all)                                       | 140                  |  |  |
| Thrombocytopenia  |                      |  |  |
| subjects affected / exposed                             | 25 / 129 (19.38%)    |  |  |
| occurrences (all)                                       | 55                   |  |  |
| General disorders and administration<br>site conditions |                      |  |  |
| Fatigue   |                      |  |  |
| subjects affected / exposed                             | 37 / 129 (28.68%)    |  |  |
| occurrences (all)                                       | 57                   |  |  |
| Pyrexia   |                      |  |  |
| subjects affected / exposed                             | 32 / 129 (24.81%)    |  |  |
| occurrences (all)                                       | 50                   |  |  |
| Oedema peripheral                                       |                      |  |  |
| subjects affected / exposed                             | 22 / 129 (17.05%)    |  |  |
| occurrences (all)                                       | 32                   |  |  |
| Asthenia  |                      |  |  |
| subjects affected / exposed                             | 15 / 129 (11.63%)    |  |  |
| occurrences (all)                                       | 19                   |  |  |
| Chills  |                      |  |  |
| subjects affected / exposed                             | 9 / 129 (6.98%)      |  |  |
| occurrences (all)                                       | 15                   |  |  |
| Gastrointestinal disorders                              |                      |  |  |
| Diarrhoea   |                      |  |  |
| subjects affected / exposed                             | 63 / 129 (48.84%)    |  |  |
| occurrences (all)                                       | 139                  |  |  |
| Nausea  |                      |  |  |
| subjects affected / exposed                             | 38 / 129 (29.46%)    |  |  |
| occurrences (all)                                       | 46                   |  |  |
| Vomiting  |                      |  |  |

|   |                   |  |  |
|---|-------------------|--|--|
| subjects affected / exposed                     | 22 / 129 (17.05%) |  |  |
| occurrences (all)                               | 25                |  |  |
| Abdominal pain                                  |                   |  |  |
| subjects affected / exposed                     | 20 / 129 (15.50%) |  |  |
| occurrences (all)                               | 24                |  |  |
| Constipation                                    |                   |  |  |
| subjects affected / exposed                     | 15 / 129 (11.63%) |  |  |
| occurrences (all)                               | 17                |  |  |
| Dry mouth                                       |                   |  |  |
| subjects affected / exposed                     | 9 / 129 (6.98%)   |  |  |
| occurrences (all)                               | 12                |  |  |
| Stomatitis                                      |                   |  |  |
| subjects affected / exposed                     | 9 / 129 (6.98%)   |  |  |
| occurrences (all)                               | 9                 |  |  |
| Respiratory, thoracic and mediastinal disorders |                   |  |  |
| Cough   |                   |  |  |
| subjects affected / exposed                     | 35 / 129 (27.13%) |  |  |
| occurrences (all)                               | 53                |  |  |
| Dyspnoea  |                   |  |  |
| subjects affected / exposed                     | 14 / 129 (10.85%) |  |  |
| occurrences (all)                               | 16                |  |  |
| Oropharyngeal pain                              |                   |  |  |
| subjects affected / exposed                     | 8 / 129 (6.20%)   |  |  |
| occurrences (all)                               | 11                |  |  |
| Skin and subcutaneous tissue disorders          |                   |  |  |
| Rash  |                   |  |  |
| subjects affected / exposed                     | 22 / 129 (17.05%) |  |  |
| occurrences (all)                               | 52                |  |  |
| Night sweats                                    |                   |  |  |
| subjects affected / exposed                     | 13 / 129 (10.08%) |  |  |
| occurrences (all)                               | 15                |  |  |
| Pruritus  |                   |  |  |
| subjects affected / exposed                     | 10 / 129 (7.75%)  |  |  |
| occurrences (all)                               | 15                |  |  |
| Hyperhidrosis                                   |                   |  |  |

|  |                      |  |  |
|--|----------------------|--|--|
| subjects affected / exposed<br>occurrences (all) | 7 / 129 (5.43%)<br>7 |  |  |
| Musculoskeletal and connective tissue disorders  |                      |  |  |
| Arthralgia                                       |                      |  |  |
| subjects affected / exposed                      | 19 / 129 (14.73%)    |  |  |
| occurrences (all)                                | 32                   |  |  |
| Back pain  |                      |  |  |
| subjects affected / exposed                      | 18 / 129 (13.95%)    |  |  |
| occurrences (all)                                | 19                   |  |  |
| Pain in extremity                                |                      |  |  |
| subjects affected / exposed                      | 13 / 129 (10.08%)    |  |  |
| occurrences (all)                                | 17                   |  |  |
| Musculoskeletal pain                             |                      |  |  |
| subjects affected / exposed                      | 8 / 129 (6.20%)      |  |  |
| occurrences (all)                                | 8                    |  |  |
| Infections and infestations                      |                      |  |  |
| Oral candidiasis                                 |                      |  |  |
| subjects affected / exposed                      | 8 / 129 (6.20%)      |  |  |
| occurrences (all)                                | 10                   |  |  |
| Urinary tract infection                          |                      |  |  |
| subjects affected / exposed                      | 7 / 129 (5.43%)      |  |  |
| occurrences (all)                                | 9                    |  |  |
| Metabolism and nutrition disorders               |                      |  |  |
| Decreased appetite                               |                      |  |  |
| subjects affected / exposed                      | 19 / 129 (14.73%)    |  |  |
| occurrences (all)                                | 30                   |  |  |
| Hypokalaemia                                     |                      |  |  |
| subjects affected / exposed                      | 18 / 129 (13.95%)    |  |  |
| occurrences (all)                                | 24                   |  |  |
| Hyperuricaemia                                   |                      |  |  |
| subjects affected / exposed                      | 11 / 129 (8.53%)     |  |  |
| occurrences (all)                                | 13                   |  |  |
| Dehydration                                      |                      |  |  |
| subjects affected / exposed                      | 8 / 129 (6.20%)      |  |  |
| occurrences (all)                                | 9                    |  |  |



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 08 April 2014    | <ul style="list-style-type: none"><li>- Added human immunodeficiency virus screening/history at Screening.</li><li>- Added guidance regarding use of vaccines, specifically the prohibition of live and live attenuated vaccines prior to and during study treatment.</li><li>- Prophylaxis for herpes simplex virus and herpes zoster virus was added as a requirement for all participants. In addition, cytomegalovirus (CMV) prophylaxis was added as a recommendation for participants with prior CMV infection that required treatment, and additional monitoring for reactivation was added as a recommendation for these participants.</li><li>- Modified Exclusion #2 to prohibit any prior treatment with phosphoinositide-3-kinase (PI3K) inhibitors and to add prior treatment with Bruton's tyrosine kinase (BTK) inhibitors to exclusion criterion.</li><li>- The statistical design of the study was updated from the previously used precision-based method to a group sequential design in the hypothesis testing framework.</li><li>- Primary objective and endpoint definition were corrected to ORR, with overall response defined as best response of CR or PR.</li><li>- TTR was added as a secondary endpoint.</li><li>- Baseline corrected QT interval (QTc) measurements using the Fridericia's correction method exclusion criterion was changed from &gt;480 milliseconds (ms) to &gt;500 ms; treatment modifications (that is, dose interruptions/holds) were updated with treatment interruption for duvelisib-treated participants now based on new Grade 3 QTc &gt;20 ms from baseline.</li><li>- Exclusion criteria were added for certain cardiac events and for participants who have had gastric bypass or other procedures that may affect absorption of duvelisib.</li><li>- The 25 mg once a day dose level was replaced with 10 mg BID for dose level -2. A new dose level of 5 mg BID (-3) was added.</li><li>- Concomitant medication sections for antimicrobial prophylaxis, use of vaccines, immunosuppressants, PI3K and BTK inhibitors, and photosafety were added.</li></ul> |
| 30 April 2015    | <ul style="list-style-type: none"><li>- Changed to allow participants to continue to receive duvelisib treatment for an additional year after 13 cycles if they have documented evidence of response (CR or PR) or stable disease. This had been amended from the original language which required a CR or PR.</li><li>- Changed to enroll approximately 80 follicular lymphoma participants, rather than at least 100. The amended estimate was based on the accrual pattern of the subtypes observed in the study.</li><li>- Change to reflect that an independent data monitoring committee (DMC), rather than an internal DMC, was assembled to periodically review all available safety information and review efficacy data at the interim analysis.</li></ul>   |
| 03 November 2015 | <ul style="list-style-type: none"><li>- Changed to state that participants who display evidence of clinical benefit after 1 year of treatment may continue to receive duvelisib until disease progression or unacceptable toxicity. This was amended from allowing participants to receive up to a total of 2 years of treatment.</li><li>- The cautionary statements on concomitant use of cytochrome P450 substrates were strengthened.</li><li>- An exploratory efficacy endpoint evaluating lymph node response rate was added.</li></ul>  |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported