



## Clinical trial results:

### A Phase II, Double-Blind, Placebo-Controlled, Randomized Study Evaluating the Safety and Efficacy of Carboplatin/Paclitaxel and Carboplatin/Paclitaxel/Bevacizumab with and without GDC-0941 in Patients with Previously Untreated Advanced or Recurrent Non-Small Cell Lung Cancer

#### Summary

|                          |                   |
|--------------------------|-------------------|
| EudraCT number           | 2011-002893-21    |
| Trial protocol           | DE HU ES NL GB IT |
| Global end of trial date | 30 March 2016     |

#### Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1 (current)  |
| This version publication date  | 13 April 2017 |
| First version publication date | 13 April 2017 |

#### Trial information

##### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | GO27912 |
|-----------------------|---------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01493843 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | F. Hoffmann-La Roche AG   |
| Sponsor organisation address | Grenzacherstrasse 124, Basel, Switzerland, CH-4070  |
| Public contact               | F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com |
| Scientific contact           | F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.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                       | 06 May 2016   |
| Is this the analysis of the primary completion data? | No            |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 30 March 2016 |
| Was the trial ended prematurely?                     | No            |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the efficacy (as measured by Progression Free Survival) of pictilisib in combination with carboplatin (C) + paclitaxel (P) in subjects with squamous non-small cell lung cancer (NSCLC) and in combination with carboplatin (C) + paclitaxel (P) + bevacizumab (B) in subjects with non-squamous NSCLC.

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

|   |                 |
|---|-----------------|
| Actual start date of recruitment                          | 20 January 2012 |
| 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 | Argentina: 3           |
| Country: Number of subjects enrolled | Australia: 18          |
| Country: Number of subjects enrolled | Brazil: 16             |
| Country: Number of subjects enrolled | Canada: 3              |
| Country: Number of subjects enrolled | Chile: 8               |
| Country: Number of subjects enrolled | Spain: 31              |
| Country: Number of subjects enrolled | France: 39             |
| Country: Number of subjects enrolled | United Kingdom: 6      |
| Country: Number of subjects enrolled | Germany: 36            |
| Country: Number of subjects enrolled | Hungary: 32            |
| Country: Number of subjects enrolled | Israel: 7              |
| Country: Number of subjects enrolled | Italy: 12              |
| Country: Number of subjects enrolled | Netherlands: 9         |
| Country: Number of subjects enrolled | Russian Federation: 90 |
| Country: Number of subjects enrolled | Ukraine: 36            |
| Country: Number of subjects enrolled | United States: 155     |
| Worldwide total number of subjects   | 501                    |
| EEA total number of subjects         | 165                    |

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)                      | 299 |
| From 65 to 84 years                       | 199 |
| 85 years and over                         | 3   |

## Subject disposition

### Recruitment

Recruitment details:

For Arms A and B subjects must have histologically documented advanced (Stage IV) or recurrent squamous NSCLC and for Arms C, D, E and F advanced (Stage IV) or recurrent non-squamous NSCLC.

### Pre-assignment

Screening details:

Subjects with squamous NSCLC were checked for phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) amplification status and subjects with non-squamous NSCLC for phosphatase and tensin homolog (PTEN) loss/low status.

### Period 1

|                              |                                 |
|------------------------------|---------------------------------|
| Period 1 title               | Overall Period (overall period) |
| Is this the baseline period? | Yes                             |
| Allocation method            | Randomised - controlled         |
| Blinding used                | Double blind                    |
| Roles blinded                | Subject, Investigator           |

### Arms

|                              |                               |
|------------------------------|-------------------------------|
| Are arms mutually exclusive? | Yes                           |
| <b>Arm title</b>             | Arm A: 340 mg pictilisib + CP |

Arm description:

Subjects with advanced (Stage IV) or recurrent squamous NSCLC were administered 340 mg pictilisib plus carboplatin (C) plus paclitaxel (P).

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | pictilisib   |
| Investigational medicinal product code |              |
| Other name                             | GDC-0941     |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

Pictilisib, 340 mg, was taken orally once daily on Days 1-14 of a 21-day cycle for four cycles. Starting with Cycle 5, pictilisib was taken once daily continuously.

|  |                       |
|--|-----------------------|
| Investigational medicinal product name | paclitaxel            |
| Investigational medicinal product code |                       |
| Other name                             |                       |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

Dosage and administration details:

Paclitaxel was administered 200 milligrams per square metre (mg/m<sup>2</sup>) IV on Day 1 of each 21-day cycle for a maximum of four cycles.

|  |                       |
|--|-----------------------|
| Investigational medicinal product name | carboplatin           |
| Investigational medicinal product code |                       |
| Other name                             |                       |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

Dosage and administration details:

Carboplatin was administered intravenously (IV) to achieve an initial target area under the concentration curve (AUC) of 6 milligrams per millilitre per minute (mg/mL per min) on Day 1 of each 21-day cycle for a maximum of four cycles.

|                  |                     |
|------------------|---------------------|
| <b>Arm title</b> | Arm B: Placebo + CP |
|------------------|---------------------|

**Arm description:**

Subjects with advanced (Stage IV) or recurrent squamous NSCLC were administered placebo corresponding to 340 mg pictilisib plus carboplatin (C) plus paclitaxel (P). Subjects with investigator-assessed radiographic progression of NSCLC per RECIST 1.1 were allowed to cross over to Arm A during the first 4 cycles with carboplatin + paclitaxel or after chemotherapy had been completed (Cycle  $\geq$  5).

|  |          |
|--|----------|
| Arm type                               | Placebo  |
| Investigational medicinal product name | Placebo  |
| Investigational medicinal product code |          |
| Other name                             |          |
| Pharmaceutical forms                   | Tablet   |
| Routes of administration               | Oral use |

**Dosage and administration details:**

Placebo corresponding to 340 mg pictilisib was taken orally once daily on Days 1-14 of a 21-day cycle for four cycles. Starting with Cycle 5, placebo was taken once daily continuously.

|  |                       |
|--|-----------------------|
| Investigational medicinal product name | carboplatin           |
| Investigational medicinal product code |                       |
| Other name                             |                       |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

**Dosage and administration details:**

Carboplatin was administered IV to achieve an initial target AUC of 6 mg/mL per min on Day 1 of each 21-day cycle for a maximum of four cycles.

|  |                       |
|--|-----------------------|
| Investigational medicinal product name | paclitaxel            |
| Investigational medicinal product code |                       |
| Other name                             |                       |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

**Dosage and administration details:**

Paclitaxel was administered 200 mg/m<sup>2</sup> IV on Day 1 of each 21-day cycle for a maximum of four cycles.

|                  |                                |
|------------------|--------------------------------|
| <b>Arm title</b> | Arm C: 340 mg pictilisib + CPB |
|------------------|--------------------------------|

**Arm description:**

Subjects with advanced (Stage IV) or recurrent non-squamous NSCLC were administered 340 mg pictilisib plus carboplatin (C) plus paclitaxel (P) plus bevacizumab (B).

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | pictilisib   |
| Investigational medicinal product code |              |
| Other name                             | GDC-0941     |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

**Dosage and administration details:**

Pictilisib, 340 mg, was taken orally once daily on Days 1-14 of a 21-day cycle for four cycles. Starting with Cycle 5, pictilisib was taken once daily continuously.

|  |                       |
|--|-----------------------|
| Investigational medicinal product name | carboplatin           |
| Investigational medicinal product code |                       |
| Other name                             |                       |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

**Dosage and administration details:**

Carboplatin was administered IV to achieve an initial target AUC of 6 mg/mL per min on Day 1 of each 21-day cycle for a maximum of four cycles.

|  |                       |
|--|-----------------------|
| Investigational medicinal product name | paclitaxel            |
| Investigational medicinal product code |                       |
| Other name                             |                       |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

**Dosage and administration details:**

Paclitaxel was administered 200 mg/m<sup>2</sup> IV on Day 1 of each 21-day cycle for a maximum of four cycles.

|  |                       |
|--|-----------------------|
| Investigational medicinal product name | bevacizumab           |
| Investigational medicinal product code |                       |
| Other name                             |                       |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

**Dosage and administration details:**

Bevacizumab, 15 milligrams per kilogram (mg/kg) was administered IV at Day 1 of each 21-day cycle for a maximum of 34 cycles.

|                  |                      |
|------------------|----------------------|
| <b>Arm title</b> | Arm D: Placebo + CPB |
|------------------|----------------------|

**Arm description:**

Subjects with advanced (Stage IV) or recurrent non-squamous NSCLC were administered placebo corresponding to 340 mg pictilisib plus carboplatin (C) plus paclitaxel (P). Subjects with investigator-assessed radiographic progression of NSCLC per RECIST 1.1 were allowed to cross over to Arm C during the first 4 cycles with carboplatin + paclitaxel + bevacizumab or after chemotherapy had been completed (Cycle  $\geq$  5).

|  |          |
|--|----------|
| Arm type                               | Placebo  |
| Investigational medicinal product name | Placebo  |
| Investigational medicinal product code |          |
| Other name                             |          |
| Pharmaceutical forms                   | Tablet   |
| Routes of administration               | Oral use |

**Dosage and administration details:**

Placebo corresponding to 340 mg pictilisib was taken orally once daily on Days 1-14 of a 21-day cycle for four cycles. Starting with Cycle 5, placebo was taken once daily continuously.

|  |                       |
|--|-----------------------|
| Investigational medicinal product name | carboplatin           |
| Investigational medicinal product code |                       |
| Other name                             |                       |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

**Dosage and administration details:**

Carboplatin was administered IV to achieve an initial target AUC of 6 mg/mL per min on Day 1 of each 21-day cycle for a maximum of four cycles.

|  |                       |
|--|-----------------------|
| Investigational medicinal product name | paclitaxel            |
| Investigational medicinal product code |                       |
| Other name                             |                       |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

**Dosage and administration details:**

Paclitaxel was administered 200 mg/m<sup>2</sup> IV on Day 1 of each 21-day cycle for a maximum of four cycles.

|  |                       |
|--|-----------------------|
| Investigational medicinal product name | bevacizumab           |
| Investigational medicinal product code |                       |
| Other name                             |                       |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

**Dosage and administration details:**

Bevacizumab, 15 milligrams per kilogram (mg/kg) was administered IV at Day 1 of each 21-day cycle for a maximum of 34 cycles.

|                  |                                |
|------------------|--------------------------------|
| <b>Arm title</b> | Arm E: 260 mg pictilisib + CPB |
|------------------|--------------------------------|

**Arm description:**

Subjects with advanced (Stage IV) or recurrent non-squamous NSCLC were administered 260 mg pictilisib plus carboplatin (C) plus paclitaxel (P) plus bevacizumab (B).

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | pictilisib   |
| Investigational medicinal product code |              |
| Other name                             | GDC-0941     |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

**Dosage and administration details:**

Pictilisib, 260 mg, was taken orally once daily on Days 1-14 of a 21-day cycle for four cycles. Starting with Cycle 5, pictilisib was taken once daily continuously.

|  |                       |
|--|-----------------------|
| Investigational medicinal product name | carboplatin           |
| Investigational medicinal product code |                       |
| Other name                             |                       |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

**Dosage and administration details:**

Carboplatin was administered IV to achieve an initial target AUC of 6 mg/mL per min on Day 1 of each 21-day cycle for a maximum of four cycles.

|  |                       |
|--|-----------------------|
| Investigational medicinal product name | paclitaxel            |
| Investigational medicinal product code |                       |
| Other name                             |                       |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

**Dosage and administration details:**

Paclitaxel was administered 200 mg/m<sup>2</sup> IV on Day 1 of each 21-day cycle for a maximum of four cycles.

|  |                       |
|--|-----------------------|
| Investigational medicinal product name | bevacizumab           |
| Investigational medicinal product code |                       |
| Other name                             |                       |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

**Dosage and administration details:**

Bevacizumab, 15 milligrams per kilogram (mg/kg) was administered IV at Day 1 of each 21-day cycle for a maximum of 34 cycles.

|                  |                      |
|------------------|----------------------|
| <b>Arm title</b> | Arm F: Placebo + CPB |
|------------------|----------------------|

**Arm description:**

Subjects with advanced (Stage IV) or recurrent non-squamous NSCLC were administered placebo corresponding to 260 mg pictilisib plus carboplatin (C) plus paclitaxel (P). Subjects with investigator-assessed radiographic progression of NSCLC per RECIST 1.1 were allowed to cross over to Arm E during the first 4 cycles with carboplatin + paclitaxel + bevacizumab or after chemotherapy had been completed (Cycle  $\geq$  5).

|          |         |
|----------|---------|
| Arm type | Placebo |
|----------|---------|

|  |          |
|--|----------|
| Investigational medicinal product name | Placebo  |
| Investigational medicinal product code |          |
| Other name                             |          |
| Pharmaceutical forms                   | Tablet   |
| Routes of administration               | Oral use |

Dosage and administration details:

Placebo corresponding to 260 mg pictilisib was taken orally once daily on Days 1-14 of a 21-day cycle for four cycles. Starting with Cycle 5, placebo was taken once daily continuously.

|  |                       |
|--|-----------------------|
| Investigational medicinal product name | carboplatin           |
| Investigational medicinal product code |                       |
| Other name                             |                       |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

Dosage and administration details:

Carboplatin was administered IV to achieve an initial target AUC of 6 mg/mL per min on Day 1 of each 21-day cycle for a maximum of four cycles.

|  |                       |
|--|-----------------------|
| Investigational medicinal product name | paclitaxel            |
| Investigational medicinal product code |                       |
| Other name                             |                       |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

Dosage and administration details:

Paclitaxel was administered 200 mg/m<sup>2</sup> IV on Day 1 of each 21-day cycle for a maximum of four cycles.

|  |                       |
|--|-----------------------|
| Investigational medicinal product name | bevacizumab           |
| Investigational medicinal product code |                       |
| Other name                             |                       |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

Dosage and administration details:

Bevacizumab, 15 milligrams per kilogram (mg/kg) was administered IV at Day 1 of each 21-day cycle for a maximum of 34 cycles.

| Number of subjects in period 1 | Arm A: 340 mg pictilisib + CP | Arm B: Placebo + CP | Arm C: 340 mg pictilisib + CPB |
|--------------------------------|-------------------------------|---------------------|--------------------------------|
| Started                        | 126                           | 125                 | 79                             |
| Completed                      | 0                             | 0                   | 0                              |
| Not completed                  | 126                           | 125                 | 79                             |
| Other                          | 15                            | 7                   | 5                              |
| Death                          | 75                            | 78                  | 59                             |
| Unknown                        | 1                             | -                   | 1                              |
| Withdrawal by Subject          | 7                             | 6                   | 5                              |
| Study Terminated by Sponsor    | 24                            | 30                  | 8                              |
| Lost to follow-up              | 4                             | 4                   | 1                              |

| Number of subjects in period 1 | Arm D: Placebo + CPB | Arm E: 260 mg pictilisib + CPB | Arm F: Placebo + CPB |
|--------------------------------|----------------------|--------------------------------|----------------------|
| Started                        | 79                   | 62                             | 30                   |



|                             |    |    |    |
|-----------------------------|----|----|----|
| Completed                   | 0  | 0  | 0  |
| Not completed               | 79 | 62 | 30 |
| Other                       | 4  | 5  | 2  |
| Death                       | 57 | 43 | 21 |
| Unknown                     | -  | -  | -  |
| Withdrawal by Subject       | 3  | 3  | 1  |
| Study Terminated by Sponsor | 11 | 11 | 6  |
| Lost to follow-up           | 4  | -  | -  |

## Baseline characteristics

### Reporting groups

|                       |                |
|-----------------------|----------------|
| Reporting group title | Overall Period |
|-----------------------|----------------|

Reporting group description: -

| Reporting group values | Overall Period | Total |  |
|------------------------|----------------|-------|--|
| Number of subjects     | 501            | 501   |  |
| Age Categorical        |                |       |  |
| Units: Subjects        |                |       |  |
| Adults (18-64 years)   | 299            | 299   |  |
| From 65-84 years       | 199            | 199   |  |
| 85 years and over      | 3              | 3     |  |
| Age Continuous         |                |       |  |
| Units: years           |                |       |  |
| arithmetic mean        | 62             |       |  |
| standard deviation     | ± 9.7          | -     |  |
| Gender Categorical     |                |       |  |
| Units: Subjects        |                |       |  |
| Female                 | 140            | 140   |  |
| Male                   | 361            | 361   |  |

## End points

### End points reporting groups

|   |                                |
|---|--------------------------------|
| Reporting group title   | Arm A: 340 mg pictilisib + CP  |
| Reporting group description:<br>Subjects with advanced (Stage IV) or recurrent squamous NSCLC were administered 340 mg pictilisib plus carboplatin (C) plus paclitaxel (P).   |                                |
| Reporting group title   | Arm B: Placebo + CP            |
| Reporting group description:<br>Subjects with advanced (Stage IV) or recurrent squamous NSCLC were administered placebo corresponding to 340 mg pictilisib plus carboplatin (C) plus paclitaxel (P). Subjects with investigator-assessed radiographic progression of NSCLC per RECIST 1.1 were allowed to cross over to Arm A during the first 4 cycles with carboplatin + paclitaxel or after chemotherapy had been completed (Cycle $\geq$ 5).  |                                |
| Reporting group title   | Arm C: 340 mg pictilisib + CPB |
| Reporting group description:<br>Subjects with advanced (Stage IV) or recurrent non-squamous NSCLC were administered 340 mg pictilisib plus carboplatin (C) plus paclitaxel (P) plus bevacizumab (B).  |                                |
| Reporting group title   | Arm D: Placebo + CPB           |
| Reporting group description:<br>Subjects with advanced (Stage IV) or recurrent non-squamous NSCLC were administered placebo corresponding to 340 mg pictilisib plus carboplatin (C) plus paclitaxel (P). Subjects with investigator-assessed radiographic progression of NSCLC per RECIST 1.1 were allowed to cross over to Arm C during the first 4 cycles with carboplatin + paclitaxel + bevacizumab or after chemotherapy had been completed (Cycle $\geq$ 5).  |                                |
| Reporting group title   | Arm E: 260 mg pictilisib + CPB |
| Reporting group description:<br>Subjects with advanced (Stage IV) or recurrent non-squamous NSCLC were administered 260 mg pictilisib plus carboplatin (C) plus paclitaxel (P) plus bevacizumab (B).  |                                |
| Reporting group title   | Arm F: Placebo + CPB           |
| Reporting group description:<br>Subjects with advanced (Stage IV) or recurrent non-squamous NSCLC were administered placebo corresponding to 260 mg pictilisib plus carboplatin (C) plus paclitaxel (P). Subjects with investigator-assessed radiographic progression of NSCLC per RECIST 1.1 were allowed to cross over to Arm E during the first 4 cycles with carboplatin + paclitaxel + bevacizumab or after chemotherapy had been completed (Cycle $\geq$ 5).  |                                |
| Subject analysis set title  | Arm A Safety Population        |
| Subject analysis set type   | Safety analysis                |
| Subject analysis set description:<br>Subjects with advanced (Stage IV) or recurrent squamous NSCLC were administered 340 mg pictilisib plus carboplatin (C) plus paclitaxel (P). Safety population included all subjects, who received at least one dose of study treatment, with subjects allocated to the treatment arm associated with the regimen actually received.  |                                |
| Subject analysis set title  | Arm B Safety Population        |
| Subject analysis set type   | Safety analysis                |
| Subject analysis set description:<br>Subjects with advanced (Stage IV) or recurrent squamous NSCLC were administered placebo corresponding to 340 mg pictilisib plus carboplatin (C) plus paclitaxel (P). Subjects with investigator-assessed radiographic progression of NSCLC per RECIST 1.1 were allowed to cross over to Arm A during the first 4 cycles with carboplatin + paclitaxel or after chemotherapy had been completed (Cycle $\geq$ 5). Safety population included all subjects, who received at least one dose of study treatment, with subjects allocated to the treatment arm associated with the regimen actually received. |                                |
| Subject analysis set title  | Arm C Safety Population        |
| Subject analysis set type   | Safety analysis                |
| Subject analysis set description:<br>Subjects with advanced (Stage IV) or recurrent non-squamous NSCLC were administered 340 mg pictilisib plus carboplatin (C) plus paclitaxel (P) plus bevacizumab (B). Safety population included all  |                                |

subjects, who received at least one dose of study treatment, with subjects allocated to the treatment arm associated with the regimen actually received.

|                            |                         |
|----------------------------|-------------------------|
| Subject analysis set title | Arm D Safety Population |
|----------------------------|-------------------------|

|                           |                 |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

Subjects with advanced (Stage IV) or recurrent non-squamous NSCLC were administered placebo corresponding to 340 mg pictilisib plus carboplatin (C) plus paclitaxel (P). Subjects with investigator-assessed radiographic progression of NSCLC per RECIST 1.1 were allowed to cross over to Arm C during the first 4 cycles with carboplatin + paclitaxel + bevacizumab or after chemotherapy had been completed (Cycle  $\geq$  5). Safety population included all subjects, who received at least one dose of study treatment, with subjects allocated to the treatment arm associated with the regimen actually received.

|                            |                         |
|----------------------------|-------------------------|
| Subject analysis set title | Arm E Safety Population |
|----------------------------|-------------------------|

|                           |                 |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

Subjects with advanced (Stage IV) or recurrent non-squamous NSCLC were administered 260 mg pictilisib plus carboplatin (C) plus paclitaxel (P) plus bevacizumab (B). Safety population included all subjects, who received at least one dose of study treatment, with subjects allocated to the treatment arm associated with the regimen actually received.

|                            |                         |
|----------------------------|-------------------------|
| Subject analysis set title | Arm F Safety Population |
|----------------------------|-------------------------|

|                           |                 |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

Subjects with advanced (Stage IV) or recurrent non-squamous NSCLC were administered placebo corresponding to 260 mg pictilisib plus carboplatin (C) plus paclitaxel (P). Subjects with investigator-assessed radiographic progression of NSCLC per RECIST 1.1 were allowed to cross over to Arm E during the first 4 cycles with carboplatin + paclitaxel + bevacizumab or after chemotherapy had been completed (Cycle  $\geq$  5). Safety population included all subjects, who received at least one dose of study treatment, with subjects allocated to the treatment arm associated with the regimen actually received.

## Primary: Progression Free Survival (PFS)

|                 |                                 |
|-----------------|---------------------------------|
| End point title | Progression Free Survival (PFS) |
|-----------------|---------------------------------|

End point description:

PFS was defined as the time from randomisation to NSCLC disease progression as assessed by the investigator per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 or death from any cause on study ( $\leq$  30 days after the last dose of study treatment), whichever occurs first. Progression according to RECIST v1.1 is defined as at least a 20% increase in the sum of diameters of target lesions with an absolute increase of at least 5 millimetre (mm) or the appearance of one or more new lesions. Tumor assessments were performed by computed tomography (CT) scan and/or magnetic resonance imaging (MRI). Intent-to-Treat (ITT) population included all randomised subjects with subjects allocated to the treatment arm to which they were randomised.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Up to approximately 2.5 years

| End point values                 | Arm A: 340 mg pictilisib + CP | Arm B: Placebo + CP | Arm C: 340 mg pictilisib + CPB | Arm D: Placebo + CPB |
|----------------------------------|-------------------------------|---------------------|--------------------------------|----------------------|
| Subject group type               | Reporting group               | Reporting group     | Reporting group                | Reporting group      |
| Number of subjects analysed      | 94                            | 90                  | 79                             | 79                   |
| Units: months                    |                               |                     |                                |                      |
| median (confidence interval 90%) | 5.45 (4.24 to 6.74)           | 5.49 (4.34 to 5.65) | 6.87 (5.52 to 9.66)            | 6.08 (5.55 to 6.9)   |

|                                  |                                |                      |  |  |
|----------------------------------|--------------------------------|----------------------|--|--|
| <b>End point values</b>          | Arm E: 260 mg pictilisib + CPB | Arm F: Placebo + CPB |  |  |
| Subject group type               | Reporting group                | Reporting group      |  |  |
| Number of subjects analysed      | 62                             | 30                   |  |  |
| Units: months                    |                                |                      |  |  |
| median (confidence interval 90%) | 6.93 (4.63 to 8.28)            | 6.6 (5.49 to 8.31)   |  |  |

## Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Arm A versus Arm B                                  |
| Statistical analysis description:       |   |
| Unstratified Analysis                   |   |
| Comparison groups                       | Arm A: 340 mg pictilisib + CP v Arm B: Placebo + CP |
| Number of subjects included in analysis | 184   |
| Analysis specification                  | Pre-specified                                       |
| Analysis type                           | superiority   |
| P-value                                 | = 0.5327  |
| Method                                  | Logrank   |
| Parameter estimate                      | Hazard ratio (HR)                                   |
| Point estimate                          | 0.89  |
| Confidence interval                     |   |
| level                                   | 90 %  |
| sides                                   | 2-sided   |
| lower limit                             | 0.66  |
| upper limit                             | 1.21  |

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Arm C versus Arm D                                    |
| Statistical analysis description:       |   |
| Unstratified Analysis                   |   |
| Comparison groups                       | Arm C: 340 mg pictilisib + CPB v Arm D: Placebo + CPB |
| Number of subjects included in analysis | 158   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | = 0.3496  |
| Method                                  | Logrank   |
| Parameter estimate                      | Hazard ratio (HR)                                     |
| Point estimate                          | 0.83  |
| Confidence interval                     |   |
| level                                   | 90 %  |
| sides                                   | 2-sided   |
| lower limit                             | 0.6   |
| upper limit                             | 1.15  |

|                                   |                    |
|-----------------------------------|--------------------|
| <b>Statistical analysis title</b> | Arm E versus Arm F |
|-----------------------------------|--------------------|

**Statistical analysis description:****Unstratified Analysis**

|   |   |
|---|---|
| Comparison groups                       | Arm E: 260 mg pictilisib + CPB v Arm F: Placebo + CPB |
| Number of subjects included in analysis | 92  |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | = 0.8866  |
| Method                                  | Logrank   |
| Parameter estimate                      | Hazard ratio (HR)                                     |
| Point estimate                          | 1.04  |
| Confidence interval                     |   |
| level                                   | 90 %  |
| sides                                   | 2-sided   |
| lower limit                             | 0.66  |
| upper limit                             | 1.64  |

**Primary: PFS in Subjects with PIK3CA Amplification**

|                 |  |
|-----------------|--|
| End point title | PFS in Subjects with PIK3CA Amplification <sup>[1]</sup> |
|-----------------|--|

**End point description:**

PFS was defined as the time from randomisation to NSCLC disease progression as assessed by the investigator per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 or death from any cause on study ( $\leq$  30 days after the last dose of study treatment), whichever occurs first. Progression according to RECIST v1.1 is defined as at least a 20% increase in the sum of diameters of target lesions with an absolute increase of at least 5 mm or the appearance of one or more new lesions. Tumor assessments were performed by CT scan and/or MRI. PIK3CA amplified subjects in the ITT population included all randomised subjects with PIK3CA amplification with subjects allocated to the treatment arm to which they were randomised.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

**End point timeframe:**

Up to approximately 2.5 years

**Notes:**

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Subjects with PIK3CA amplification were only represented in arms A and B. Therefore, only arms A and B were included in this endpoint.

|                                  |                               |                     |  |  |
|----------------------------------|-------------------------------|---------------------|--|--|
| <b>End point values</b>          | Arm A: 340 mg pictilisib + CP | Arm B: Placebo + CP |  |  |
| Subject group type               | Reporting group               | Reporting group     |  |  |
| Number of subjects analysed      | 30                            | 27                  |  |  |
| Units: months                    |                               |                     |  |  |
| median (confidence interval 90%) | 6.6 (4.5 to 6.93)             | 5.29 (4.27 to 5.55) |  |  |

**Statistical analyses**

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | PIK3CA amplified subjects Arm A versus Arm B |
|-----------------------------------|--|

**Statistical analysis description:****Unstratified Analysis**

|                   |   |
|-------------------|---|
| Comparison groups | Arm A: 340 mg pictilisib + CP v Arm B: Placebo + CP |
|-------------------|---|

|   |                   |
|---|-------------------|
| Number of subjects included in analysis | 57                |
| Analysis specification                  | Pre-specified     |
| Analysis type                           | superiority       |
| P-value                                 | = 0.5388          |
| Method                                  | Logrank           |
| Parameter estimate                      | Hazard ratio (HR) |
| Point estimate                          | 0.81              |
| Confidence interval                     |                   |
| level                                   | 90 %              |
| sides                                   | 2-sided           |
| lower limit                             | 0.45              |
| upper limit                             | 1.44              |

### Primary: PFS in Subjects with PTEN Loss/low

|                 |   |
|-----------------|---|
| End point title | PFS in Subjects with PTEN Loss/low <sup>[2]</sup> |
|-----------------|---|

End point description:

PFS was defined as the time from randomisation to NSCLC disease progression as assessed by the investigator per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 or death from any cause on study (</= 30 days after the last dose of study treatment), whichever occurs first. Progression according to RECIST v1.1 is defined as at least a 20% increase in the sum of diameters of target lesions with an absolute increase of at least 5 mm or the appearance of one or more new lesions. Tumor assessments were performed by CT scan and/or MRI. Subjects with PTEN loss/low in the ITT population included all randomised subjects with PTEN loss/low with subjects allocated to the treatment arm to which they were randomised.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Up to approximately 2.5 years

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Subjects with PTEN loss/low were only represented in arms C and D. Therefore, only arms C and D were included in this endpoint.

| End point values                 | Arm C: 340 mg pictilisib + CPB | Arm D: Placebo + CPB |  |  |
|----------------------------------|--------------------------------|----------------------|--|--|
| Subject group type               | Reporting group                | Reporting group      |  |  |
| Number of subjects analysed      | 28                             | 46                   |  |  |
| Units: months                    |                                |                      |  |  |
| median (confidence interval 90%) | 6.9 (5.52 to 9.69)             | 5.62 (5.13 to 6.08)  |  |  |

### Statistical analyses

|                            |                                     |
|----------------------------|-------------------------------------|
| Statistical analysis title | PTEN loss/low in Arm C versus Arm D |
|----------------------------|-------------------------------------|

Statistical analysis description:

Unstratified Analysis

|                   |   |
|-------------------|---|
| Comparison groups | Arm C: 340 mg pictilisib + CPB v Arm D: Placebo + CPB |
|-------------------|---|

|   |                   |
|---|-------------------|
| Number of subjects included in analysis | 74                |
| Analysis specification                  | Pre-specified     |
| Analysis type                           | superiority       |
| P-value                                 | = 0.2199          |
| Method                                  | Logrank           |
| Parameter estimate                      | Hazard ratio (HR) |
| Point estimate                          | 0.71              |
| Confidence interval                     |                   |
| level                                   | 90 %              |
| sides                                   | 2-sided           |
| lower limit                             | 0.45              |
| upper limit                             | 1.13              |

## Secondary: Objective Tumor Response

|   |                          |
|---|--------------------------|
| End point title   | Objective Tumor Response |
| End point description:  |                          |
| Objective tumor response was assessed by the investigator using RECIST v1.1 and had to be confirmed $\geq 28$ days after initial response. Objective tumor response was defined as percentage of subjects with partial response (PR) or complete response (CR). PR: $\geq 30\%$ decrease in the sum of the longest diameter of target lesions; CR: disappearance of all target lesions; Objective tumor response = CR + PR. Tumor assessments were performed by CT scan and/or MRI. ITT population included all randomised subjects with subjects allocated to the treatment arm to which they were randomised. |                          |
| End point type  | Secondary                |
| End point timeframe:  |                          |
| Up to approximately 2.5 years   |                          |

| End point values              | Arm A: 340 mg pictilisib + CP | Arm B: Placebo + CP | Arm C: 340 mg pictilisib + CPB | Arm D: Placebo + CPB |
|-------------------------------|-------------------------------|---------------------|--------------------------------|----------------------|
| Subject group type            | Reporting group               | Reporting group     | Reporting group                | Reporting group      |
| Number of subjects analysed   | 94                            | 90                  | 79                             | 79                   |
| Units: Percentage of subjects |                               |                     |                                |                      |
| number (not applicable)       | 24.5                          | 30                  | 36.7                           | 29.1                 |

| End point values              | Arm E: 260 mg pictilisib + CPB | Arm F: Placebo + CPB |  |  |
|-------------------------------|--------------------------------|----------------------|--|--|
| Subject group type            | Reporting group                | Reporting group      |  |  |
| Number of subjects analysed   | 62                             | 30                   |  |  |
| Units: Percentage of subjects |                                |                      |  |  |
| number (not applicable)       | 25.8                           | 43.3                 |  |  |

## Statistical analyses



No statistical analyses for this end point

### Secondary: Objective Tumor Response in Subjects with PIK3CA Amplification

|                 |   |
|-----------------|---|
| End point title | Objective Tumor Response in Subjects with PIK3CA Amplification <sup>[3]</sup> |
|-----------------|---|

End point description:

Objective tumor response was assessed by the investigator using RECIST v1.1 and had to be confirmed  $\geq 28$  days after initial response. Objective tumor response was defined as percentage of subjects with partial response (PR) or complete response (CR). PR:  $\geq 30\%$  decrease in the sum of the longest diameter of target lesions; CR: disappearance of all target lesions; Objective tumor response = CR + PR. Tumor assessments were performed by CT scan and/or MRI. ITT population included all randomised subjects with PIK3CA amplification with subjects allocated to the treatment arm to which they were randomised.

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

End point timeframe:

Up to approximately 2.5 years

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Subjects with PIK3CA amplification were only represented in arms A and B. Therefore, only arms A and B were included in this endpoint.

| End point values              | Arm A: 340 mg pictilisib + CP | Arm B: Placebo + CP |  |  |
|-------------------------------|-------------------------------|---------------------|--|--|
| Subject group type            | Reporting group               | Reporting group     |  |  |
| Number of subjects analysed   | 30                            | 27                  |  |  |
| Units: Percentage of subjects |                               |                     |  |  |
| number (not applicable)       | 16.7                          | 33.3                |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Objective Tumor Response in Subjects with PTEN Loss/low

|                 |  |
|-----------------|--|
| End point title | Objective Tumor Response in Subjects with PTEN Loss/low <sup>[4]</sup> |
|-----------------|--|

End point description:

Objective tumor response was assessed by the investigator using RECIST v1.1 and had to be confirmed  $\geq 28$  days after initial response. Objective tumor response was defined as percentage of subjects with partial response (PR) or complete response (CR). PR:  $\geq 30\%$  decrease in the sum of the longest diameter of target lesions; CR: disappearance of all target lesions; Objective tumor response = CR + PR. Tumor assessments were performed by CT scan and/or MRI. ITT population included all randomised subjects with PTEN loss/low with subjects allocated to the treatment arm to which they were randomised.

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

End point timeframe:

Up to approximately 2.5 years

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Subjects with PTEN loss/low were only represented in arms C and D. Therefore, only arms C and D were included in this endpoint.

| End point values              | Arm C: 340 mg pictilisib + CPB | Arm D: Placebo + CPB |  |  |
|-------------------------------|--------------------------------|----------------------|--|--|
| Subject group type            | Reporting group                | Reporting group      |  |  |
| Number of subjects analysed   | 28                             | 46                   |  |  |
| Units: Percentage of subjects |                                |                      |  |  |
| number (not applicable)       | 39.3                           | 28.3                 |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Duration of Objective Response (DoR)

|  |                                      |
|--|--------------------------------------|
| End point title  | Duration of Objective Response (DoR) |
| End point description:   |                                      |
| DoR was defined as the time from first observation of an objective tumor response until first observation of disease progression as assessed by the investigator using RECIST v1.1. Objective tumor response was defined as percentage of participants with partial response (PR) or complete response (CR). PR: $\geq 30\%$ decrease in the sum of the longest diameter of target lesions; CR: disappearance of all target lesions; Objective tumor response = CR + PR. Disease progression was defined as at least a 20% increase in the sum of diameters of target lesions with an absolute increase of at least 5 mm or the appearance of one or more new lesions. Tumor assessments were performed by CT scan and/or MRI. ITT population included all randomised subjects with subjects allocated to the treatment arm to which they were randomised. |                                      |
| End point type   | Secondary                            |
| End point timeframe:   |                                      |
| Up to approximately 2.5 years  |                                      |

| End point values              | Arm A: 340 mg pictilisib + CP | Arm B: Placebo + CP | Arm C: 340 mg pictilisib + CPB | Arm D: Placebo + CPB |
|-------------------------------|-------------------------------|---------------------|--------------------------------|----------------------|
| Subject group type            | Reporting group               | Reporting group     | Reporting group                | Reporting group      |
| Number of subjects analysed   | 0 <sup>[5]</sup>              | 0 <sup>[6]</sup>    | 0 <sup>[7]</sup>               | 0 <sup>[8]</sup>     |
| Units: months                 |                               |                     |                                |                      |
| median (full range (min-max)) | ( to )                        | ( to )              | ( to )                         | ( to )               |

Notes:

[5] - The Sponsor has discontinued the clinical development of pictilisib. DoR data were not analysed.

[6] - The Sponsor has discontinued the clinical development of pictilisib. DoR data were not analysed.

[7] - The Sponsor has discontinued the clinical development of pictilisib. DoR data were not analysed.

[8] - The Sponsor has discontinued the clinical development of pictilisib. DoR data were not analysed.

| End point values              | Arm E: 260 mg pictilisib + CPB | Arm F: Placebo + CPB |  |  |
|-------------------------------|--------------------------------|----------------------|--|--|
| Subject group type            | Reporting group                | Reporting group      |  |  |
| Number of subjects analysed   | 0 <sup>[9]</sup>               | 0 <sup>[10]</sup>    |  |  |
| Units: months                 |                                |                      |  |  |
| median (full range (min-max)) | ( to )                         | ( to )               |  |  |

Notes:

[9] - The Sponsor has discontinued the clinical development of pictilisib. DoR data were not analysed.

[10] - The Sponsor has discontinued the clinical development of pictilisib. DoR data were not analysed.

## Statistical analyses

No statistical analyses for this end point

### Secondary: DoR in Subjects with PIK3CA Amplification

|                 |   |
|-----------------|---|
| End point title | DoR in Subjects with PIK3CA Amplification <sup>[11]</sup> |
|-----------------|---|

End point description:

DoR was defined as the time from first observation of an objective tumor response until first observation of disease progression as assessed by the investigator using RECIST v1.1. Objective tumor response was defined as percentage of participants with partial response (PR) or complete response (CR). PR:  $\geq 30\%$  decrease in the sum of the longest diameter of target lesions; CR: disappearance of all target lesions; Objective tumor response = CR + PR. Disease progression was defined as at least a 20% increase in the sum of diameters of target lesions with an absolute increase of at least 5 mm or the appearance of one or more new lesions. Tumor assessments were performed by CT scan and/or MRI. ITT population included all randomised subjects with PIK3CA amplification with subjects allocated to the treatment arm to which they were randomised.

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

End point timeframe:

Up to approximately 2.5 years

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Subjects with PIK3CA amplification were only represented in arms A and B. Therefore, only arms A and B were included in this endpoint.

| End point values              | Arm A: 340 mg pictilisib + CP | Arm B: Placebo + CP |  |  |
|-------------------------------|-------------------------------|---------------------|--|--|
| Subject group type            | Reporting group               | Reporting group     |  |  |
| Number of subjects analysed   | 0 <sup>[12]</sup>             | 0 <sup>[13]</sup>   |  |  |
| Units: months                 |                               |                     |  |  |
| median (full range (min-max)) | ( to )                        | ( to )              |  |  |

Notes:

[12] - The Sponsor has discontinued the clinical development of pictilisib. DoR data were not analysed.

[13] - The Sponsor has discontinued the clinical development of pictilisib. DoR data were not analysed.

## Statistical analyses

No statistical analyses for this end point

### Secondary: DoR in Subjects with PTEN Loss/low

|                 |  |
|-----------------|--|
| End point title | DoR in Subjects with PTEN Loss/low <sup>[14]</sup> |
|-----------------|--|

End point description:

DoR was defined as the time from first observation of an objective tumor response until first observation of disease progression as assessed by the investigator using RECIST v1.1. Objective tumor response was defined as percentage of participants with partial response (PR) or complete response (CR). PR:  $\geq 30\%$  decrease in the sum of the longest diameter of target lesions; CR: disappearance of all target lesions; Objective tumor response = CR + PR. Disease progression was defined as at least a 20% increase in the sum of diameters of target lesions with an absolute increase of at least 5 mm or the appearance of one or more new lesions. Tumor assessments were performed by CT scan and/or MRI. ITT population included all randomised subjects with PTEN loss/low with subjects allocated to the treatment arm to which they were randomised.

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

End point timeframe:

Up to approximately 2.5 years

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Subjects with PTEN loss/low were only represented in arms C and D. Therefore, only arms C and D were included in this endpoint.

| End point values              | Arm C: 340 mg pictilisib + CPB | Arm D: Placebo + CPB |  |  |
|-------------------------------|--------------------------------|----------------------|--|--|
| Subject group type            | Reporting group                | Reporting group      |  |  |
| Number of subjects analysed   | 0 <sup>[15]</sup>              | 0 <sup>[16]</sup>    |  |  |
| Units: months                 |                                |                      |  |  |
| median (full range (min-max)) | ( to )                         | ( to )               |  |  |

Notes:

[15] - The Sponsor has discontinued the clinical development of pictilisib. DoR data were not analysed.

[16] - The Sponsor has discontinued the clinical development of pictilisib. DoR data were not analysed.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Overall Survival (OS)

|   |                       |
|---|-----------------------|
| End point title   | Overall Survival (OS) |
| End point description:  |                       |
| OS was defined as the time from randomisation until death from any cause. ITT population included all randomised subjects with subjects allocated to the treatment arm to which they were randomised. 9999=NE=not estimable |                       |
| End point type  | Secondary             |
| End point timeframe:  |                       |
| Up to approximately 2.5 years   |                       |

| End point values                 | Arm A: 340 mg pictilisib + CP | Arm B: Placebo + CP   | Arm C: 340 mg pictilisib + CPB | Arm D: Placebo + CPB   |
|----------------------------------|-------------------------------|-----------------------|--------------------------------|------------------------|
| Subject group type               | Reporting group               | Reporting group       | Reporting group                | Reporting group        |
| Number of subjects analysed      | 94                            | 90                    | 79                             | 79                     |
| Units: months                    |                               |                       |                                |                        |
| median (confidence interval 90%) | 12.16 (9.23 to 14.92)         | 12.39 (9.26 to 15.05) | 13.57 (12.12 to 20.7)          | 16.07 (10.51 to 18.63) |

| End point values                 | Arm E: 260 mg pictilisib + CPB | Arm F: Placebo + CPB |  |  |
|----------------------------------|--------------------------------|----------------------|--|--|
| Subject group type               | Reporting group                | Reporting group      |  |  |
| Number of subjects analysed      | 62                             | 30                   |  |  |
| Units: months                    |                                |                      |  |  |
| median (confidence interval 90%) | 11.47 (8.02 to 15.8)           | 14.23 (9 to 9999)    |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: OS in Subjects with PIK3CA Amplification

|                 |  |
|-----------------|--|
| End point title | OS in Subjects with PIK3CA Amplification <sup>[17]</sup> |
|-----------------|--|

End point description:

OS was defined as the time from randomisation until death from any cause. ITT population included all randomised subjects with PIK3CA amplification with subjects allocated to the treatment arm to which they were randomised. 9999=NE=not estimable

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

End point timeframe:

Up to approximately 2.5 years

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Subjects with PIK3CA amplification were only represented in arms A and B. Therefore, only arms A and B were included in this endpoint.

| End point values                 | Arm A: 340 mg pictilisib + CP | Arm B: Placebo + CP |  |  |
|----------------------------------|-------------------------------|---------------------|--|--|
| Subject group type               | Reporting group               | Reporting group     |  |  |
| Number of subjects analysed      | 30                            | 27                  |  |  |
| Units: months                    |                               |                     |  |  |
| median (confidence interval 90%) | 15.05 (9.46 to 20.37)         | 11.7 (8.51 to 9999) |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: OS in Subjects with PTEN Loss/low

|                 |   |
|-----------------|---|
| End point title | OS in Subjects with PTEN Loss/low <sup>[18]</sup> |
|-----------------|---|

End point description:

OS was defined as the time from randomisation until death from any cause. ITT population included all randomised subjects with PTEN loss/low with subjects allocated to the treatment arm to which they were randomised.

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

End point timeframe:

Up to approximately 2.5 years

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Subjects with PTEN loss/low were only represented in arms C and D. Therefore, only arms C and D were included in this endpoint.

| End point values                 | Arm C: 340 mg pictilisib + CPB | Arm D: Placebo + CPB  |  |  |
|----------------------------------|--------------------------------|-----------------------|--|--|
| Subject group type               | Reporting group                | Reporting group       |  |  |
| Number of subjects analysed      | 28                             | 46                    |  |  |
| Units: months                    |                                |                       |  |  |
| median (confidence interval 90%) | 14.52 (12.12 to 20.86)         | 11.27 (8.28 to 18.14) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects with Adverse Events

|  |  |
|--|--|
| End point title  | Percentage of Subjects with Adverse Events |
| End point description:   |  |
| An adverse event is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product. Preexisting conditions which worsen during a study are also considered as adverse events. |  |
| End point type   | Secondary                                  |
| End point timeframe:   |  |
| Up to approximately 4 years  |  |

| End point values              | Arm A Safety Population | Arm B Safety Population | Arm C Safety Population | Arm D Safety Population |
|-------------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
| Subject group type            | Subject analysis set    | Subject analysis set    | Subject analysis set    | Subject analysis set    |
| Number of subjects analysed   | 133                     | 115                     | 82                      | 73                      |
| Units: percentage of subjects |                         |                         |                         |                         |
| number (not applicable)       | 94.7                    | 97.4                    | 98.8                    | 100                     |

| End point values              | Arm E Safety Population | Arm F Safety Population |  |  |
|-------------------------------|-------------------------|-------------------------|--|--|
| Subject group type            | Subject analysis set    | Subject analysis set    |  |  |
| Number of subjects analysed   | 59                      | 26                      |  |  |
| Units: percentage of subjects |                         |                         |  |  |
| number (not applicable)       | 94.9                    | 100                     |  |  |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to approximately 4 years

Adverse event reporting additional description:

Safety population included all subjects, who received at least one dose of study treatment, with subjects allocated to the treatment arm associated with the regimen actually received.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 19.0 |
|--------------------|------|

### Reporting groups

|                       |                               |
|-----------------------|-------------------------------|
| Reporting group title | Arm A: 340 mg pictilisib + CP |
|-----------------------|-------------------------------|

Reporting group description:

Subjects with advanced (Stage IV) or recurrent squamous NSCLC were administered 340 mg pictilisib plus carboplatin (C) plus paclitaxel (P).

|                       |                     |
|-----------------------|---------------------|
| Reporting group title | Arm B: Placebo + CP |
|-----------------------|---------------------|

Reporting group description:

Subjects with advanced (Stage IV) or recurrent squamous NSCLC were administered placebo corresponding to 340 mg pictilisib plus carboplatin (C) plus paclitaxel (P). Subjects with investigator-assessed radiographic progression of NSCLC per RECIST 1.1 were allowed to cross over to Arm A during the first 4 cycles with carboplatin + paclitaxel or after chemotherapy had been completed (Cycle  $\geq$  5).

|                       |                                |
|-----------------------|--------------------------------|
| Reporting group title | Arm C: 340 mg pictilisib + CPB |
|-----------------------|--------------------------------|

Reporting group description:

Subjects with advanced (Stage IV) or recurrent non-squamous NSCLC were administered 340 mg pictilisib plus carboplatin (C) plus paclitaxel (P) plus bevacizumab (B).

|                       |                      |
|-----------------------|----------------------|
| Reporting group title | Arm D: Placebo + CPB |
|-----------------------|----------------------|

Reporting group description:

Subjects with advanced (Stage IV) or recurrent non-squamous NSCLC were administered placebo corresponding to 340 mg pictilisib plus carboplatin (C) plus paclitaxel (P). Subjects with investigator-assessed radiographic progression of NSCLC per RECIST 1.1 were allowed to cross over to Arm C during the first 4 cycles with carboplatin + paclitaxel + bevacizumab or after chemotherapy had been completed (Cycle  $\geq$  5).

|                       |                                |
|-----------------------|--------------------------------|
| Reporting group title | Arm E: 260 mg pictilisib + CPB |
|-----------------------|--------------------------------|

Reporting group description:

Subjects with advanced (Stage IV) or recurrent non-squamous NSCLC were administered 260 mg pictilisib plus carboplatin (C) plus paclitaxel (P) plus bevacizumab (B).

|                       |                      |
|-----------------------|----------------------|
| Reporting group title | Arm F: Placebo + CPB |
|-----------------------|----------------------|

Reporting group description:

Subjects with advanced (Stage IV) or recurrent non-squamous NSCLC were administered placebo corresponding to 260 mg pictilisib plus carboplatin (C) plus paclitaxel (P). Subjects with investigator-assessed radiographic progression of NSCLC per RECIST 1.1 were allowed to cross over to Arm E during the first 4 cycles with carboplatin + paclitaxel + bevacizumab or after chemotherapy had been completed (Cycle  $\geq$  5).

| Serious adverse events                            | Arm A: 340 mg pictilisib + CP | Arm B: Placebo + CP | Arm C: 340 mg pictilisib + CPB |
|---|-------------------------------|---------------------|--------------------------------|
| Total subjects affected by serious adverse events |                               |                     |                                |
| subjects affected / exposed                       | 48 / 133 (36.09%)             | 34 / 115 (29.57%)   | 40 / 82 (48.78%)               |
| number of deaths (all causes)                     | 17                            | 6                   | 5                              |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| number of deaths resulting from adverse events                      |                 |                 |                |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                 |                 |                |
| Non-small cell lung cancer  |                 |                 |                |
| subjects affected / exposed   | 5 / 133 (3.76%) | 1 / 115 (0.87%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all                     | 0 / 5           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all                          | 0 / 5           | 0 / 1           | 0 / 0          |
| Lung neoplasm malignant   |                 |                 |                |
| subjects affected / exposed   | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 1 / 82 (1.22%) |
| occurrences causally related to treatment / all                     | 0 / 0           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0           | 0 / 1          |
| Metastases to meninges  |                 |                 |                |
| subjects affected / exposed   | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all                     | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0           | 0 / 0          |
| Metastatic pain   |                 |                 |                |
| subjects affected / exposed   | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 1 / 82 (1.22%) |
| occurrences causally related to treatment / all                     | 0 / 0           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0           | 0 / 0          |
| Vascular disorders  |                 |                 |                |
| Hypotension   |                 |                 |                |
| subjects affected / exposed   | 1 / 133 (0.75%) | 2 / 115 (1.74%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all                     | 0 / 1           | 2 / 2           | 0 / 0          |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0           | 0 / 0          |
| Deep vein thrombosis  |                 |                 |                |
| subjects affected / exposed   | 1 / 133 (0.75%) | 1 / 115 (0.87%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all                     | 0 / 1           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0           | 0 / 0          |
| Embolism  |                 |                 |                |
| subjects affected / exposed   | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all                     | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0           | 0 / 0          |
| Orthostatic hypotension   |                 |                 |                |



|  |                 |                 |                |
|--|-----------------|-----------------|----------------|
| subjects affected / exposed                          | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 1 / 82 (1.22%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0          |
| Peripheral arterial occlusive disease                |                 |                 |                |
| subjects affected / exposed                          | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0          |
| Phlebitis  |                 |                 |                |
| subjects affected / exposed                          | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 1 / 82 (1.22%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 1 / 1          |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0          |
| General disorders and administration site conditions |                 |                 |                |
| Pyrexia  |                 |                 |                |
| subjects affected / exposed                          | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 3 / 82 (3.66%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 3 / 5          |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0          |
| Asthenia   |                 |                 |                |
| subjects affected / exposed                          | 2 / 133 (1.50%) | 1 / 115 (0.87%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all      | 2 / 2           | 1 / 1           | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0          |
| Death  |                 |                 |                |
| subjects affected / exposed                          | 1 / 133 (0.75%) | 0 / 115 (0.00%) | 1 / 82 (1.22%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 1           | 0 / 0           | 0 / 1          |
| Fatigue  |                 |                 |                |
| subjects affected / exposed                          | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 2 / 82 (2.44%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 2 / 2          |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0          |
| General physical health deterioration                |                 |                 |                |
| subjects affected / exposed                          | 1 / 133 (0.75%) | 1 / 115 (0.87%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0          |
| Chest pain   |                 |                 |                |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 1 / 82 (1.22%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Disease progression                             |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Malaise   |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 1 / 115 (0.87%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Immune system disorders                         |                 |                 |                |
| Anaphylactic shock                              |                 |                 |                |
| subjects affected / exposed                     | 1 / 133 (0.75%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Anaphylactic reaction                           |                 |                 |                |
| subjects affected / exposed                     | 1 / 133 (0.75%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Drug hypersensitivity                           |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Hypersensitivity                                |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 1 / 82 (1.22%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Respiratory, thoracic and mediastinal disorders |                 |                 |                |
| Pulmonary embolism                              |                 |                 |                |
| subjects affected / exposed                     | 4 / 133 (3.01%) | 1 / 115 (0.87%) | 2 / 82 (2.44%) |
| occurrences causally related to treatment / all | 1 / 4           | 0 / 1           | 1 / 2          |
| deaths causally related to treatment / all      | 1 / 2           | 0 / 1           | 1 / 1          |

|   |                 |                 |                |  |
|---|-----------------|-----------------|----------------|--|
| Dyspnoea  |                 |                 |                |  |
| subjects affected / exposed                     | 4 / 133 (3.01%) | 0 / 115 (0.00%) | 2 / 82 (2.44%) |  |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 0           | 0 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |  |
| Pneumothorax                                    |                 |                 |                |  |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 1 / 115 (0.87%) | 2 / 82 (2.44%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |  |
| Pulmonary haemorrhage                           |                 |                 |                |  |
| subjects affected / exposed                     | 1 / 133 (0.75%) | 1 / 115 (0.87%) | 0 / 82 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           | 0 / 0          |  |
| Chronic obstructive pulmonary disease           |                 |                 |                |  |
| subjects affected / exposed                     | 1 / 133 (0.75%) | 1 / 115 (0.87%) | 0 / 82 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0          |  |
| Haemoptysis                                     |                 |                 |                |  |
| subjects affected / exposed                     | 1 / 133 (0.75%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |  |
| Pneumonitis                                     |                 |                 |                |  |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |  |
| Respiratory failure                             |                 |                 |                |  |
| subjects affected / exposed                     | 1 / 133 (0.75%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0          |  |
| Epistaxis                                       |                 |                 |                |  |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 1 / 82 (1.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |  |
| Hypoxia   |                 |                 |                |  |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 1 / 82 (1.22%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Pleuritic pain                                  |                 |                 |                |
| subjects affected / exposed                     | 2 / 133 (1.50%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Pulmonary oedema                                |                 |                 |                |
| subjects affected / exposed                     | 1 / 133 (0.75%) | 0 / 115 (0.00%) | 1 / 82 (1.22%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 1 / 1           | 0 / 0           | 0 / 1          |
| Acquired tracheo-oesophageal fistula            |                 |                 |                |
| subjects affected / exposed                     | 1 / 133 (0.75%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Acute pulmonary oedema                          |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Acute respiratory failure                       |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 1 / 115 (0.87%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Aspiration                                      |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Interstitial lung disease                       |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Oesophagobronchial fistula                      |                 |                 |                |

|  |                 |                 |                |
|--|-----------------|-----------------|----------------|
| subjects affected / exposed                                    | 0 / 133 (0.00%) | 1 / 115 (0.87%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all                | 0 / 0           | 1 / 1           | 0 / 0          |
| deaths causally related to treatment / all                     | 0 / 0           | 0 / 0           | 0 / 0          |
| Pleural effusion   |                 |                 |                |
| subjects affected / exposed                                    | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all                | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all                     | 0 / 0           | 0 / 0           | 0 / 0          |
| Pneumonia aspiration   |                 |                 |                |
| subjects affected / exposed                                    | 0 / 133 (0.00%) | 1 / 115 (0.87%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all                | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all                     | 0 / 0           | 0 / 0           | 0 / 0          |
| Psychiatric disorders  |                 |                 |                |
| Delirium   |                 |                 |                |
| subjects affected / exposed                                    | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all                | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all                     | 0 / 0           | 0 / 0           | 0 / 0          |
| Confusional state  |                 |                 |                |
| subjects affected / exposed                                    | 0 / 133 (0.00%) | 1 / 115 (0.87%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all                | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all                     | 0 / 0           | 0 / 0           | 0 / 0          |
| Hallucination  |                 |                 |                |
| subjects affected / exposed                                    | 1 / 133 (0.75%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all                | 1 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all                     | 0 / 0           | 0 / 0           | 0 / 0          |
| Investigations   |                 |                 |                |
| Eastern cooperative oncology group performance status worsened |                 |                 |                |
| subjects affected / exposed                                    | 1 / 133 (0.75%) | 1 / 115 (0.87%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all                | 1 / 1           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all                     | 0 / 0           | 0 / 0           | 0 / 0          |
| Blood alkaline phosphatase increased                           |                 |                 |                |
| subjects affected / exposed                                    | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all                | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all                     | 0 / 0           | 0 / 0           | 0 / 0          |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| Blood bilirubin increased                       |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Neutrophil count decreased                      |                 |                 |                |
| subjects affected / exposed                     | 1 / 133 (0.75%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Injury, poisoning and procedural complications  |                 |                 |                |
| Fall  |                 |                 |                |
| subjects affected / exposed                     | 1 / 133 (0.75%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Hip fracture                                    |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 1 / 115 (0.87%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Infusion related reaction                       |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 1 / 82 (1.22%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Injury  |                 |                 |                |
| subjects affected / exposed                     | 1 / 133 (0.75%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Laceration                                      |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Poisoning                                       |                 |                 |                |
| subjects affected / exposed                     | 1 / 133 (0.75%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| Pulmonary contusion                             |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 1 / 82 (1.22%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1          |
| Radiation necrosis                              |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Toxicity to various agents                      |                 |                 |                |
| subjects affected / exposed                     | 1 / 133 (0.75%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Cardiac disorders                               |                 |                 |                |
| Acute coronary syndrome                         |                 |                 |                |
| subjects affected / exposed                     | 3 / 133 (2.26%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 2 / 3           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Cardiopulmonary failure                         |                 |                 |                |
| subjects affected / exposed                     | 1 / 133 (0.75%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0          |
| Myocardial infarction                           |                 |                 |                |
| subjects affected / exposed                     | 1 / 133 (0.75%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Atrial fibrillation                             |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Atrial flutter                                  |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Cardiac arrest                                  |                 |                 |                |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 0 / 133 (0.00%) | 1 / 115 (0.87%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0          |
| Cardio-respiratory arrest                       |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Ventricular fibrillation                        |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Nervous system disorders                        |                 |                 |                |
| Cerebrovascular accident                        |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 1 / 82 (1.22%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Hemiparesis                                     |                 |                 |                |
| subjects affected / exposed                     | 1 / 133 (0.75%) | 1 / 115 (0.87%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Cerebral amyloid angiopathy                     |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Cerebral ischaemia                              |                 |                 |                |
| subjects affected / exposed                     | 1 / 133 (0.75%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Decreased vibratory sense                       |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Loss of proprioception                          |                 |                 |                |



|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Neuralgia                                       |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 1 / 82 (1.22%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Orthostatic intolerance                         |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Seizure   |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Syncope   |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 1 / 115 (0.87%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Transient ischaemic attack                      |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Blood and lymphatic system disorders            |                 |                 |                |
| Febrile neutropenia                             |                 |                 |                |
| subjects affected / exposed                     | 2 / 133 (1.50%) | 4 / 115 (3.48%) | 3 / 82 (3.66%) |
| occurrences causally related to treatment / all | 2 / 2           | 4 / 4           | 2 / 3          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Anaemia   |                 |                 |                |
| subjects affected / exposed                     | 1 / 133 (0.75%) | 2 / 115 (1.74%) | 2 / 82 (2.44%) |
| occurrences causally related to treatment / all | 1 / 1           | 4 / 4           | 2 / 2          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Neutropenia                                     |                 |                 |                |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 2 / 133 (1.50%) | 1 / 115 (0.87%) | 1 / 82 (1.22%) |
| occurrences causally related to treatment / all | 2 / 2           | 1 / 1           | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Pancytopenia                                    |                 |                 |                |
| subjects affected / exposed                     | 1 / 133 (0.75%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Febrile bone marrow aplasia                     |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 1 / 82 (1.22%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Leukopenia                                      |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 1 / 82 (1.22%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Gastrointestinal disorders                      |                 |                 |                |
| Diarrhoea                                       |                 |                 |                |
| subjects affected / exposed                     | 2 / 133 (1.50%) | 0 / 115 (0.00%) | 2 / 82 (2.44%) |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0           | 1 / 2          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Vomiting  |                 |                 |                |
| subjects affected / exposed                     | 2 / 133 (1.50%) | 1 / 115 (0.87%) | 3 / 82 (3.66%) |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 1           | 5 / 5          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Nausea  |                 |                 |                |
| subjects affected / exposed                     | 1 / 133 (0.75%) | 0 / 115 (0.00%) | 3 / 82 (3.66%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 3 / 3          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Abdominal pain                                  |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 2 / 82 (2.44%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 2          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Duodenal ulcer                                  |                 |                 |                |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 1 / 133 (0.75%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Dysphagia                                       |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 1 / 115 (0.87%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Gastrointestinal haemorrhage                    |                 |                 |                |
| subjects affected / exposed                     | 1 / 133 (0.75%) | 0 / 115 (0.00%) | 1 / 82 (1.22%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Pneumatosis intestinalis                        |                 |                 |                |
| subjects affected / exposed                     | 1 / 133 (0.75%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Upper gastrointestinal haemorrhage              |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 1 / 82 (1.22%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Colitis   |                 |                 |                |
| subjects affected / exposed                     | 1 / 133 (0.75%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Constipation                                    |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Diverticular perforation                        |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 1 / 82 (1.22%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Duodenal ulcer haemorrhage                      |                 |                 |                |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Duodenal ulcer perforation                      |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 1 / 82 (1.22%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Gastric perforation                             |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Gastrointestinal perforation                    |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Haematemesis                                    |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 1 / 115 (0.87%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Intestinal obstruction                          |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Oesophageal mass                                |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 1 / 82 (1.22%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Rectal haemorrhage                              |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Salivary gland calculus                         |                 |                 |                |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 1 / 82 (1.22%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Hepatobiliary disorders                         |                 |                 |                |
| Cholecystitis acute                             |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Cholelithiasis                                  |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 1 / 82 (1.22%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Skin and subcutaneous tissue disorders          |                 |                 |                |
| Rash maculo-papular                             |                 |                 |                |
| subjects affected / exposed                     | 3 / 133 (2.26%) | 0 / 115 (0.00%) | 2 / 82 (2.44%) |
| occurrences causally related to treatment / all | 3 / 3           | 0 / 0           | 4 / 4          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Rash macular                                    |                 |                 |                |
| subjects affected / exposed                     | 1 / 133 (0.75%) | 0 / 115 (0.00%) | 2 / 82 (2.44%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 2 / 2          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Dermatitis allergic                             |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 1 / 82 (1.22%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Rash  |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Renal and urinary disorders                     |                 |                 |                |
| Renal failure                                   |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 1 / 82 (1.22%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| Acute kidney injury                             |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Acute prerenal failure                          |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 1 / 115 (0.87%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Bladder perforation                             |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Dysuria   |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 1 / 82 (1.22%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Haematuria                                      |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Renal colic                                     |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Renal impairment                                |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Urinary retention                               |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 1 / 115 (0.87%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Musculoskeletal and connective tissue disorders |                 |                 |                |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| Arthralgia                                      |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 1 / 82 (1.22%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Muscular weakness                               |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Pain in extremity                               |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 1 / 82 (1.22%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Musculoskeletal chest pain                      |                 |                 |                |
| subjects affected / exposed                     | 1 / 133 (0.75%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Musculoskeletal pain                            |                 |                 |                |
| subjects affected / exposed                     | 1 / 133 (0.75%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Myalgia   |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Pathological fracture                           |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 1 / 115 (0.87%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Infections and infestations                     |                 |                 |                |
| Pneumonia                                       |                 |                 |                |
| subjects affected / exposed                     | 8 / 133 (6.02%) | 7 / 115 (6.09%) | 6 / 82 (7.32%) |
| occurrences causally related to treatment / all | 0 / 9           | 2 / 7           | 2 / 6          |
| deaths causally related to treatment / all      | 0 / 3           | 0 / 0           | 0 / 0          |
| Bronchitis                                      |                 |                 |                |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 0 / 133 (0.00%) | 1 / 115 (0.87%) | 1 / 82 (1.22%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Sepsis  |                 |                 |                |
| subjects affected / exposed                     | 3 / 133 (2.26%) | 1 / 115 (0.87%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 2 / 3           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0          |
| Lung infection                                  |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Abscess   |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 1 / 115 (0.87%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Anal abscess                                    |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Appendicitis                                    |                 |                 |                |
| subjects affected / exposed                     | 1 / 133 (0.75%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Arthropod-borne disease                         |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 1 / 115 (0.87%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Cellulitis                                      |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 1 / 82 (1.22%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Cholecystitis infective                         |                 |                 |                |



|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 1 / 133 (0.75%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Cystitis  |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Empyema   |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 1 / 82 (1.22%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Gastroenteritis                                 |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Infectious pleural effusion                     |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Influenza                                       |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Lower respiratory tract infection               |                 |                 |                |
| subjects affected / exposed                     | 1 / 133 (0.75%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Meningitis listeria                             |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 1 / 82 (1.22%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Neutropenic sepsis                              |                 |                 |                |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Oesophageal candidiasis                         |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 1 / 82 (1.22%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Otitis media                                    |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 1 / 82 (1.22%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Peritonitis                                     |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Pleural infection                               |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Respiratory tract infection                     |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 1 / 115 (0.87%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0          |
| Scrotal infection                               |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Septic shock                                    |                 |                 |                |
| subjects affected / exposed                     | 1 / 133 (0.75%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 1 / 1           | 0 / 0           | 0 / 0          |
| Streptococcal sepsis                            |                 |                 |                |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Toxic shock syndrome                            |                 |                 |                |
| subjects affected / exposed                     | 1 / 133 (0.75%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Urinary tract infection                         |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 1 / 82 (1.22%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Metabolism and nutrition disorders              |                 |                 |                |
| Dehydration                                     |                 |                 |                |
| subjects affected / exposed                     | 1 / 133 (0.75%) | 1 / 115 (0.87%) | 1 / 82 (1.22%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 1           | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Decreased appetite                              |                 |                 |                |
| subjects affected / exposed                     | 2 / 133 (1.50%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Hyponatraemia                                   |                 |                 |                |
| subjects affected / exposed                     | 1 / 133 (0.75%) | 1 / 115 (0.87%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Hypercalcaemia                                  |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 0 / 115 (0.00%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Hyperkalaemia                                   |                 |                 |                |
| subjects affected / exposed                     | 0 / 133 (0.00%) | 1 / 115 (0.87%) | 0 / 82 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |

|                               |                  |               |                  |
|-------------------------------|------------------|---------------|------------------|
| <b>Serious adverse events</b> | Arm D: Placebo + | Arm E: 260 mg | Arm F: Placebo + |
|-------------------------------|------------------|---------------|------------------|

|   | CPB              | pictilisib + CPB | CPB              |
|---|------------------|------------------|------------------|
| Total subjects affected by serious adverse events                   |                  |                  |                  |
| subjects affected / exposed   | 33 / 73 (45.21%) | 32 / 59 (54.24%) | 12 / 26 (46.15%) |
| number of deaths (all causes)                                       | 7                | 13               | 5                |
| number of deaths resulting from adverse events                      |                  |                  |                  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                  |                  |                  |
| Non-small cell lung cancer  |                  |                  |                  |
| subjects affected / exposed   | 3 / 73 (4.11%)   | 2 / 59 (3.39%)   | 1 / 26 (3.85%)   |
| occurrences causally related to treatment / all                     | 0 / 3            | 0 / 2            | 0 / 1            |
| deaths causally related to treatment / all                          | 0 / 3            | 0 / 2            | 0 / 1            |
| Lung neoplasm malignant   |                  |                  |                  |
| subjects affected / exposed   | 0 / 73 (0.00%)   | 0 / 59 (0.00%)   | 0 / 26 (0.00%)   |
| occurrences causally related to treatment / all                     | 0 / 0            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all                          | 0 / 0            | 0 / 0            | 0 / 0            |
| Metastases to meninges  |                  |                  |                  |
| subjects affected / exposed   | 1 / 73 (1.37%)   | 0 / 59 (0.00%)   | 0 / 26 (0.00%)   |
| occurrences causally related to treatment / all                     | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all                          | 0 / 0            | 0 / 0            | 0 / 0            |
| Metastatic pain   |                  |                  |                  |
| subjects affected / exposed   | 0 / 73 (0.00%)   | 0 / 59 (0.00%)   | 0 / 26 (0.00%)   |
| occurrences causally related to treatment / all                     | 0 / 0            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all                          | 0 / 0            | 0 / 0            | 0 / 0            |
| Vascular disorders  |                  |                  |                  |
| Hypotension   |                  |                  |                  |
| subjects affected / exposed   | 2 / 73 (2.74%)   | 0 / 59 (0.00%)   | 0 / 26 (0.00%)   |
| occurrences causally related to treatment / all                     | 0 / 3            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all                          | 0 / 0            | 0 / 0            | 0 / 0            |
| Deep vein thrombosis  |                  |                  |                  |
| subjects affected / exposed   | 0 / 73 (0.00%)   | 0 / 59 (0.00%)   | 0 / 26 (0.00%)   |
| occurrences causally related to treatment / all                     | 0 / 0            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all                          | 0 / 0            | 0 / 0            | 0 / 0            |
| Embolism  |                  |                  |                  |

|  |                |                |                |
|--|----------------|----------------|----------------|
| subjects affected / exposed                          | 0 / 73 (0.00%) | 1 / 59 (1.69%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 1 / 1          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Orthostatic hypotension                              |                |                |                |
| subjects affected / exposed                          | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Peripheral arterial occlusive disease                |                |                |                |
| subjects affected / exposed                          | 1 / 73 (1.37%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Phlebitis  |                |                |                |
| subjects affected / exposed                          | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| General disorders and administration site conditions |                |                |                |
| Pyrexia  |                |                |                |
| subjects affected / exposed                          | 4 / 73 (5.48%) | 1 / 59 (1.69%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 5          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Asthenia   |                |                |                |
| subjects affected / exposed                          | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 1 / 26 (3.85%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Death  |                |                |                |
| subjects affected / exposed                          | 0 / 73 (0.00%) | 2 / 59 (3.39%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 2          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 2          | 0 / 0          |
| Fatigue  |                |                |                |
| subjects affected / exposed                          | 0 / 73 (0.00%) | 1 / 59 (1.69%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| General physical health deterioration                |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 1 / 26 (3.85%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1          |
| Chest pain                                      |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Disease progression                             |                |                |                |
| subjects affected / exposed                     | 1 / 73 (1.37%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 0          |
| Malaise   |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Immune system disorders                         |                |                |                |
| Anaphylactic shock                              |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 59 (1.69%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Anaphylactic reaction                           |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Drug hypersensitivity                           |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 1 / 26 (3.85%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Hypersensitivity                                |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Respiratory, thoracic and mediastinal disorders |                |                |                |

|   |                |                |                |  |
|---|----------------|----------------|----------------|--|
| Pulmonary embolism                              |                |                |                |  |
| subjects affected / exposed                     | 1 / 73 (1.37%) | 4 / 59 (6.78%) | 2 / 26 (7.69%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 3 / 4          | 1 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1          |  |
| Dyspnoea  |                |                |                |  |
| subjects affected / exposed                     | 1 / 73 (1.37%) | 2 / 59 (3.39%) | 0 / 26 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 2          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |  |
| Pneumothorax                                    |                |                |                |  |
| subjects affected / exposed                     | 1 / 73 (1.37%) | 1 / 59 (1.69%) | 1 / 26 (3.85%) |  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 1          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |  |
| Pulmonary haemorrhage                           |                |                |                |  |
| subjects affected / exposed                     | 2 / 73 (2.74%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 3          | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 0          |  |
| Chronic obstructive pulmonary disease           |                |                |                |  |
| subjects affected / exposed                     | 1 / 73 (1.37%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |  |
| Haemoptysis                                     |                |                |                |  |
| subjects affected / exposed                     | 1 / 73 (1.37%) | 1 / 59 (1.69%) | 0 / 26 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 1 / 1          | 0 / 0          |  |
| Pneumonitis                                     |                |                |                |  |
| subjects affected / exposed                     | 2 / 73 (2.74%) | 0 / 59 (0.00%) | 1 / 26 (3.85%) |  |
| occurrences causally related to treatment / all | 2 / 2          | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |  |
| Respiratory failure                             |                |                |                |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 2 / 26 (7.69%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1          |  |
| Epistaxis                                       |                |                |                |  |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 59 (1.69%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Hypoxia   |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 1 / 26 (3.85%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pleuritic pain                                  |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pulmonary oedema                                |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Acquired tracheo-oesophageal fistula            |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Acute pulmonary oedema                          |                |                |                |
| subjects affected / exposed                     | 1 / 73 (1.37%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Acute respiratory failure                       |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Aspiration                                      |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 59 (1.69%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0          |
| Interstitial lung disease                       |                |                |                |



|  |                |                |                |
|--|----------------|----------------|----------------|
| subjects affected / exposed                                    | 1 / 73 (1.37%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all                | 1 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all                     | 0 / 0          | 0 / 0          | 0 / 0          |
| Oesophagobronchial fistula                                     |                |                |                |
| subjects affected / exposed                                    | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all                | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all                     | 0 / 0          | 0 / 0          | 0 / 0          |
| Pleural effusion   |                |                |                |
| subjects affected / exposed                                    | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 1 / 26 (3.85%) |
| occurrences causally related to treatment / all                | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all                     | 0 / 0          | 0 / 0          | 0 / 0          |
| Pneumonia aspiration   |                |                |                |
| subjects affected / exposed                                    | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all                | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all                     | 0 / 0          | 0 / 0          | 0 / 0          |
| Psychiatric disorders  |                |                |                |
| Delirium   |                |                |                |
| subjects affected / exposed                                    | 2 / 73 (2.74%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all                | 0 / 2          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all                     | 0 / 0          | 0 / 0          | 0 / 0          |
| Confusional state  |                |                |                |
| subjects affected / exposed                                    | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all                | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all                     | 0 / 0          | 0 / 0          | 0 / 0          |
| Hallucination  |                |                |                |
| subjects affected / exposed                                    | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all                | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all                     | 0 / 0          | 0 / 0          | 0 / 0          |
| Investigations   |                |                |                |
| Eastern cooperative oncology group performance status worsened |                |                |                |
| subjects affected / exposed                                    | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all                | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all                     | 0 / 0          | 0 / 0          | 0 / 0          |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Blood alkaline phosphatase increased            |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 59 (1.69%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Blood bilirubin increased                       |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 59 (1.69%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Neutrophil count decreased                      |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Injury, poisoning and procedural complications  |                |                |                |
| Fall  |                |                |                |
| subjects affected / exposed                     | 2 / 73 (2.74%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Hip fracture                                    |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Infusion related reaction                       |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Injury  |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Laceration                                      |                |                |                |
| subjects affected / exposed                     | 1 / 73 (1.37%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Poisoning                                       |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pulmonary contusion                             |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Radiation necrosis                              |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 59 (1.69%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Toxicity to various agents                      |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cardiac disorders                               |                |                |                |
| Acute coronary syndrome                         |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cardiopulmonary failure                         |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 59 (1.69%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0          |
| Myocardial infarction                           |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 59 (1.69%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Atrial fibrillation                             |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 1 / 26 (3.85%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Atrial flutter                                  |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 1 / 73 (1.37%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cardiac arrest                                  |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cardio-respiratory arrest                       |                |                |                |
| subjects affected / exposed                     | 1 / 73 (1.37%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 0          |
| Ventricular fibrillation                        |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 1 / 26 (3.85%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1          |
| Nervous system disorders                        |                |                |                |
| Cerebrovascular accident                        |                |                |                |
| subjects affected / exposed                     | 1 / 73 (1.37%) | 1 / 59 (1.69%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2          | 1 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Hemiparesis                                     |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cerebral amyloid angiopathy                     |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 1 / 26 (3.85%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cerebral ischaemia                              |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Decreased vibratory sense                       |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 1 / 73 (1.37%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Loss of proprioception                          |                |                |                |
| subjects affected / exposed                     | 1 / 73 (1.37%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Neuralgia                                       |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Orthostatic intolerance                         |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 59 (1.69%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Seizure   |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 59 (1.69%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Syncope   |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Transient ischaemic attack                      |                |                |                |
| subjects affected / exposed                     | 1 / 73 (1.37%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Blood and lymphatic system disorders            |                |                |                |
| Febrile neutropenia                             |                |                |                |
| subjects affected / exposed                     | 3 / 73 (4.11%) | 3 / 59 (5.08%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 3 / 3          | 3 / 3          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Anaemia   |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 1 / 73 (1.37%) | 1 / 59 (1.69%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Neutropenia                                     |                |                |                |
| subjects affected / exposed                     | 1 / 73 (1.37%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pancytopenia                                    |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 59 (1.69%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Febrile bone marrow aplasia                     |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Leukopenia                                      |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastrointestinal disorders                      |                |                |                |
| Diarrhoea                                       |                |                |                |
| subjects affected / exposed                     | 1 / 73 (1.37%) | 1 / 59 (1.69%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 1 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Vomiting  |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Nausea  |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Abdominal pain                                  |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Duodenal ulcer                                  |                |                |                |
| subjects affected / exposed                     | 1 / 73 (1.37%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Dysphagia                                       |                |                |                |
| subjects affected / exposed                     | 1 / 73 (1.37%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastrointestinal haemorrhage                    |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pneumatosis intestinalis                        |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 1 / 26 (3.85%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Upper gastrointestinal haemorrhage              |                |                |                |
| subjects affected / exposed                     | 1 / 73 (1.37%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Colitis   |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Constipation                                    |                |                |                |
| subjects affected / exposed                     | 1 / 73 (1.37%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Diverticular perforation                        |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Duodenal ulcer haemorrhage                      |                |                |                |
| subjects affected / exposed                     | 1 / 73 (1.37%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Duodenal ulcer perforation                      |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastric perforation                             |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 59 (1.69%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 1 / 1          | 0 / 0          |
| Gastrointestinal perforation                    |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 59 (1.69%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 1 / 1          | 0 / 0          |
| Haematemesis                                    |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Intestinal obstruction                          |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 59 (1.69%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0          |
| Oesophageal mass                                |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Rectal haemorrhage                              |                |                |                |



|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 1 / 26 (3.85%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Salivary gland calculus                         |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Hepatobiliary disorders                         |                |                |                |
| Cholecystitis acute                             |                |                |                |
| subjects affected / exposed                     | 1 / 73 (1.37%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cholelithiasis                                  |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Skin and subcutaneous tissue disorders          |                |                |                |
| Rash maculo-papular                             |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Rash macular                                    |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Dermatitis allergic                             |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 59 (1.69%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Rash  |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 59 (1.69%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Renal and urinary disorders                     |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Renal failure                                   |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 59 (1.69%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0          |
| Acute kidney injury                             |                |                |                |
| subjects affected / exposed                     | 1 / 73 (1.37%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Acute prerenal failure                          |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Bladder perforation                             |                |                |                |
| subjects affected / exposed                     | 1 / 73 (1.37%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Dysuria   |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Haematuria                                      |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 59 (1.69%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Renal colic                                     |                |                |                |
| subjects affected / exposed                     | 1 / 73 (1.37%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Renal impairment                                |                |                |                |
| subjects affected / exposed                     | 1 / 73 (1.37%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 0          |
| Urinary retention                               |                |                |                |

|  |                |                |                |
|--|----------------|----------------|----------------|
| subjects affected / exposed                            | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all        | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0          | 0 / 0          |
| <b>Musculoskeletal and connective tissue disorders</b> |                |                |                |
| Arthralgia   |                |                |                |
| subjects affected / exposed                            | 1 / 73 (1.37%) | 0 / 59 (0.00%) | 1 / 26 (3.85%) |
| occurrences causally related to treatment / all        | 0 / 1          | 0 / 0          | 0 / 2          |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0          | 0 / 0          |
| Muscular weakness                                      |                |                |                |
| subjects affected / exposed                            | 0 / 73 (0.00%) | 2 / 59 (3.39%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all        | 0 / 0          | 1 / 2          | 0 / 0          |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0          | 0 / 0          |
| Pain in extremity                                      |                |                |                |
| subjects affected / exposed                            | 0 / 73 (0.00%) | 1 / 59 (1.69%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all        | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0          | 0 / 0          |
| Musculoskeletal chest pain                             |                |                |                |
| subjects affected / exposed                            | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all        | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0          | 0 / 0          |
| Musculoskeletal pain                                   |                |                |                |
| subjects affected / exposed                            | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all        | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0          | 0 / 0          |
| Myalgia  |                |                |                |
| subjects affected / exposed                            | 1 / 73 (1.37%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all        | 1 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0          | 0 / 0          |
| Pathological fracture                                  |                |                |                |
| subjects affected / exposed                            | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all        | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0          | 0 / 0          |
| <b>Infections and infestations</b>                     |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Pneumonia                                       |                |                |                |
| subjects affected / exposed                     | 1 / 73 (1.37%) | 5 / 59 (8.47%) | 1 / 26 (3.85%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 5          | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 2          | 0 / 0          |
| Bronchitis                                      |                |                |                |
| subjects affected / exposed                     | 3 / 73 (4.11%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 7          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 0          |
| Sepsis  |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Lung infection                                  |                |                |                |
| subjects affected / exposed                     | 2 / 73 (2.74%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Abscess   |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Anal abscess                                    |                |                |                |
| subjects affected / exposed                     | 1 / 73 (1.37%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Appendicitis                                    |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Arthropod-borne disease                         |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cellulitis                                      |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cholecystitis infective                         |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cystitis  |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 59 (1.69%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Empyema   |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastroenteritis                                 |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 59 (1.69%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Infectious pleural effusion                     |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 1 / 26 (3.85%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 2 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Influenza                                       |                |                |                |
| subjects affected / exposed                     | 1 / 73 (1.37%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Lower respiratory tract infection               |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Meningitis listeria                             |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Neutropenic sepsis                              |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 59 (1.69%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Oesophageal candidiasis                         |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Otitis media                                    |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Peritonitis                                     |                |                |                |
| subjects affected / exposed                     | 1 / 73 (1.37%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 0          |
| Pleural infection                               |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 59 (1.69%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Respiratory tract infection                     |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Scrotal infection                               |                |                |                |
| subjects affected / exposed                     | 1 / 73 (1.37%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Septic shock                                    |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Streptococcal sepsis                            |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 59 (1.69%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0          |
| Toxic shock syndrome                            |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Urinary tract infection                         |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Metabolism and nutrition disorders              |                |                |                |
| Dehydration                                     |                |                |                |
| subjects affected / exposed                     | 3 / 73 (4.11%) | 2 / 59 (3.39%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 3 / 5          | 1 / 2          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Decreased appetite                              |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Hyponatraemia                                   |                |                |                |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Hypercalcaemia                                  |                |                |                |
| subjects affected / exposed                     | 1 / 73 (1.37%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Hyperkalaemia                                   |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 59 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

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

| <b>Non-serious adverse events</b>                     | Arm A: 340 mg pictilisib + CP | Arm B: Placebo + CP | Arm C: 340 mg pictilisib + CPB |
|---|-------------------------------|---------------------|--------------------------------|
| Total subjects affected by non-serious adverse events |                               |                     |                                |
| subjects affected / exposed                           | 122 / 133 (91.73%)            | 109 / 115 (94.78%)  | 81 / 82 (98.78%)               |
| Vascular disorders                                    |                               |                     |                                |
| Hypertension  |                               |                     |                                |
| subjects affected / exposed                           | 8 / 133 (6.02%)               | 7 / 115 (6.09%)     | 13 / 82 (15.85%)               |
| occurrences (all)                                     | 10                            | 10                  | 20                             |
| Hypotension   |                               |                     |                                |
| subjects affected / exposed                           | 8 / 133 (6.02%)               | 4 / 115 (3.48%)     | 1 / 82 (1.22%)                 |
| occurrences (all)                                     | 8                             | 7                   | 1                              |
| General disorders and administration site conditions  |                               |                     |                                |
| Fatigue   |                               |                     |                                |
| subjects affected / exposed                           | 33 / 133 (24.81%)             | 32 / 115 (27.83%)   | 30 / 82 (36.59%)               |
| occurrences (all)                                     | 53                            | 46                  | 58                             |
| Asthenia  |                               |                     |                                |
| subjects affected / exposed                           | 22 / 133 (16.54%)             | 24 / 115 (20.87%)   | 26 / 82 (31.71%)               |
| occurrences (all)                                     | 47                            | 37                  | 42                             |
| Pyrexia   |                               |                     |                                |
| subjects affected / exposed                           | 12 / 133 (9.02%)              | 9 / 115 (7.83%)     | 17 / 82 (20.73%)               |
| occurrences (all)                                     | 20                            | 10                  | 27                             |
| Chest pain  |                               |                     |                                |
| subjects affected / exposed                           | 12 / 133 (9.02%)              | 8 / 115 (6.96%)     | 7 / 82 (8.54%)                 |
| occurrences (all)                                     | 12                            | 10                  | 10                             |
| Mucosal inflammation                                  |                               |                     |                                |
| subjects affected / exposed                           | 9 / 133 (6.77%)               | 1 / 115 (0.87%)     | 9 / 82 (10.98%)                |
| occurrences (all)                                     | 11                            | 1                   | 17                             |
| Oedema peripheral                                     |                               |                     |                                |
| subjects affected / exposed                           | 5 / 133 (3.76%)               | 8 / 115 (6.96%)     | 9 / 82 (10.98%)                |
| occurrences (all)                                     | 7                             | 12                  | 11                             |



|   |                   |                   |                  |
|---|-------------------|-------------------|------------------|
| Pain  |                   |                   |                  |
| subjects affected / exposed                     | 6 / 133 (4.51%)   | 10 / 115 (8.70%)  | 5 / 82 (6.10%)   |
| occurrences (all)                               | 6                 | 11                | 6                |
| Chills  |                   |                   |                  |
| subjects affected / exposed                     | 3 / 133 (2.26%)   | 1 / 115 (0.87%)   | 6 / 82 (7.32%)   |
| occurrences (all)                               | 4                 | 1                 | 7                |
| Non-cardiac chest pain                          |                   |                   |                  |
| subjects affected / exposed                     | 0 / 133 (0.00%)   | 6 / 115 (5.22%)   | 1 / 82 (1.22%)   |
| occurrences (all)                               | 0                 | 6                 | 1                |
| Influenza like illness                          |                   |                   |                  |
| subjects affected / exposed                     | 3 / 133 (2.26%)   | 2 / 115 (1.74%)   | 1 / 82 (1.22%)   |
| occurrences (all)                               | 4                 | 3                 | 1                |
| General physical health deterioration           |                   |                   |                  |
| subjects affected / exposed                     | 0 / 133 (0.00%)   | 2 / 115 (1.74%)   | 1 / 82 (1.22%)   |
| occurrences (all)                               | 0                 | 2                 | 1                |
| Respiratory, thoracic and mediastinal disorders |                   |                   |                  |
| Cough   |                   |                   |                  |
| subjects affected / exposed                     | 22 / 133 (16.54%) | 26 / 115 (22.61%) | 21 / 82 (25.61%) |
| occurrences (all)                               | 28                | 33                | 31               |
| Dyspnoea  |                   |                   |                  |
| subjects affected / exposed                     | 20 / 133 (15.04%) | 21 / 115 (18.26%) | 18 / 82 (21.95%) |
| occurrences (all)                               | 24                | 24                | 25               |
| Epistaxis                                       |                   |                   |                  |
| subjects affected / exposed                     | 4 / 133 (3.01%)   | 5 / 115 (4.35%)   | 23 / 82 (28.05%) |
| occurrences (all)                               | 4                 | 5                 | 34               |
| Dysphonia                                       |                   |                   |                  |
| subjects affected / exposed                     | 4 / 133 (3.01%)   | 4 / 115 (3.48%)   | 8 / 82 (9.76%)   |
| occurrences (all)                               | 4                 | 4                 | 8                |
| Haemoptysis                                     |                   |                   |                  |
| subjects affected / exposed                     | 5 / 133 (3.76%)   | 5 / 115 (4.35%)   | 3 / 82 (3.66%)   |
| occurrences (all)                               | 6                 | 6                 | 4                |
| Productive cough                                |                   |                   |                  |
| subjects affected / exposed                     | 2 / 133 (1.50%)   | 6 / 115 (5.22%)   | 3 / 82 (3.66%)   |
| occurrences (all)                               | 4                 | 6                 | 3                |
| Oropharyngeal pain                              |                   |                   |                  |

|  |                        |                        |                        |
|--|------------------------|------------------------|------------------------|
| subjects affected / exposed<br>occurrences (all)                             | 5 / 133 (3.76%)<br>9   | 1 / 115 (0.87%)<br>1   | 5 / 82 (6.10%)<br>5    |
| Dyspnoea exertional<br>subjects affected / exposed<br>occurrences (all)      | 2 / 133 (1.50%)<br>2   | 2 / 115 (1.74%)<br>2   | 3 / 82 (3.66%)<br>3    |
| Pleural effusion<br>subjects affected / exposed<br>occurrences (all)         | 3 / 133 (2.26%)<br>3   | 4 / 115 (3.48%)<br>4   | 0 / 82 (0.00%)<br>0    |
| Hiccups<br>subjects affected / exposed<br>occurrences (all)                  | 1 / 133 (0.75%)<br>1   | 1 / 115 (0.87%)<br>1   | 0 / 82 (0.00%)<br>0    |
| Rhinorrhoea<br>subjects affected / exposed<br>occurrences (all)              | 0 / 133 (0.00%)<br>0   | 1 / 115 (0.87%)<br>1   | 1 / 82 (1.22%)<br>1    |
| Pulmonary embolism<br>subjects affected / exposed<br>occurrences (all)       | 0 / 133 (0.00%)<br>0   | 0 / 115 (0.00%)<br>0   | 2 / 82 (2.44%)<br>2    |
| Psychiatric disorders  |                        |                        |                        |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)                 | 9 / 133 (6.77%)<br>9   | 11 / 115 (9.57%)<br>13 | 14 / 82 (17.07%)<br>14 |
| Depression<br>subjects affected / exposed<br>occurrences (all)               | 3 / 133 (2.26%)<br>3   | 7 / 115 (6.09%)<br>7   | 6 / 82 (7.32%)<br>6    |
| Anxiety<br>subjects affected / exposed<br>occurrences (all)                  | 4 / 133 (3.01%)<br>4   | 4 / 115 (3.48%)<br>4   | 4 / 82 (4.88%)<br>4    |
| Investigations   |                        |                        |                        |
| Weight decreased<br>subjects affected / exposed<br>occurrences (all)         | 13 / 133 (9.77%)<br>17 | 9 / 115 (7.83%)<br>10  | 18 / 82 (21.95%)<br>19 |
| Platelet count decreased<br>subjects affected / exposed<br>occurrences (all) | 11 / 133 (8.27%)<br>17 | 4 / 115 (3.48%)<br>12  | 6 / 82 (7.32%)<br>7    |
| Alanine aminotransferase increased   |                        |                        |                        |

|  |                   |                   |                  |
|--|-------------------|-------------------|------------------|
| subjects affected / exposed                    | 10 / 133 (7.52%)  | 9 / 115 (7.83%)   | 1 / 82 (1.22%)   |
| occurrences (all)                              | 16                | 11                | 1                |
| Aspartate aminotransferase increased           |                   |                   |                  |
| subjects affected / exposed                    | 7 / 133 (5.26%)   | 7 / 115 (6.09%)   | 1 / 82 (1.22%)   |
| occurrences (all)                              | 9                 | 11                | 1                |
| Neutrophil count decreased                     |                   |                   |                  |
| subjects affected / exposed                    | 7 / 133 (5.26%)   | 3 / 115 (2.61%)   | 2 / 82 (2.44%)   |
| occurrences (all)                              | 14                | 3                 | 2                |
| White blood cell count decreased               |                   |                   |                  |
| subjects affected / exposed                    | 2 / 133 (1.50%)   | 5 / 115 (4.35%)   | 2 / 82 (2.44%)   |
| occurrences (all)                              | 2                 | 7                 | 5                |
| Blood alkaline phosphatase increased           |                   |                   |                  |
| subjects affected / exposed                    | 3 / 133 (2.26%)   | 0 / 115 (0.00%)   | 1 / 82 (1.22%)   |
| occurrences (all)                              | 3                 | 0                 | 2                |
| Blood bilirubin increased                      |                   |                   |                  |
| subjects affected / exposed                    | 3 / 133 (2.26%)   | 0 / 115 (0.00%)   | 3 / 82 (3.66%)   |
| occurrences (all)                              | 4                 | 0                 | 5                |
| Injury, poisoning and procedural complications |                   |                   |                  |
| Fall   |                   |                   |                  |
| subjects affected / exposed                    | 2 / 133 (1.50%)   | 1 / 115 (0.87%)   | 3 / 82 (3.66%)   |
| occurrences (all)                              | 2                 | 1                 | 3                |
| Cardiac disorders                              |                   |                   |                  |
| Sinus tachycardia                              |                   |                   |                  |
| subjects affected / exposed                    | 2 / 133 (1.50%)   | 2 / 115 (1.74%)   | 1 / 82 (1.22%)   |
| occurrences (all)                              | 3                 | 2                 | 1                |
| Nervous system disorders                       |                   |                   |                  |
| Neuropathy peripheral                          |                   |                   |                  |
| subjects affected / exposed                    | 23 / 133 (17.29%) | 18 / 115 (15.65%) | 17 / 82 (20.73%) |
| occurrences (all)                              | 32                | 21                | 25               |
| Dizziness                                      |                   |                   |                  |
| subjects affected / exposed                    | 17 / 133 (12.78%) | 11 / 115 (9.57%)  | 12 / 82 (14.63%) |
| occurrences (all)                              | 18                | 12                | 14               |
| Headache                                       |                   |                   |                  |
| subjects affected / exposed                    | 10 / 133 (7.52%)  | 10 / 115 (8.70%)  | 9 / 82 (10.98%)  |
| occurrences (all)                              | 13                | 16                | 20               |
| Peripheral sensory neuropathy                  |                   |                   |                  |

|                                      |                   |                   |                  |
|--------------------------------------|-------------------|-------------------|------------------|
| subjects affected / exposed          | 16 / 133 (12.03%) | 13 / 115 (11.30%) | 13 / 82 (15.85%) |
| occurrences (all)                    | 20                | 17                | 22               |
| Paraesthesia                         |                   |                   |                  |
| subjects affected / exposed          | 13 / 133 (9.77%)  | 12 / 115 (10.43%) | 8 / 82 (9.76%)   |
| occurrences (all)                    | 19                | 20                | 10               |
| Dysgeusia                            |                   |                   |                  |
| subjects affected / exposed          | 13 / 133 (9.77%)  | 6 / 115 (5.22%)   | 12 / 82 (14.63%) |
| occurrences (all)                    | 13                | 6                 | 12               |
| Hypoaesthesia                        |                   |                   |                  |
| subjects affected / exposed          | 8 / 133 (6.02%)   | 5 / 115 (4.35%)   | 1 / 82 (1.22%)   |
| occurrences (all)                    | 8                 | 8                 | 2                |
| Polyneuropathy                       |                   |                   |                  |
| subjects affected / exposed          | 1 / 133 (0.75%)   | 0 / 115 (0.00%)   | 3 / 82 (3.66%)   |
| occurrences (all)                    | 6                 | 0                 | 4                |
| Tremor                               |                   |                   |                  |
| subjects affected / exposed          | 2 / 133 (1.50%)   | 2 / 115 (1.74%)   | 2 / 82 (2.44%)   |
| occurrences (all)                    | 2                 | 2                 | 2                |
| Blood and lymphatic system disorders |                   |                   |                  |
| Anaemia                              |                   |                   |                  |
| subjects affected / exposed          | 43 / 133 (32.33%) | 39 / 115 (33.91%) | 19 / 82 (23.17%) |
| occurrences (all)                    | 66                | 66                | 21               |
| Neutropenia                          |                   |                   |                  |
| subjects affected / exposed          | 31 / 133 (23.31%) | 35 / 115 (30.43%) | 23 / 82 (28.05%) |
| occurrences (all)                    | 50                | 60                | 40               |
| Thrombocytopenia                     |                   |                   |                  |
| subjects affected / exposed          | 23 / 133 (17.29%) | 12 / 115 (10.43%) | 14 / 82 (17.07%) |
| occurrences (all)                    | 40                | 21                | 29               |
| Leukopenia                           |                   |                   |                  |
| subjects affected / exposed          | 5 / 133 (3.76%)   | 5 / 115 (4.35%)   | 9 / 82 (10.98%)  |
| occurrences (all)                    | 5                 | 6                 | 15               |
| Lymphopenia                          |                   |                   |                  |
| subjects affected / exposed          | 2 / 133 (1.50%)   | 2 / 115 (1.74%)   | 1 / 82 (1.22%)   |
| occurrences (all)                    | 5                 | 2                 | 1                |
| Eye disorders                        |                   |                   |                  |
| Vision blurred                       |                   |                   |                  |

|  |                      |                      |                     |
|--|----------------------|----------------------|---------------------|
| subjects affected / exposed<br>occurrences (all) | 1 / 133 (0.75%)<br>1 | 5 / 115 (4.35%)<br>6 | 4 / 82 (4.88%)<br>4 |
| Gastrointestinal disorders                       |                      |                      |                     |
| Diarrhoea  |                      |                      |                     |
| subjects affected / exposed                      | 41 / 133 (30.83%)    | 19 / 115 (16.52%)    | 44 / 82 (53.66%)    |
| occurrences (all)                                | 85                   | 28                   | 120                 |
| Nausea   |                      |                      |                     |
| subjects affected / exposed                      | 35 / 133 (26.32%)    | 29 / 115 (25.22%)    | 46 / 82 (56.10%)    |
| occurrences (all)                                | 59                   | 45                   | 96                  |
| Vomiting   |                      |                      |                     |
| subjects affected / exposed                      | 27 / 133 (20.30%)    | 15 / 115 (13.04%)    | 28 / 82 (34.15%)    |
| occurrences (all)                                | 41                   | 20                   | 63                  |
| Constipation                                     |                      |                      |                     |
| subjects affected / exposed                      | 19 / 133 (14.29%)    | 22 / 115 (19.13%)    | 19 / 82 (23.17%)    |
| occurrences (all)                                | 22                   | 32                   | 24                  |
| Abdominal pain                                   |                      |                      |                     |
| subjects affected / exposed                      | 9 / 133 (6.77%)      | 3 / 115 (2.61%)      | 9 / 82 (10.98%)     |
| occurrences (all)                                | 10                   | 3                    | 26                  |
| Abdominal pain upper                             |                      |                      |                     |
| subjects affected / exposed                      | 7 / 133 (5.26%)      | 5 / 115 (4.35%)      | 9 / 82 (10.98%)     |
| occurrences (all)                                | 8                    | 5                    | 10                  |
| Stomatitis                                       |                      |                      |                     |
| subjects affected / exposed                      | 11 / 133 (8.27%)     | 2 / 115 (1.74%)      | 11 / 82 (13.41%)    |
| occurrences (all)                                | 13                   | 2                    | 15                  |
| Dyspepsia  |                      |                      |                     |
| subjects affected / exposed                      | 7 / 133 (5.26%)      | 5 / 115 (4.35%)      | 8 / 82 (9.76%)      |
| occurrences (all)                                | 13                   | 5                    | 8                   |
| Dysphagia  |                      |                      |                     |
| subjects affected / exposed                      | 5 / 133 (3.76%)      | 2 / 115 (1.74%)      | 6 / 82 (7.32%)      |
| occurrences (all)                                | 5                    | 3                    | 6                   |
| Haemorrhoids                                     |                      |                      |                     |
| subjects affected / exposed                      | 0 / 133 (0.00%)      | 1 / 115 (0.87%)      | 5 / 82 (6.10%)      |
| occurrences (all)                                | 0                    | 1                    | 7                   |
| Paraesthesia oral                                |                      |                      |                     |
| subjects affected / exposed                      | 0 / 133 (0.00%)      | 0 / 115 (0.00%)      | 0 / 82 (0.00%)      |
| occurrences (all)                                | 0                    | 0                    | 0                   |

|   |                   |                   |                  |
|---|-------------------|-------------------|------------------|
| Skin and subcutaneous tissue disorders          |                   |                   |                  |
| Alopecia  |                   |                   |                  |
| subjects affected / exposed                     | 42 / 133 (31.58%) | 43 / 115 (37.39%) | 34 / 82 (41.46%) |
| occurrences (all)                               | 51                | 48                | 47               |
| Pruritus  |                   |                   |                  |
| subjects affected / exposed                     | 14 / 133 (10.53%) | 6 / 115 (5.22%)   | 14 / 82 (17.07%) |
| occurrences (all)                               | 19                | 6                 | 18               |
| Rash maculo-papular                             |                   |                   |                  |
| subjects affected / exposed                     | 18 / 133 (13.53%) | 3 / 115 (2.61%)   | 14 / 82 (17.07%) |
| occurrences (all)                               | 45                | 4                 | 31               |
| Dry skin  |                   |                   |                  |
| subjects affected / exposed                     | 7 / 133 (5.26%)   | 3 / 115 (2.61%)   | 13 / 82 (15.85%) |
| occurrences (all)                               | 7                 | 3                 | 17               |
| Rash macular                                    |                   |                   |                  |
| subjects affected / exposed                     | 11 / 133 (8.27%)  | 0 / 115 (0.00%)   | 13 / 82 (15.85%) |
| occurrences (all)                               | 14                | 0                 | 16               |
| Rash papular                                    |                   |                   |                  |
| subjects affected / exposed                     | 13 / 133 (9.77%)  | 3 / 115 (2.61%)   | 7 / 82 (8.54%)   |
| occurrences (all)                               | 16                | 3                 | 12               |
| Erythema  |                   |                   |                  |
| subjects affected / exposed                     | 8 / 133 (6.02%)   | 2 / 115 (1.74%)   | 6 / 82 (7.32%)   |
| occurrences (all)                               | 9                 | 2                 | 6                |
| Rash  |                   |                   |                  |
| subjects affected / exposed                     | 6 / 133 (4.51%)   | 1 / 115 (0.87%)   | 3 / 82 (3.66%)   |
| occurrences (all)                               | 8                 | 1                 | 4                |
| Decubitus ulcer                                 |                   |                   |                  |
| subjects affected / exposed                     | 1 / 133 (0.75%)   | 2 / 115 (1.74%)   | 0 / 82 (0.00%)   |
| occurrences (all)                               | 1                 | 2                 | 0                |
| Renal and urinary disorders                     |                   |                   |                  |
| Proteinuria                                     |                   |                   |                  |
| subjects affected / exposed                     | 0 / 133 (0.00%)   | 0 / 115 (0.00%)   | 5 / 82 (6.10%)   |
| occurrences (all)                               | 0                 | 0                 | 8                |
| Renal failure                                   |                   |                   |                  |
| subjects affected / exposed                     | 1 / 133 (0.75%)   | 0 / 115 (0.00%)   | 0 / 82 (0.00%)   |
| occurrences (all)                               | 2                 | 0                 | 0                |
| Musculoskeletal and connective tissue disorders |                   |                   |                  |

|                             |                   |                   |                  |
|-----------------------------|-------------------|-------------------|------------------|
| Arthralgia                  |                   |                   |                  |
| subjects affected / exposed | 26 / 133 (19.55%) | 22 / 115 (19.13%) | 21 / 82 (25.61%) |
| occurrences (all)           | 33                | 35                | 28               |
| Myalgia                     |                   |                   |                  |
| subjects affected / exposed | 13 / 133 (9.77%)  | 15 / 115 (13.04%) | 13 / 82 (15.85%) |
| occurrences (all)           | 17                | 15                | 16               |
| Pain in extremity           |                   |                   |                  |
| subjects affected / exposed | 17 / 133 (12.78%) | 9 / 115 (7.83%)   | 11 / 82 (13.41%) |
| occurrences (all)           | 29                | 14                | 13               |
| Back pain                   |                   |                   |                  |
| subjects affected / exposed | 6 / 133 (4.51%)   | 9 / 115 (7.83%)   | 14 / 82 (17.07%) |
| occurrences (all)           | 6                 | 9                 | 18               |
| Musculoskeletal pain        |                   |                   |                  |
| subjects affected / exposed | 5 / 133 (3.76%)   | 3 / 115 (2.61%)   | 12 / 82 (14.63%) |
| occurrences (all)           | 5                 | 3                 | 14               |
| Bone pain                   |                   |                   |                  |
| subjects affected / exposed | 4 / 133 (3.01%)   | 4 / 115 (3.48%)   | 5 / 82 (6.10%)   |
| occurrences (all)           | 5                 | 8                 | 6                |
| Muscular weakness           |                   |                   |                  |
| subjects affected / exposed | 4 / 133 (3.01%)   | 5 / 115 (4.35%)   | 4 / 82 (4.88%)   |
| occurrences (all)           | 5                 | 5                 | 7                |
| Neck pain                   |                   |                   |                  |
| subjects affected / exposed | 0 / 133 (0.00%)   | 1 / 115 (0.87%)   | 2 / 82 (2.44%)   |
| occurrences (all)           | 0                 | 1                 | 2                |
| Pain in jaw                 |                   |                   |                  |
| subjects affected / exposed | 1 / 133 (0.75%)   | 0 / 115 (0.00%)   | 0 / 82 (0.00%)   |
| occurrences (all)           | 1                 | 0                 | 0                |
| Groin pain                  |                   |                   |                  |
| subjects affected / exposed | 0 / 133 (0.00%)   | 0 / 115 (0.00%)   | 1 / 82 (1.22%)   |
| occurrences (all)           | 0                 | 0                 | 1                |
| Infections and infestations |                   |                   |                  |
| Urinary tract infection     |                   |                   |                  |
| subjects affected / exposed | 4 / 133 (3.01%)   | 4 / 115 (3.48%)   | 11 / 82 (13.41%) |
| occurrences (all)           | 4                 | 4                 | 13               |
| Nasopharyngitis             |                   |                   |                  |

|   |                         |                         |                        |
|---|-------------------------|-------------------------|------------------------|
| subjects affected / exposed<br>occurrences (all)                                      | 1 / 133 (0.75%)<br>1    | 3 / 115 (2.61%)<br>3    | 4 / 82 (4.88%)<br>4    |
| Bronchitis<br>subjects affected / exposed<br>occurrences (all)                        | 4 / 133 (3.01%)<br>5    | 5 / 115 (4.35%)<br>6    | 3 / 82 (3.66%)<br>8    |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 4 / 133 (3.01%)<br>5    | 4 / 115 (3.48%)<br>4    | 4 / 82 (4.88%)<br>5    |
| Rhinitis<br>subjects affected / exposed<br>occurrences (all)                          | 3 / 133 (2.26%)<br>3    | 0 / 115 (0.00%)<br>0    | 5 / 82 (6.10%)<br>7    |
| Pneumonia<br>subjects affected / exposed<br>occurrences (all)                         | 5 / 133 (3.76%)<br>5    | 4 / 115 (3.48%)<br>4    | 0 / 82 (0.00%)<br>0    |
| Sinusitis<br>subjects affected / exposed<br>occurrences (all)                         | 1 / 133 (0.75%)<br>1    | 1 / 115 (0.87%)<br>1    | 4 / 82 (4.88%)<br>4    |
| Metabolism and nutrition disorders  |                         |                         |                        |
| Decreased appetite<br>subjects affected / exposed<br>occurrences (all)                | 29 / 133 (21.80%)<br>34 | 20 / 115 (17.39%)<br>27 | 29 / 82 (35.37%)<br>36 |
| Dehydration<br>subjects affected / exposed<br>occurrences (all)                       | 8 / 133 (6.02%)<br>10   | 12 / 115 (10.43%)<br>16 | 8 / 82 (9.76%)<br>8    |
| Hyperglycaemia<br>subjects affected / exposed<br>occurrences (all)                    | 16 / 133 (12.03%)<br>26 | 14 / 115 (12.17%)<br>23 | 6 / 82 (7.32%)<br>16   |
| Hypomagnesaemia<br>subjects affected / exposed<br>occurrences (all)                   | 10 / 133 (7.52%)<br>11  | 5 / 115 (4.35%)<br>5    | 5 / 82 (6.10%)<br>8    |
| Hypokalaemia<br>subjects affected / exposed<br>occurrences (all)                      | 9 / 133 (6.77%)<br>14   | 3 / 115 (2.61%)<br>4    | 7 / 82 (8.54%)<br>12   |
| Hyponatraemia<br>subjects affected / exposed<br>occurrences (all)                     | 5 / 133 (3.76%)<br>6    | 3 / 115 (2.61%)<br>4    | 3 / 82 (3.66%)<br>5    |



|   |                      |                      |                     |
|---|----------------------|----------------------|---------------------|
| Hypocalcaemia<br>subjects affected / exposed<br>occurrences (all) | 2 / 133 (1.50%)<br>3 | 0 / 115 (0.00%)<br>0 | 3 / 82 (3.66%)<br>4 |
|---|----------------------|----------------------|---------------------|

| <b>Non-serious adverse events</b>  | Arm D: Placebo + CPB   | Arm E: 260 mg pictilisib + CPB | Arm F: Placebo + CPB  |
|--|------------------------|--------------------------------|-----------------------|
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed | 71 / 73 (97.26%)       | 55 / 59 (93.22%)               | 25 / 26 (96.15%)      |
| Vascular disorders   |                        |                                |                       |
| Hypertension<br>subjects affected / exposed<br>occurrences (all)                     | 11 / 73 (15.07%)<br>14 | 11 / 59 (18.64%)<br>12         | 1 / 26 (3.85%)<br>1   |
| Hypotension<br>subjects affected / exposed<br>occurrences (all)                      | 2 / 73 (2.74%)<br>2    | 2 / 59 (3.39%)<br>6            | 1 / 26 (3.85%)<br>1   |
| General disorders and administration site conditions                                 |                        |                                |                       |
| Fatigue<br>subjects affected / exposed<br>occurrences (all)                          | 21 / 73 (28.77%)<br>32 | 21 / 59 (35.59%)<br>34         | 9 / 26 (34.62%)<br>20 |
| Asthenia<br>subjects affected / exposed<br>occurrences (all)                         | 20 / 73 (27.40%)<br>38 | 18 / 59 (30.51%)<br>33         | 5 / 26 (19.23%)<br>5  |
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)                          | 7 / 73 (9.59%)<br>7    | 11 / 59 (18.64%)<br>14         | 2 / 26 (7.69%)<br>2   |
| Chest pain<br>subjects affected / exposed<br>occurrences (all)                       | 12 / 73 (16.44%)<br>13 | 0 / 59 (0.00%)<br>0            | 1 / 26 (3.85%)<br>1   |
| Mucosal inflammation<br>subjects affected / exposed<br>occurrences (all)             | 3 / 73 (4.11%)<br>3    | 5 / 59 (8.47%)<br>5            | 2 / 26 (7.69%)<br>2   |
| Oedema peripheral<br>subjects affected / exposed<br>occurrences (all)                | 2 / 73 (2.74%)<br>3    | 2 / 59 (3.39%)<br>3            | 3 / 26 (11.54%)<br>3  |
| Pain<br>subjects affected / exposed<br>occurrences (all)                             | 2 / 73 (2.74%)<br>2    | 2 / 59 (3.39%)<br>2            | 2 / 26 (7.69%)<br>2   |

|   |                  |                  |                 |
|---|------------------|------------------|-----------------|
| Chills  |                  |                  |                 |
| subjects affected / exposed                     | 5 / 73 (6.85%)   | 2 / 59 (3.39%)   | 0 / 26 (0.00%)  |
| occurrences (all)                               | 6                | 2                | 0               |
| Non-cardiac chest pain                          |                  |                  |                 |
| subjects affected / exposed                     | 2 / 73 (2.74%)   | 2 / 59 (3.39%)   | 2 / 26 (7.69%)  |
| occurrences (all)                               | 2                | 4                | 2               |
| Influenza like illness                          |                  |                  |                 |
| subjects affected / exposed                     | 0 / 73 (0.00%)   | 3 / 59 (5.08%)   | 1 / 26 (3.85%)  |
| occurrences (all)                               | 0                | 3                | 1               |
| General physical health deterioration           |                  |                  |                 |
| subjects affected / exposed                     | 0 / 73 (0.00%)   | 3 / 59 (5.08%)   | 0 / 26 (0.00%)  |
| occurrences (all)                               | 0                | 3                | 0               |
| Respiratory, thoracic and mediastinal disorders |                  |                  |                 |
| Cough   |                  |                  |                 |
| subjects affected / exposed                     | 16 / 73 (21.92%) | 11 / 59 (18.64%) | 6 / 26 (23.08%) |
| occurrences (all)                               | 21               | 15               | 7               |
| Dyspnoea  |                  |                  |                 |
| subjects affected / exposed                     | 11 / 73 (15.07%) | 9 / 59 (15.25%)  | 7 / 26 (26.92%) |
| occurrences (all)                               | 17               | 12               | 11              |
| Epistaxis                                       |                  |                  |                 |
| subjects affected / exposed                     | 18 / 73 (24.66%) | 16 / 59 (27.12%) | 7 / 26 (26.92%) |
| occurrences (all)                               | 24               | 18               | 8               |
| Dysphonia                                       |                  |                  |                 |
| subjects affected / exposed                     | 4 / 73 (5.48%)   | 4 / 59 (6.78%)   | 2 / 26 (7.69%)  |
| occurrences (all)                               | 6                | 4                | 2               |
| Haemoptysis                                     |                  |                  |                 |
| subjects affected / exposed                     | 8 / 73 (10.96%)  | 1 / 59 (1.69%)   | 3 / 26 (11.54%) |
| occurrences (all)                               | 10               | 1                | 3               |
| Productive cough                                |                  |                  |                 |
| subjects affected / exposed                     | 7 / 73 (9.59%)   | 1 / 59 (1.69%)   | 0 / 26 (0.00%)  |
| occurrences (all)                               | 14               | 1                | 0               |
| Oropharyngeal pain                              |                  |                  |                 |
| subjects affected / exposed                     | 3 / 73 (4.11%)   | 2 / 59 (3.39%)   | 0 / 26 (0.00%)  |
| occurrences (all)                               | 3                | 3                | 0               |
| Dyspnoea exertional                             |                  |                  |                 |

|                                      |                  |                 |                 |
|--------------------------------------|------------------|-----------------|-----------------|
| subjects affected / exposed          | 1 / 73 (1.37%)   | 2 / 59 (3.39%)  | 2 / 26 (7.69%)  |
| occurrences (all)                    | 1                | 2               | 2               |
| Pleural effusion                     |                  |                 |                 |
| subjects affected / exposed          | 0 / 73 (0.00%)   | 3 / 59 (5.08%)  | 0 / 26 (0.00%)  |
| occurrences (all)                    | 0                | 3               | 0               |
| Hiccups                              |                  |                 |                 |
| subjects affected / exposed          | 3 / 73 (4.11%)   | 3 / 59 (5.08%)  | 1 / 26 (3.85%)  |
| occurrences (all)                    | 4                | 3               | 1               |
| Rhinorrhoea                          |                  |                 |                 |
| subjects affected / exposed          | 2 / 73 (2.74%)   | 3 / 59 (5.08%)  | 1 / 26 (3.85%)  |
| occurrences (all)                    | 2                | 3               | 1               |
| Pulmonary embolism                   |                  |                 |                 |
| subjects affected / exposed          | 4 / 73 (5.48%)   | 1 / 59 (1.69%)  | 0 / 26 (0.00%)  |
| occurrences (all)                    | 4                | 1               | 0               |
| Psychiatric disorders                |                  |                 |                 |
| Insomnia                             |                  |                 |                 |
| subjects affected / exposed          | 10 / 73 (13.70%) | 5 / 59 (8.47%)  | 4 / 26 (15.38%) |
| occurrences (all)                    | 13               | 6               | 5               |
| Depression                           |                  |                 |                 |
| subjects affected / exposed          | 5 / 73 (6.85%)   | 6 / 59 (10.17%) | 2 / 26 (7.69%)  |
| occurrences (all)                    | 6                | 6               | 2               |
| Anxiety                              |                  |                 |                 |
| subjects affected / exposed          | 8 / 73 (10.96%)  | 3 / 59 (5.08%)  | 1 / 26 (3.85%)  |
| occurrences (all)                    | 10               | 6               | 1               |
| Investigations                       |                  |                 |                 |
| Weight decreased                     |                  |                 |                 |
| subjects affected / exposed          | 10 / 73 (13.70%) | 9 / 59 (15.25%) | 5 / 26 (19.23%) |
| occurrences (all)                    | 12               | 16              | 5               |
| Platelet count decreased             |                  |                 |                 |
| subjects affected / exposed          | 3 / 73 (4.11%)   | 3 / 59 (5.08%)  | 2 / 26 (7.69%)  |
| occurrences (all)                    | 4                | 6               | 2               |
| Alanine aminotransferase increased   |                  |                 |                 |
| subjects affected / exposed          | 2 / 73 (2.74%)   | 2 / 59 (3.39%)  | 3 / 26 (11.54%) |
| occurrences (all)                    | 2                | 2               | 4               |
| Aspartate aminotransferase increased |                  |                 |                 |

|  |                        |                        |                      |
|--|------------------------|------------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)   | 2 / 73 (2.74%)<br>6    | 2 / 59 (3.39%)<br>2    | 4 / 26 (15.38%)<br>5 |
| Neutrophil count decreased<br>subjects affected / exposed<br>occurrences (all)                             | 1 / 73 (1.37%)<br>1    | 4 / 59 (6.78%)<br>5    | 1 / 26 (3.85%)<br>1  |
| White blood cell count decreased<br>subjects affected / exposed<br>occurrences (all)                       | 0 / 73 (0.00%)<br>0    | 2 / 59 (3.39%)<br>3    | 2 / 26 (7.69%)<br>2  |
| Blood alkaline phosphatase increased<br>subjects affected / exposed<br>occurrences (all)                   | 2 / 73 (2.74%)<br>2    | 3 / 59 (5.08%)<br>3    | 0 / 26 (0.00%)<br>0  |
| Blood bilirubin increased<br>subjects affected / exposed<br>occurrences (all)                              | 0 / 73 (0.00%)<br>0    | 3 / 59 (5.08%)<br>3    | 0 / 26 (0.00%)<br>0  |
| Injury, poisoning and procedural complications<br>Fall<br>subjects affected / exposed<br>occurrences (all) | 5 / 73 (6.85%)<br>6    | 2 / 59 (3.39%)<br>2    | 1 / 26 (3.85%)<br>1  |
| Cardiac disorders<br>Sinus tachycardia<br>subjects affected / exposed<br>occurrences (all)                 | 2 / 73 (2.74%)<br>2    | 1 / 59 (1.69%)<br>1    | 2 / 26 (7.69%)<br>2  |
| Nervous system disorders<br>Neuropathy peripheral<br>subjects affected / exposed<br>occurrences (all)      | 17 / 73 (23.29%)<br>19 | 6 / 59 (10.17%)<br>8   | 6 / 26 (23.08%)<br>8 |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)  | 11 / 73 (15.07%)<br>12 | 7 / 59 (11.86%)<br>10  | 7 / 26 (26.92%)<br>9 |
| Headache<br>subjects affected / exposed<br>occurrences (all)   | 11 / 73 (15.07%)<br>15 | 15 / 59 (25.42%)<br>18 | 4 / 26 (15.38%)<br>7 |
| Peripheral sensory neuropathy<br>subjects affected / exposed<br>occurrences (all)                          | 4 / 73 (5.48%)<br>6    | 7 / 59 (11.86%)<br>10  | 3 / 26 (11.54%)<br>5 |
| Paraesthesia   |                        |                        |                      |

|                                      |                  |                  |                 |
|--------------------------------------|------------------|------------------|-----------------|
| subjects affected / exposed          | 7 / 73 (9.59%)   | 8 / 59 (13.56%)  | 1 / 26 (3.85%)  |
| occurrences (all)                    | 11               | 9                | 2               |
| Dysgeusia                            |                  |                  |                 |
| subjects affected / exposed          | 4 / 73 (5.48%)   | 13 / 59 (22.03%) | 0 / 26 (0.00%)  |
| occurrences (all)                    | 4                | 18               | 0               |
| Hypoaesthesia                        |                  |                  |                 |
| subjects affected / exposed          | 1 / 73 (1.37%)   | 4 / 59 (6.78%)   | 0 / 26 (0.00%)  |
| occurrences (all)                    | 1                | 5                | 0               |
| Polyneuropathy                       |                  |                  |                 |
| subjects affected / exposed          | 2 / 73 (2.74%)   | 6 / 59 (10.17%)  | 1 / 26 (3.85%)  |
| occurrences (all)                    | 4                | 8                | 1               |
| Tremor                               |                  |                  |                 |
| subjects affected / exposed          | 1 / 73 (1.37%)   | 5 / 59 (8.47%)   | 0 / 26 (0.00%)  |
| occurrences (all)                    | 2                | 5                | 0               |
| Blood and lymphatic system disorders |                  |                  |                 |
| Anaemia                              |                  |                  |                 |
| subjects affected / exposed          | 11 / 73 (15.07%) | 9 / 59 (15.25%)  | 7 / 26 (26.92%) |
| occurrences (all)                    | 23               | 20               | 15              |
| Neutropenia                          |                  |                  |                 |
| subjects affected / exposed          | 15 / 73 (20.55%) | 13 / 59 (22.03%) | 8 / 26 (30.77%) |
| occurrences (all)                    | 25               | 21               | 10              |
| Thrombocytopenia                     |                  |                  |                 |
| subjects affected / exposed          | 7 / 73 (9.59%)   | 5 / 59 (8.47%)   | 3 / 26 (11.54%) |
| occurrences (all)                    | 13               | 5                | 3               |
| Leukopenia                           |                  |                  |                 |
| subjects affected / exposed          | 3 / 73 (4.11%)   | 2 / 59 (3.39%)   | 2 / 26 (7.69%)  |
| occurrences (all)                    | 4                | 2                | 2               |
| Lymphopenia                          |                  |                  |                 |
| subjects affected / exposed          | 0 / 73 (0.00%)   | 1 / 59 (1.69%)   | 2 / 26 (7.69%)  |
| occurrences (all)                    | 0                | 3                | 4               |
| Eye disorders                        |                  |                  |                 |
| Vision blurred                       |                  |                  |                 |
| subjects affected / exposed          | 2 / 73 (2.74%)   | 3 / 59 (5.08%)   | 1 / 26 (3.85%)  |
| occurrences (all)                    | 3                | 3                | 1               |
| Gastrointestinal disorders           |                  |                  |                 |

|  |                  |                  |                 |
|--|------------------|------------------|-----------------|
| Diarrhoea                              |                  |                  |                 |
| subjects affected / exposed            | 28 / 73 (38.36%) | 29 / 59 (49.15%) | 9 / 26 (34.62%) |
| occurrences (all)                      | 39               | 48               | 11              |
| Nausea                                 |                  |                  |                 |
| subjects affected / exposed            | 23 / 73 (31.51%) | 25 / 59 (42.37%) | 6 / 26 (23.08%) |
| occurrences (all)                      | 33               | 34               | 9               |
| Vomiting                               |                  |                  |                 |
| subjects affected / exposed            | 18 / 73 (24.66%) | 16 / 59 (27.12%) | 4 / 26 (15.38%) |
| occurrences (all)                      | 30               | 27               | 4               |
| Constipation                           |                  |                  |                 |
| subjects affected / exposed            | 21 / 73 (28.77%) | 14 / 59 (23.73%) | 9 / 26 (34.62%) |
| occurrences (all)                      | 27               | 17               | 9               |
| Abdominal pain                         |                  |                  |                 |
| subjects affected / exposed            | 9 / 73 (12.33%)  | 3 / 59 (5.08%)   | 4 / 26 (15.38%) |
| occurrences (all)                      | 12               | 3                | 5               |
| Abdominal pain upper                   |                  |                  |                 |
| subjects affected / exposed            | 8 / 73 (10.96%)  | 6 / 59 (10.17%)  | 2 / 26 (7.69%)  |
| occurrences (all)                      | 9                | 6                | 2               |
| Stomatitis                             |                  |                  |                 |
| subjects affected / exposed            | 3 / 73 (4.11%)   | 8 / 59 (13.56%)  | 2 / 26 (7.69%)  |
| occurrences (all)                      | 5                | 11               | 7               |
| Dyspepsia                              |                  |                  |                 |
| subjects affected / exposed            | 6 / 73 (8.22%)   | 5 / 59 (8.47%)   | 3 / 26 (11.54%) |
| occurrences (all)                      | 7                | 13               | 3               |
| Dysphagia                              |                  |                  |                 |
| subjects affected / exposed            | 2 / 73 (2.74%)   | 3 / 59 (5.08%)   | 0 / 26 (0.00%)  |
| occurrences (all)                      | 2                | 3                | 0               |
| Haemorrhoids                           |                  |                  |                 |
| subjects affected / exposed            | 1 / 73 (1.37%)   | 1 / 59 (1.69%)   | 1 / 26 (3.85%)  |
| occurrences (all)                      | 1                | 1                | 1               |
| Paraesthesia oral                      |                  |                  |                 |
| subjects affected / exposed            | 0 / 73 (0.00%)   | 0 / 59 (0.00%)   | 2 / 26 (7.69%)  |
| occurrences (all)                      | 0                | 0                | 2               |
| Skin and subcutaneous tissue disorders |                  |                  |                 |
| Alopecia                               |                  |                  |                 |

|  |                        |                        |                        |
|--|------------------------|------------------------|------------------------|
| subjects affected / exposed<br>occurrences (all) | 27 / 73 (36.99%)<br>34 | 14 / 59 (23.73%)<br>19 | 10 / 26 (38.46%)<br>11 |
| Pruritus   |                        |                        |                        |
| subjects affected / exposed<br>occurrences (all) | 10 / 73 (13.70%)<br>11 | 6 / 59 (10.17%)<br>7   | 2 / 26 (7.69%)<br>2    |
| Rash maculo-papular                              |                        |                        |                        |
| subjects affected / exposed<br>occurrences (all) | 4 / 73 (5.48%)<br>9    | 8 / 59 (13.56%)<br>19  | 0 / 26 (0.00%)<br>0    |
| Dry skin   |                        |                        |                        |
| subjects affected / exposed<br>occurrences (all) | 4 / 73 (5.48%)<br>4    | 5 / 59 (8.47%)<br>5    | 2 / 26 (7.69%)<br>2    |
| Rash macular                                     |                        |                        |                        |
| subjects affected / exposed<br>occurrences (all) | 1 / 73 (1.37%)<br>1    | 5 / 59 (8.47%)<br>9    | 2 / 26 (7.69%)<br>2    |
| Rash papular                                     |                        |                        |                        |
| subjects affected / exposed<br>occurrences (all) | 0 / 73 (0.00%)<br>0    | 4 / 59 (6.78%)<br>6    | 2 / 26 (7.69%)<br>2    |
| Erythema   |                        |                        |                        |
| subjects affected / exposed<br>occurrences (all) | 4 / 73 (5.48%)<br>5    | 4 / 59 (6.78%)<br>4    | 0 / 26 (0.00%)<br>0    |
| Rash   |                        |                        |                        |
| subjects affected / exposed<br>occurrences (all) | 2 / 73 (2.74%)<br>2    | 9 / 59 (15.25%)<br>11  | 1 / 26 (3.85%)<br>1    |
| Decubitus ulcer                                  |                        |                        |                        |
| subjects affected / exposed<br>occurrences (all) | 0 / 73 (0.00%)<br>0    | 4 / 59 (6.78%)<br>4    | 0 / 26 (0.00%)<br>0    |
| Renal and urinary disorders                      |                        |                        |                        |
| Proteinuria                                      |                        |                        |                        |
| subjects affected / exposed<br>occurrences (all) | 5 / 73 (6.85%)<br>15   | 4 / 59 (6.78%)<br>7    | 4 / 26 (15.38%)<br>4   |
| Renal failure                                    |                        |                        |                        |
| subjects affected / exposed<br>occurrences (all) | 1 / 73 (1.37%)<br>1    | 0 / 59 (0.00%)<br>0    | 2 / 26 (7.69%)<br>3    |
| Musculoskeletal and connective tissue disorders  |                        |                        |                        |

|                             |                  |                  |                 |
|-----------------------------|------------------|------------------|-----------------|
| Arthralgia                  |                  |                  |                 |
| subjects affected / exposed | 12 / 73 (16.44%) | 15 / 59 (25.42%) | 6 / 26 (23.08%) |
| occurrences (all)           | 21               | 16               | 9               |
| Myalgia                     |                  |                  |                 |
| subjects affected / exposed | 6 / 73 (8.22%)   | 8 / 59 (13.56%)  | 5 / 26 (19.23%) |
| occurrences (all)           | 15               | 9                | 6               |
| Pain in extremity           |                  |                  |                 |
| subjects affected / exposed | 9 / 73 (12.33%)  | 11 / 59 (18.64%) | 1 / 26 (3.85%)  |
| occurrences (all)           | 13               | 17               | 2               |
| Back pain                   |                  |                  |                 |
| subjects affected / exposed | 9 / 73 (12.33%)  | 5 / 59 (8.47%)   | 4 / 26 (15.38%) |
| occurrences (all)           | 11               | 6                | 9               |
| Musculoskeletal pain        |                  |                  |                 |
| subjects affected / exposed | 5 / 73 (6.85%)   | 3 / 59 (5.08%)   | 0 / 26 (0.00%)  |
| occurrences (all)           | 6                | 3                | 0               |
| Bone pain                   |                  |                  |                 |
| subjects affected / exposed | 7 / 73 (9.59%)   | 5 / 59 (8.47%)   | 2 / 26 (7.69%)  |
| occurrences (all)           | 12               | 5                | 4               |
| Muscular weakness           |                  |                  |                 |
| subjects affected / exposed | 1 / 73 (1.37%)   | 6 / 59 (10.17%)  | 3 / 26 (11.54%) |
| occurrences (all)           | 3                | 9                | 3               |
| Neck pain                   |                  |                  |                 |
| subjects affected / exposed | 5 / 73 (6.85%)   | 0 / 59 (0.00%)   | 0 / 26 (0.00%)  |
| occurrences (all)           | 5                | 0                | 0               |
| Pain in jaw                 |                  |                  |                 |
| subjects affected / exposed | 1 / 73 (1.37%)   | 3 / 59 (5.08%)   | 0 / 26 (0.00%)  |
| occurrences (all)           | 1                | 4                | 0               |
| Groin pain                  |                  |                  |                 |
| subjects affected / exposed | 0 / 73 (0.00%)   | 3 / 59 (5.08%)   | 0 / 26 (0.00%)  |
| occurrences (all)           | 0                | 3                | 0               |
| Infections and infestations |                  |                  |                 |
| Urinary tract infection     |                  |                  |                 |
| subjects affected / exposed | 3 / 73 (4.11%)   | 7 / 59 (11.86%)  | 0 / 26 (0.00%)  |
| occurrences (all)           | 3                | 11               | 0               |
| Nasopharyngitis             |                  |                  |                 |



|   |                        |                        |                        |
|---|------------------------|------------------------|------------------------|
| subjects affected / exposed<br>occurrences (all)                                      | 4 / 73 (5.48%)<br>5    | 6 / 59 (10.17%)<br>7   | 4 / 26 (15.38%)<br>5   |
| Bronchitis<br>subjects affected / exposed<br>occurrences (all)                        | 3 / 73 (4.11%)<br>3    | 2 / 59 (3.39%)<br>2    | 2 / 26 (7.69%)<br>2    |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 0 / 73 (0.00%)<br>0    | 4 / 59 (6.78%)<br>4    | 0 / 26 (0.00%)<br>0    |
| Rhinitis<br>subjects affected / exposed<br>occurrences (all)                          | 2 / 73 (2.74%)<br>2    | 4 / 59 (6.78%)<br>5    | 0 / 26 (0.00%)<br>0    |
| Pneumonia<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 73 (0.00%)<br>0    | 1 / 59 (1.69%)<br>1    | 2 / 26 (7.69%)<br>2    |
| Sinusitis<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 73 (0.00%)<br>0    | 3 / 59 (5.08%)<br>3    | 0 / 26 (0.00%)<br>0    |
| Metabolism and nutrition disorders  |                        |                        |                        |
| Decreased appetite<br>subjects affected / exposed<br>occurrences (all)                | 16 / 73 (21.92%)<br>16 | 23 / 59 (38.98%)<br>32 | 11 / 26 (42.31%)<br>14 |
| Dehydration<br>subjects affected / exposed<br>occurrences (all)                       | 7 / 73 (9.59%)<br>10   | 10 / 59 (16.95%)<br>17 | 4 / 26 (15.38%)<br>7   |
| Hyperglycaemia<br>subjects affected / exposed<br>occurrences (all)                    | 1 / 73 (1.37%)<br>1    | 6 / 59 (10.17%)<br>15  | 4 / 26 (15.38%)<br>8   |
| Hypomagnesaemia<br>subjects affected / exposed<br>occurrences (all)                   | 2 / 73 (2.74%)<br>2    | 8 / 59 (13.56%)<br>10  | 0 / 26 (0.00%)<br>0    |
| Hypokalaemia<br>subjects affected / exposed<br>occurrences (all)                      | 3 / 73 (4.11%)<br>3    | 5 / 59 (8.47%)<br>8    | 2 / 26 (7.69%)<br>2    |
| Hyponatraemia<br>subjects affected / exposed<br>occurrences (all)                     | 4 / 73 (5.48%)<br>4    | 2 / 59 (3.39%)<br>2    | 3 / 26 (11.54%)<br>3   |

|   |                     |                     |                     |
|---|---------------------|---------------------|---------------------|
| Hypocalcaemia<br>subjects affected / exposed<br>occurrences (all) | 2 / 73 (2.74%)<br>2 | 1 / 59 (1.69%)<br>1 | 2 / 26 (7.69%)<br>4 |
|---|---------------------|---------------------|---------------------|

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment   |
|------------------|---|
| 06 February 2012 | One inclusion criterion was modified to require all subjects to continue the use of contraception for 6 months after the last dose of paclitaxel and the duration of follow-up of female patients for pregnancy events was modified to be consistent with the use of contraception for 6 months after paclitaxel exposure. The schedule of assessments was changed to add pregnancy testing of female patients of childbearing potential prior to each cycle of study treatment. A criterion was added to exclude subjects with active inflammatory diseases that require immunosuppressants, including small or large intestine inflammation such as Crohn's disease or ulcerative colitis. The contraindication of therapeutic warfarin use with GDC-0941 and bevacizumab has been removed from the exclusion criterion and the list of excluded medications.   |
| 15 January 2013  | The study design was modified to include the evaluation of pictilisib at a dose of 260 mg in subjects with non-squamous NSCLC. The risks associated with pictilisib was updated with new safety information. Modifications to the Inclusion/Exclusion criteria were added: 1) subjects with a history of carcinoma in situ were to be allowed to enroll in study, 2) exclusion of subjects with epidermal growth factor receptor (EGFR) mutation was limited to those whose mutation is associated with response to tyrosine kinase inhibitors. Triplicate 12-lead electrocardiogram (ECG) assessments were replaced with single 12-lead ECGs. Subjects with the following adverse events (AEs) of special interest were to be monitored and evaluated closely for their response to clinical intervention: Grade 4 or symptomatic Grade 3 hyperglycemia, Grade 3 rash, or Grade 2 pneumonitis. The statistical methods were modified to reflect the changes to the study design. |
| 19 December 2013 | In order to have sufficient number of subjects to assess PFS in the PIK3CA amplified subgroup (co-primary endpoint), the total number of subjects in Arms A and B was increased from 146 to approximately 250 subjects with squamous NSCLC to take into account a higher percentage of subject tumor samples being unevaluable with the phosphoinositide 3-kinase (PI3K) fluorescence in situ hybridisation (FISH) assay. Further clarification around exclusion criteria was provided as follows: Exclusion: Active inflammatory diseases that require immunosuppressants, including small or large intestine inflammation, such as Crohn's or ulcerative colitis. Subjects receiving immunosuppressants were considered to have active disease and were not allowed.  |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported