



## Clinical trial results:

### A 3-Arm Phase 2 Double-Blind Randomized Study of Gemcitabine, Abraxane® plus Placebo versus Gemcitabine, Abraxane® plus 1 or 2 Truncated Courses of Demcizumab in Subjects with 1st-Line Metastatic Pancreatic Ductal Adenocarcinoma

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2014-003355-56 |
| Trial protocol           | ES GB BE       |
| Global end of trial date | 08 May 2017    |

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 07 December 2017 |
| First version publication date | 07 December 2017 |

#### Trial information

##### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | M18-006 |
|-----------------------|---------|

##### Additional study identifiers

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

Notes:

#### Sponsors

|                              |                                                                                                              |
|------------------------------|--------------------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | OncoMed Pharmaceuticals, Inc                                                                                 |
| Sponsor organisation address | 800 Chesapeake Drive, Redwood City, CA, United States, 94063                                                 |
| Public contact               | Robert Stagg, VP, Clinical Research, OncoMed Pharmaceuticals, Inc., +1 925 3239548, Robert.stagg@oncomed.com |
| Scientific contact           | Robert Stagg, VP, Clinical Research, OncoMed Pharmaceuticals, Inc., +1 925 3239548, Robert.stagg@oncomed.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                       | 19 July 2017 |
| Is this the analysis of the primary completion data? | Yes          |
| Primary completion date                              | 08 May 2017  |
| Global end of trial reached?                         | Yes          |
| Global end of trial date                             | 08 May 2017  |
| Was the trial ended prematurely?                     | Yes          |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study was to compare the efficacy of placebo/placebo arm to the pooled demcizumab arm (i.e., placebo/placebo arm to demcizumab/placebo and demcizumab/demcizumab arms) in subjects with first-line metastatic pancreatic ductal adenocarcinoma.

Protection of trial subjects:

Subjects experiencing a Grade 2 infusion reaction of dyspnea (asymptomatic bronchospasm) or generalized urticaria should be premedicated prior to subsequent infusions. Premedications may include medications such as corticosteroids, diphenhydramine, and/or bronchodilators as indicated. If an infusion reaction occurred, administration was stopped and appropriate medical care was administered. Once the infusion reaction was resolved, and at investigator discretion, the infusion was resumed at one-half of the initial rate of infusion. All subsequent infusions for that subject were then administered at the reduced rate of infusion.

Background therapy:

Subjects who received adjuvant hormonal therapy, such as tamoxifen for a history of breast cancer, continued to receive this treatment. A deep venous thrombosis prophylaxis during a hospitalization according to institutional standards was permitted.

Evidence for comparator: -

|                                                           |                  |
|-----------------------------------------------------------|------------------|
| Actual start date of recruitment                          | 31 December 2014 |
| 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 | Australia: 56     |
| Country: Number of subjects enrolled | Canada: 12        |
| Country: Number of subjects enrolled | United States: 50 |
| Country: Number of subjects enrolled | Spain: 71         |
| Country: Number of subjects enrolled | United Kingdom: 9 |
| Country: Number of subjects enrolled | Belgium: 6        |
| Worldwide total number of subjects   | 204               |
| EEA total number of subjects         | 86                |

Notes:

### Subjects enrolled per age group

|          |   |
|----------|---|
| In utero | 0 |
|----------|---|

|                                           |     |
|-------------------------------------------|-----|
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 0   |
| Adolescents (12-17 years)                 | 0   |
| Adults (18-64 years)                      | 100 |
| From 65 to 84 years                       | 103 |
| 85 years and over                         | 1   |

## Subject disposition

### Recruitment

Recruitment details:

Subjects aged  $\geq 21$  years with cytologically or histologically confirmed metastatic pancreatic ductal adenocarcinoma were included. Prior chemotherapy and/or radiotherapy either in the adjuvant or neoadjuvant setting or for metastatic disease was not allowed.

### Pre-assignment

Screening details:

Prior to randomization, subjects underwent screening to determine study eligibility. Screening assessments were to include CT scans of the chest, abdomen, and pelvis, as well as MRI of the brain. CT scan of the neck or bone scan was performed if clinically indicated.

### Period 1

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

Blinding implementation details:

This was a Phase 2, randomized, double-blind controlled study. Placebo was a clear to slightly opalescent, colorless to slightly yellow liquid formulation of 50 mM histidine, 100 mM sodium chloride, 45 mM sucrose, and 0.01% (v/v) polysorbate-20, pH 6.0.

### Arms

|                              |                     |
|------------------------------|---------------------|
| Are arms mutually exclusive? | Yes                 |
| <b>Arm title</b>             | Placebo/placebo arm |

Arm description:

Abraxane and gemcitabine plus placebo (3 cycles), Abraxane and gemcitabine (3 cycles), Abraxane and gemcitabine plus placebo (3 cycles), and then Abraxane and gemcitabine until disease progression.

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

Dosage and administration details:

Placebo was a clear to slightly opalescent, colorless to slightly yellow liquid formulation of 50 mM histidine, 100 mM sodium chloride, 45 mM sucrose, and 0.01% (v/v) polysorbate-20, pH 6.0.

|                  |                    |
|------------------|--------------------|
| <b>Arm title</b> | Demcizumab/placebo |
|------------------|--------------------|

Arm description:

Abraxane and gemcitabine plus demcizumab (3 cycles), Abraxane and gemcitabine (3 cycles), Abraxane and gemcitabine plus placebo (3 cycles), and then Abraxane and gemcitabine until disease progression.

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

Dosage and administration details:

Demcizumab 3.5 mg/kg (or placebo) was administered once every 2 weeks for 6 doses (i.e., the last dose was given on Day 70). A second course of demcizumab 3.5 mg/kg or placebo was administered once every 2 weeks for 6 doses starting at Day 168 if the subject's Day 168 BNP was  $\leq 100$  pg/mL, peak tricuspid velocity was  $\leq 3.0$  m/s, and LVEF was  $\geq 50\%$ , and the subject had not developed pulmonary

hypertension or heart failure while on study. No dose reductions were allowed for required modifications of demcizumab/placebo dosing.

Demcizumab was supplied at a concentration of 10 mg/mL in a 25-mL single-use glass vial filled to 20 mL to deliver a total of 200 mg per vial.

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

Dosage and administration details:

Placebo was a clear to slightly opalescent, colorless to slightly yellow liquid formulation of 50 mM histidine, 100 mM sodium chloride, 45 mM sucrose, and 0.01% (v/v) polysorbate-20, pH 6.0.

|                  |                       |
|------------------|-----------------------|
| <b>Arm title</b> | Demcizumab/demcizumab |
|------------------|-----------------------|

Arm description:

Abraxane and gemcitabine plus demcizumab (3 cycles), Abraxane and gemcitabine (3 cycles), Abraxane and gemcitabine plus demcizumab (3 cycles), and then Abraxane and gemcitabine until disease progression.

|                                        |                                       |
|----------------------------------------|---------------------------------------|
| Arm type                               | Experimental                          |
| Investigational medicinal product name | Demcizumab                            |
| Investigational medicinal product code |                                       |
| Other name                             |                                       |
| Pharmaceutical forms                   | Concentrate for solution for infusion |
| Routes of administration               | Intravenous use                       |

Dosage and administration details:

Demcizumab 3.5 mg/kg (or placebo) was administered once every 2 weeks for 6 doses (i.e., the last dose was given on Day 70). A second course of demcizumab 3.5 mg/kg or placebo was administered once every 2 weeks for 6 doses starting at Day 168 if the subject's Day 168 BNP was  $\leq 100$  pg/mL, peak tricuspid velocity was  $\leq 3.0$  m/s, and LVEF was  $\geq 50\%$ , and the subject had not developed pulmonary hypertension or heart failure while on study. No dose reductions were allowed for required modifications of demcizumab/placebo dosing.

Demcizumab was supplied at a concentration of 10 mg/mL in a 25-mL single-use glass vial filled to 20 mL to deliver a total of 200 mg per vial.

| <b>Number of subjects in period 1</b> | Placebo/placebo arm | Demcizumab/placebo | Demcizumab/demcizumab |
|---------------------------------------|---------------------|--------------------|-----------------------|
| Started                               | 68                  | 71                 | 65                    |
| Completed                             | 16                  | 18                 | 9                     |
| Not completed                         | 52                  | 53                 | 56                    |
| Use of other anticancer therapy       | -                   | -                  | 1                     |
| Physician decision                    | 2                   | 5                  | 2                     |
| Consent withdrawn by subject          | -                   | 4                  | 1                     |
| Disease progression                   | 34                  | 28                 | 34                    |
| Adverse event, non-fatal              | 3                   | 5                  | 5                     |
| Death                                 | 5                   | 4                  | 3                     |
| Other                                 | 8                   | 7                  | 10                    |



## Baseline characteristics

### Reporting groups

|                                                                                                                                                                                                                                             |                       |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| Reporting group title                                                                                                                                                                                                                       | Placebo/placebo arm   |
| Reporting group description:<br>Abraxane and gemcitabine plus placebo (3 cycles), Abraxane and gemcitabine (3 cycles), Abraxane and gemcitabine plus placebo (3 cycles), and then Abraxane and gemcitabine until disease progression.       |                       |
| Reporting group title                                                                                                                                                                                                                       | Demcizumab/placebo    |
| Reporting group description:<br>Abraxane and gemcitabine plus demcizumab (3 cycles), Abraxane and gemcitabine (3 cycles), Abraxane and gemcitabine plus placebo (3 cycles), and then Abraxane and gemcitabine until disease progression.    |                       |
| Reporting group title                                                                                                                                                                                                                       | Demcizumab/demcizumab |
| Reporting group description:<br>Abraxane and gemcitabine plus demcizumab (3 cycles), Abraxane and gemcitabine (3 cycles), Abraxane and gemcitabine plus demcizumab (3 cycles), and then Abraxane and gemcitabine until disease progression. |                       |

| Reporting group values                             | Placebo/placebo arm | Demcizumab/placebo | Demcizumab/demcizumab |
|----------------------------------------------------|---------------------|--------------------|-----------------------|
| Number of subjects                                 | 68                  | 71                 | 65                    |
| Age categorical<br>Units: Subjects                 |                     |                    |                       |
| In utero                                           | 0                   | 0                  | 0                     |
| Preterm newborn infants (gestational age < 37 wks) | 0                   | 0                  | 0                     |
| Newborns (0-27 days)                               | 0                   | 0                  | 0                     |
| Infants and toddlers (28 days-23 months)           | 0                   | 0                  | 0                     |
| Children (2-11 years)                              | 0                   | 0                  | 0                     |
| Adolescents (12-17 years)                          | 0                   | 0                  | 0                     |
| Adults (18-64 years)                               | 37                  | 34                 | 30                    |
| From 65-84 years                                   | 31                  | 36                 | 35                    |
| 85 years and over                                  | 0                   | 1                  | 0                     |
| Gender categorical<br>Units: Subjects              |                     |                    |                       |
| Female                                             | 27                  | 31                 | 30                    |
| Male                                               | 41                  | 40                 | 35                    |

| Reporting group values                             | Total |  |  |
|----------------------------------------------------|-------|--|--|
| Number of subjects                                 | 204   |  |  |
| Age categorical<br>Units: Subjects                 |       |  |  |
| In utero                                           | 0     |  |  |
| Preterm newborn infants (gestational age < 37 wks) | 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)                               | 101   |  |  |
| From 65-84 years                                   | 102   |  |  |

|                   |   |  |  |
|-------------------|---|--|--|
| 85 years and over | 1 |  |  |
|-------------------|---|--|--|

|                                       |     |  |  |
|---------------------------------------|-----|--|--|
| Gender categorical<br>Units: Subjects |     |  |  |
| Female                                | 88  |  |  |
| Male                                  | 116 |  |  |

### Subject analysis sets

|                            |                    |
|----------------------------|--------------------|
| Subject analysis set title | ITT analysis set   |
| Subject analysis set type  | Intention-to-treat |

Subject analysis set description:

The ITT population comprised all subjects who received at least 1 partial or complete dose of demcizumab or placebo. All baseline characteristics and demographic, efficacy, immunogenicity, and biomarker data were analyzed using the ITT population.

|                                                                                                                                                                                                                                                           |                  |  |  |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|--|--|
| <b>Reporting group values</b>                                                                                                                                                                                                                             | ITT analysis set |  |  |
| Number of subjects                                                                                                                                                                                                                                        | 204              |  |  |
| Age categorical<br>Units: Subjects                                                                                                                                                                                                                        |                  |  |  |
| In utero<br>Preterm newborn infants (gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over |                  |  |  |
| Gender categorical<br>Units: Subjects                                                                                                                                                                                                                     |                  |  |  |
| Female                                                                                                                                                                                                                                                    | 88               |  |  |
| Male                                                                                                                                                                                                                                                      | 116              |  |  |

## End points

### End points reporting groups

|                                                                                                                                                                                                                                                                                              |                       |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| Reporting group title                                                                                                                                                                                                                                                                        | Placebo/placebo arm   |
| Reporting group description:<br>Abraxane and gemcitabine plus placebo (3 cycles), Abraxane and gemcitabine (3 cycles), Abraxane and gemcitabine plus placebo (3 cycles), and then Abraxane and gemcitabine until disease progression.                                                        |                       |
| Reporting group title                                                                                                                                                                                                                                                                        | Demcizumab/placebo    |
| Reporting group description:<br>Abraxane and gemcitabine plus demcizumab (3 cycles), Abraxane and gemcitabine (3 cycles), Abraxane and gemcitabine plus placebo (3 cycles), and then Abraxane and gemcitabine until disease progression.                                                     |                       |
| Reporting group title                                                                                                                                                                                                                                                                        | Demcizumab/demcizumab |
| Reporting group description:<br>Abraxane and gemcitabine plus demcizumab (3 cycles), Abraxane and gemcitabine (3 cycles), Abraxane and gemcitabine plus demcizumab (3 cycles), and then Abraxane and gemcitabine until disease progression.                                                  |                       |
| Subject analysis set title                                                                                                                                                                                                                                                                   | ITT analysis set      |
| Subject analysis set type                                                                                                                                                                                                                                                                    | Intention-to-treat    |
| Subject analysis set description:<br>The ITT population comprised all subjects who received at least 1 partial or complete dose of demcizumab or placebo. All baseline characteristics and demographic, efficacy, immunogenicity, and biomarker data were analyzed using the ITT population. |                       |

### Primary: To compare the hazard of progression in the placebo/placebo arm and the pooled demcizumab arm

|                                                                                                                                                                                                                                                                                                                                                             |                                                                                               |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                             | To compare the hazard of progression in the placebo/placebo arm and the pooled demcizumab arm |
| End point description:<br>The primary endpoint is to compare the hazard of progression using the investigator-assessed progression-free survival (PFS) time between subjects in the placebo/placebo arm and the pooled demcizumab arm (i.e., demcizumab/placebo arm + demcizumab/demcizumab arm) in first-line metastatic pancreatic ductal adenocarcinoma. |                                                                                               |
| End point type                                                                                                                                                                                                                                                                                                                                              | Primary                                                                                       |
| End point timeframe:<br>Investigator-assessed progression-free survival (PFS) time.                                                                                                                                                                                                                                                                         |                                                                                               |

| End point values                            | Placebo/placebo arm | Demcizumab/placebo | Demcizumab/demcizumab |  |
|---------------------------------------------|---------------------|--------------------|-----------------------|--|
| Subject group type                          | Reporting group     | Reporting group    | Reporting group       |  |
| Number of subjects analysed                 | 68                  | 71                 | 65                    |  |
| Units: progression-free survival (PFS) time |                     |                    |                       |  |
| number (not applicable)                     | 68                  | 71                 | 65                    |  |

### Statistical analyses

|                                                                                                                                       |                                               |
|---------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|
| Statistical analysis title                                                                                                            | Statistical analysis plan dated 08 March 2017 |
| Statistical analysis description:<br>Efficacy was compared of placebo/placebo arm to the pooled demcizumab arm (i.e., placebo/placebo |                                               |

arm to demcizumab/placebo and demcizumab/demcizumab arms) in subjects with first-line metastatic pancreatic ductal adenocarcinoma.

|                                         |                                                                  |
|-----------------------------------------|------------------------------------------------------------------|
| Comparison groups                       | Demcizumab/placebo v Demcizumab/demcizumab v Placebo/placebo arm |
| Number of subjects included in analysis | 204                                                              |
| Analysis specification                  | Pre-specified                                                    |
| Analysis type                           | superiority <sup>[1]</sup>                                       |
| P-value                                 | = 0.7158                                                         |
| Method                                  | Wilcoxon (Mann-Whitney)                                          |
| Parameter estimate                      | Hazard ratio (HR)                                                |
| Confidence interval                     |                                                                  |
| level                                   | 95 %                                                             |
| sides                                   | 2-sided                                                          |
| lower limit                             | 3.81                                                             |
| upper limit                             | 7.36                                                             |
| Variability estimate                    | Standard deviation                                               |

Notes:

[1] - Gemcitabine was administered by intravenous (IV) infusion at a dose of 1000 mg/m<sup>2</sup> on Days 1, 8, and 15 of each 28-day treatment cycle. Abraxane was administered by IV infusion at a dose of 125 mg/m<sup>2</sup> over 30 minutes on Days 1, 8, and 15 of each 28-day treatment cycle. Demcizumab 3.5 mg/kg or placebo was administered by IV infusion (prior to the administration of Abraxane and gemcitabine) once every 2 weeks for either 1 or 2 70-day courses.

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Investigators were required to follow their respective IRB or IEC requirements for the reporting of serious adverse events (SAEs)

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

### Dictionary used

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

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

### Reporting groups

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | Placebo/placebo |
|-----------------------|-----------------|

Reporting group description: -

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | Demcizumab/placebo |
|-----------------------|--------------------|

Reporting group description: -

|                       |                       |
|-----------------------|-----------------------|
| Reporting group title | Demcizumab/Demcizumab |
|-----------------------|-----------------------|

Reporting group description: -

| Serious adverse events                                              | Placebo/placebo  | Demcizumab/placebo | Demcizumab/Demcizumab |
|---------------------------------------------------------------------|------------------|--------------------|-----------------------|
| Total subjects affected by serious adverse events                   |                  |                    |                       |
| subjects affected / exposed                                         | 40 / 68 (58.82%) | 49 / 71 (69.01%)   | 34 / 65 (52.31%)      |
| number of deaths (all causes)                                       | 5                | 12                 | 3                     |
| number of deaths resulting from adverse events                      | 5                | 12                 | 3                     |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                  |                    |                       |
| Cancer pain                                                         |                  |                    |                       |
| subjects affected / exposed                                         | 1 / 68 (1.47%)   | 0 / 71 (0.00%)     | 0 / 65 (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                 |
| Hepatic neoplasm                                                    |                  |                    |                       |
| subjects affected / exposed                                         | 0 / 68 (0.00%)   | 1 / 71 (1.41%)     | 0 / 65 (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                 |
| Metastases to central nervous system                                |                  |                    |                       |
| subjects affected / exposed                                         | 0 / 68 (0.00%)   | 1 / 71 (1.41%)     | 0 / 65 (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                 |
| Tumour rupture                                                      |                  |                    |                       |

|                                                      |                |                |                |
|------------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                          | 0 / 68 (0.00%) | 1 / 71 (1.41%) | 0 / 65 (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          |
| Vascular disorders                                   |                |                |                |
| Deep vein thrombosis                                 |                |                |                |
| subjects affected / exposed                          | 0 / 68 (0.00%) | 1 / 71 (1.41%) | 0 / 65 (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          |
| Embolism                                             |                |                |                |
| subjects affected / exposed                          | 0 / 68 (0.00%) | 0 / 71 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Hypotension                                          |                |                |                |
| subjects affected / exposed                          | 1 / 68 (1.47%) | 0 / 71 (0.00%) | 0 / 65 (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          |
| General disorders and administration site conditions |                |                |                |
| Pyrexia                                              |                |                |                |
| subjects affected / exposed                          | 6 / 68 (8.82%) | 3 / 71 (4.23%) | 6 / 65 (9.23%) |
| occurrences causally related to treatment / all      | 1 / 6          | 1 / 3          | 0 / 6          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Chest discomfort                                     |                |                |                |
| subjects affected / exposed                          | 0 / 68 (0.00%) | 1 / 71 (1.41%) | 0 / 65 (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          |
| Multiple organ dysfunction syndrome                  |                |                |                |
| subjects affected / exposed                          | 0 / 68 (0.00%) | 1 / 71 (1.41%) | 0 / 65 (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          |
| Peripheral swelling                                  |                |                |                |
| subjects affected / exposed                          | 0 / 68 (0.00%) | 1 / 71 (1.41%) | 0 / 65 (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          |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| Systemic inflammatory response syndrome         |                |                |                |
| subjects affected / exposed                     | 0 / 68 (0.00%) | 0 / 71 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Respiratory, thoracic and mediastinal disorders |                |                |                |
| Dyspnoea                                        |                |                |                |
| subjects affected / exposed                     | 2 / 68 (2.94%) | 2 / 71 (2.82%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 2          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pleural effusion                                |                |                |                |
| subjects affected / exposed                     | 2 / 68 (2.94%) | 1 / 71 (1.41%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pulmonary embolism                              |                |                |                |
| subjects affected / exposed                     | 2 / 68 (2.94%) | 0 / 71 (0.00%) | 0 / 65 (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 hypertension                          |                |                |                |
| subjects affected / exposed                     | 0 / 68 (0.00%) | 2 / 71 (2.82%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 2 / 2          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Respiratory failure                             |                |                |                |
| subjects affected / exposed                     | 1 / 68 (1.47%) | 0 / 71 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 1 / 1          | 0 / 0          | 0 / 0          |
| Acute respiratory distress syndrome             |                |                |                |
| subjects affected / exposed                     | 1 / 68 (1.47%) | 0 / 71 (0.00%) | 0 / 65 (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          |
| Orthopnoea                                      |                |                |                |
| subjects affected / exposed                     | 0 / 68 (0.00%) | 1 / 71 (1.41%) | 0 / 65 (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          |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| Pneumonitis                                     |                |                |                |
| subjects affected / exposed                     | 1 / 68 (1.47%) | 0 / 71 (0.00%) | 0 / 65 (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          |
| Pneumothorax                                    |                |                |                |
| subjects affected / exposed                     | 1 / 68 (1.47%) | 0 / 71 (0.00%) | 0 / 65 (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 oedema                                |                |                |                |
| subjects affected / exposed                     | 0 / 68 (0.00%) | 0 / 71 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Psychiatric disorders                           |                |                |                |
| Anxiety                                         |                |                |                |
| subjects affected / exposed                     | 1 / 68 (1.47%) | 1 / 71 (1.41%) | 0 / 65 (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          |
| Confusional state                               |                |                |                |
| subjects affected / exposed                     | 1 / 68 (1.47%) | 0 / 71 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Delirium                                        |                |                |                |
| subjects affected / exposed                     | 0 / 68 (0.00%) | 1 / 71 (1.41%) | 0 / 65 (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          |
| Mental status changes                           |                |                |                |
| subjects affected / exposed                     | 0 / 68 (0.00%) | 0 / 71 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Product issues                                  |                |                |                |
| Device dislocation                              |                |                |                |
| subjects affected / exposed                     | 0 / 68 (0.00%) | 1 / 71 (1.41%) | 0 / 65 (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          |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| Investigations                                  |                |                |                |
| Blood bilirubin increased                       |                |                |                |
| subjects affected / exposed                     | 1 / 68 (1.47%) | 0 / 71 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Liver function test increased                   |                |                |                |
| subjects affected / exposed                     | 1 / 68 (1.47%) | 0 / 71 (0.00%) | 0 / 65 (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          |
| Neutrophil count decreased                      |                |                |                |
| subjects affected / exposed                     | 0 / 68 (0.00%) | 0 / 71 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Transaminases increased                         |                |                |                |
| subjects affected / exposed                     | 0 / 68 (0.00%) | 1 / 71 (1.41%) | 0 / 65 (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          |
| White blood cell count decreased                |                |                |                |
| subjects affected / exposed                     | 0 / 68 (0.00%) | 0 / 71 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Injury, poisoning and procedural complications  |                |                |                |
| Fall                                            |                |                |                |
| subjects affected / exposed                     | 2 / 68 (2.94%) | 0 / 71 (0.00%) | 0 / 65 (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          |
| Toxicity to various agents                      |                |                |                |
| subjects affected / exposed                     | 1 / 68 (1.47%) | 1 / 71 (1.41%) | 0 / 65 (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          |
| Anaesthetic complication                        |                |                |                |
| subjects affected / exposed                     | 0 / 68 (0.00%) | 0 / 71 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| Hip fracture                                    |                |                |                |
| subjects affected / exposed                     | 0 / 68 (0.00%) | 1 / 71 (1.41%) | 0 / 65 (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          |
| Procedural pain                                 |                |                |                |
| subjects affected / exposed                     | 0 / 68 (0.00%) | 0 / 71 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cardiac disorders                               |                |                |                |
| Cardiac failure                                 |                |                |                |
| subjects affected / exposed                     | 0 / 68 (0.00%) | 2 / 71 (2.82%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 2          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Angina pectoris                                 |                |                |                |
| subjects affected / exposed                     | 0 / 68 (0.00%) | 2 / 71 (2.82%) | 0 / 65 (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          |
| Atrial fibrillation                             |                |                |                |
| subjects affected / exposed                     | 0 / 68 (0.00%) | 1 / 71 (1.41%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Acute myocardial infarction                     |                |                |                |
| subjects affected / exposed                     | 0 / 68 (0.00%) | 1 / 71 (1.41%) | 0 / 65 (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          |
| Cardiac arrest                                  |                |                |                |
| subjects affected / exposed                     | 0 / 68 (0.00%) | 1 / 71 (1.41%) | 0 / 65 (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          |
| Cardiac failure congestive                      |                |                |                |
| subjects affected / exposed                     | 0 / 68 (0.00%) | 1 / 71 (1.41%) | 0 / 65 (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          |
| Nervous system disorders                        |                |                |                |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| Syncope                                         |                |                |                |
| subjects affected / exposed                     | 1 / 68 (1.47%) | 0 / 71 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Transient ischaemic attack                      |                |                |                |
| subjects affected / exposed                     | 0 / 68 (0.00%) | 1 / 71 (1.41%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cerebral haemorrhage                            |                |                |                |
| subjects affected / exposed                     | 0 / 68 (0.00%) | 0 / 71 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1          |
| Cerebral infarction                             |                |                |                |
| subjects affected / exposed                     | 1 / 68 (1.47%) | 0 / 71 (0.00%) | 0 / 65 (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          |
| Cerebrovascular accident                        |                |                |                |
| subjects affected / exposed                     | 0 / 68 (0.00%) | 1 / 71 (1.41%) | 0 / 65 (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          |
| Generalised tonic-clonic seizure                |                |                |                |
| subjects affected / exposed                     | 1 / 68 (1.47%) | 0 / 71 (0.00%) | 0 / 65 (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          |
| Peroneal nerve palsy                            |                |                |                |
| subjects affected / exposed                     | 0 / 68 (0.00%) | 1 / 71 (1.41%) | 0 / 65 (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          |
| Presyncope                                      |                |                |                |
| subjects affected / exposed                     | 0 / 68 (0.00%) | 0 / 71 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Blood and lymphatic system disorders            |                |                |                |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| Febrile neutropenia                             |                |                |                |
| subjects affected / exposed                     | 4 / 68 (5.88%) | 1 / 71 (1.41%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 1 / 4          | 1 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 1 / 1          | 0 / 0          |
| Anaemia                                         |                |                |                |
| subjects affected / exposed                     | 3 / 68 (4.41%) | 0 / 71 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 3 / 3          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Neutropenia                                     |                |                |                |
| subjects affected / exposed                     | 1 / 68 (1.47%) | 1 / 71 (1.41%) | 2 / 65 (3.08%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1          | 1 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Haemolytic anaemia                              |                |                |                |
| subjects affected / exposed                     | 0 / 68 (0.00%) | 2 / 71 (2.82%) | 0 / 65 (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          |
| Haemolytic uraemic syndrome                     |                |                |                |
| subjects affected / exposed                     | 0 / 68 (0.00%) | 1 / 71 (1.41%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pancytopenia                                    |                |                |                |
| subjects affected / exposed                     | 0 / 68 (0.00%) | 0 / 71 (0.00%) | 2 / 65 (3.08%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Thrombotic thrombocytopenic purpura             |                |                |                |
| subjects affected / exposed                     | 0 / 68 (0.00%) | 0 / 71 (0.00%) | 2 / 65 (3.08%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Iron deficiency anaemia                         |                |                |                |
| subjects affected / exposed                     | 0 / 68 (0.00%) | 1 / 71 (1.41%) | 0 / 65 (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          |
| Thrombocytopenia                                |                |                |                |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 1 / 68 (1.47%) | 0 / 71 (0.00%) | 0 / 65 (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          |
| Ear and labyrinth disorders                     |                |                |                |
| Vertigo                                         |                |                |                |
| subjects affected / exposed                     | 1 / 68 (1.47%) | 0 / 71 (0.00%) | 0 / 65 (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          |
| Papilloedema                                    |                |                |                |
| subjects affected / exposed                     | 0 / 68 (0.00%) | 0 / 71 (0.00%) | 1 / 65 (1.54%) |
| 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                      |                |                |                |
| Vomiting                                        |                |                |                |
| subjects affected / exposed                     | 5 / 68 (7.35%) | 4 / 71 (5.63%) | 5 / 65 (7.69%) |
| occurrences causally related to treatment / all | 1 / 5          | 1 / 4          | 1 / 5          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Diarrhoea                                       |                |                |                |
| subjects affected / exposed                     | 1 / 68 (1.47%) | 4 / 71 (5.63%) | 3 / 65 (4.62%) |
| occurrences causally related to treatment / all | 1 / 1          | 1 / 4          | 1 / 3          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Abdominal pain                                  |                |                |                |
| subjects affected / exposed                     | 4 / 68 (5.88%) | 0 / 71 (0.00%) | 3 / 65 (4.62%) |
| occurrences causally related to treatment / all | 0 / 4          | 0 / 0          | 0 / 3          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Nausea                                          |                |                |                |
| subjects affected / exposed                     | 4 / 68 (5.88%) | 1 / 71 (1.41%) | 2 / 65 (3.08%) |
| occurrences causally related to treatment / all | 0 / 4          | 0 / 1          | 1 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastrointestinal haemorrhage                    |                |                |                |
| subjects affected / exposed                     | 0 / 68 (0.00%) | 2 / 71 (2.82%) | 2 / 65 (3.08%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 2          | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 1 / 1          | 0 / 1          |
| Ascites                                         |                |                |                |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 1 / 68 (1.47%) | 2 / 71 (2.82%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 2          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Abdominal pain upper                            |                |                |                |
| subjects affected / exposed                     | 1 / 68 (1.47%) | 1 / 71 (1.41%) | 0 / 65 (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          |
| Colitis                                         |                |                |                |
| subjects affected / exposed                     | 1 / 68 (1.47%) | 1 / 71 (1.41%) | 0 / 65 (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          |
| Enterocolitis                                   |                |                |                |
| subjects affected / exposed                     | 0 / 68 (0.00%) | 1 / 71 (1.41%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastritis                                       |                |                |                |
| subjects affected / exposed                     | 0 / 68 (0.00%) | 2 / 71 (2.82%) | 0 / 65 (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          |
| Intestinal obstruction                          |                |                |                |
| subjects affected / exposed                     | 0 / 68 (0.00%) | 1 / 71 (1.41%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 1          |
| Small intestinal haemorrhage                    |                |                |                |
| subjects affected / exposed                     | 0 / 68 (0.00%) | 1 / 71 (1.41%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 1 / 1          | 0 / 0          |
| Upper gastrointestinal haemorrhage              |                |                |                |
| subjects affected / exposed                     | 0 / 68 (0.00%) | 2 / 71 (2.82%) | 0 / 65 (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          |
| Anal fissure                                    |                |                |                |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 68 (0.00%) | 1 / 71 (1.41%) | 0 / 65 (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          |
| Colonic fistula                                 |                |                |                |
| subjects affected / exposed                     | 0 / 68 (0.00%) | 1 / 71 (1.41%) | 0 / 65 (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          |
| Constipation                                    |                |                |                |
| subjects affected / exposed                     | 1 / 68 (1.47%) | 0 / 71 (0.00%) | 0 / 65 (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 / 68 (0.00%) | 0 / 71 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Duodenal ulcer                                  |                |                |                |
| subjects affected / exposed                     | 0 / 68 (0.00%) | 1 / 71 (1.41%) | 0 / 65 (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          |
| Gastric haemorrhage                             |                |                |                |
| subjects affected / exposed                     | 1 / 68 (1.47%) | 0 / 71 (0.00%) | 0 / 65 (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          |
| Haematemesis                                    |                |                |                |
| subjects affected / exposed                     | 1 / 68 (1.47%) | 0 / 71 (0.00%) | 0 / 65 (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          |
| Ileus                                           |                |                |                |
| subjects affected / exposed                     | 0 / 68 (0.00%) | 1 / 71 (1.41%) | 0 / 65 (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 stenosis                             |                |                |                |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 68 (0.00%) | 1 / 71 (1.41%) | 0 / 65 (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          |
| Intra-abdominal haemorrhage                     |                |                |                |
| subjects affected / exposed                     | 0 / 68 (0.00%) | 1 / 71 (1.41%) | 0 / 65 (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          |
| Large intestinal obstruction                    |                |                |                |
| subjects affected / exposed                     | 0 / 68 (0.00%) | 1 / 71 (1.41%) | 0 / 65 (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          |
| Pancreatic duct obstruction                     |                |                |                |
| subjects affected / exposed                     | 0 / 68 (0.00%) | 0 / 71 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pancreatic insufficiency                        |                |                |                |
| subjects affected / exposed                     | 1 / 68 (1.47%) | 0 / 71 (0.00%) | 0 / 65 (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          |
| Hepatobiliary disorders                         |                |                |                |
| Jaundice cholestatic                            |                |                |                |
| subjects affected / exposed                     | 1 / 68 (1.47%) | 1 / 71 (1.41%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cholangitis                                     |                |                |                |
| subjects affected / exposed                     | 1 / 68 (1.47%) | 1 / 71 (1.41%) | 0 / 65 (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          |
| Bile duct obstruction                           |                |                |                |
| subjects affected / exposed                     | 0 / 68 (0.00%) | 1 / 71 (1.41%) | 0 / 65 (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          |
| Bile duct stenosis                              |                |                |                |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 68 (0.00%) | 0 / 71 (0.00%) | 1 / 65 (1.54%) |
| 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 acute                             |                |                |                |
| subjects affected / exposed                     | 0 / 68 (0.00%) | 1 / 71 (1.41%) | 0 / 65 (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          |
| Cholestasis                                     |                |                |                |
| subjects affected / exposed                     | 0 / 68 (0.00%) | 0 / 71 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Hepatic haematoma                               |                |                |                |
| subjects affected / exposed                     | 1 / 68 (1.47%) | 0 / 71 (0.00%) | 0 / 65 (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          |
| Hyperbilirubinaemia                             |                |                |                |
| subjects affected / exposed                     | 0 / 68 (0.00%) | 1 / 71 (1.41%) | 0 / 65 (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          |
| Jaundice                                        |                |                |                |
| subjects affected / exposed                     | 0 / 68 (0.00%) | 1 / 71 (1.41%) | 0 / 65 (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          |
| Portal vein thrombosis                          |                |                |                |
| subjects affected / exposed                     | 0 / 68 (0.00%) | 1 / 71 (1.41%) | 0 / 65 (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          |
| Skin and subcutaneous tissue disorders          |                |                |                |
| Erythema                                        |                |                |                |
| subjects affected / exposed                     | 0 / 68 (0.00%) | 1 / 71 (1.41%) | 0 / 65 (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 / 68 (0.00%) | 1 / 71 (1.41%) | 0 / 65 (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 and urinary disorders                     |                |                |                |
| Acute kidney injury                             |                |                |                |
| subjects affected / exposed                     | 0 / 68 (0.00%) | 0 / 71 (0.00%) | 3 / 65 (4.62%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 3          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Renal failure                                   |                |                |                |
| subjects affected / exposed                     | 1 / 68 (1.47%) | 0 / 71 (0.00%) | 0 / 65 (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          |
| Renal injury                                    |                |                |                |
| subjects affected / exposed                     | 0 / 68 (0.00%) | 0 / 71 (0.00%) | 1 / 65 (1.54%) |
| 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 and connective tissue disorders |                |                |                |
| Back pain                                       |                |                |                |
| subjects affected / exposed                     | 2 / 68 (2.94%) | 1 / 71 (1.41%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Myalgia                                         |                |                |                |
| subjects affected / exposed                     | 0 / 68 (0.00%) | 0 / 71 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Vertebral lesion                                |                |                |                |
| subjects affected / exposed                     | 1 / 68 (1.47%) | 0 / 71 (0.00%) | 0 / 65 (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          |
| Infections and infestations                     |                |                |                |
| Sepsis                                          |                |                |                |
| subjects affected / exposed                     | 3 / 68 (4.41%) | 4 / 71 (5.63%) | 4 / 65 (6.15%) |
| occurrences causally related to treatment / all | 0 / 3          | 0 / 4          | 0 / 4          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0          |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| Liver abscess                                   |                |                |                |
| subjects affected / exposed                     | 2 / 68 (2.94%) | 2 / 71 (2.82%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 2          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Urinary tract infection                         |                |                |                |
| subjects affected / exposed                     | 2 / 68 (2.94%) | 1 / 71 (1.41%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 1          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cellulitis                                      |                |                |                |
| subjects affected / exposed                     | 1 / 68 (1.47%) | 2 / 71 (2.82%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 1 / 2          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pneumonia                                       |                |                |                |
| subjects affected / exposed                     | 2 / 68 (2.94%) | 1 / 71 (1.41%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 1          | 0 / 0          |
| Urosepsis                                       |                |                |                |
| subjects affected / exposed                     | 2 / 68 (2.94%) | 0 / 71 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Abdominal abscess                               |                |                |                |
| subjects affected / exposed                     | 1 / 68 (1.47%) | 0 / 71 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Bacteraemia                                     |                |                |                |
| subjects affected / exposed                     | 0 / 68 (0.00%) | 2 / 71 (2.82%) | 0 / 65 (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          |
| Lower respiratory tract infection               |                |                |                |
| subjects affected / exposed                     | 1 / 68 (1.47%) | 0 / 71 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Neutropenic sepsis                              |                |                |                |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 68 (0.00%) | 1 / 71 (1.41%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Bacterial infection                             |                |                |                |
| subjects affected / exposed                     | 1 / 68 (1.47%) | 0 / 71 (0.00%) | 0 / 65 (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          |
| Bacterial sepsis                                |                |                |                |
| subjects affected / exposed                     | 0 / 68 (0.00%) | 1 / 71 (1.41%) | 0 / 65 (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          |
| Bronchitis                                      |                |                |                |
| subjects affected / exposed                     | 0 / 68 (0.00%) | 1 / 71 (1.41%) | 0 / 65 (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          |
| Colonic abscess                                 |                |                |                |
| subjects affected / exposed                     | 0 / 68 (0.00%) | 0 / 71 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cystitis                                        |                |                |                |
| subjects affected / exposed                     | 0 / 68 (0.00%) | 0 / 71 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Device related infection                        |                |                |                |
| subjects affected / exposed                     | 1 / 68 (1.47%) | 0 / 71 (0.00%) | 0 / 65 (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          |
| Escherichia bacteraemia                         |                |                |                |
| subjects affected / exposed                     | 0 / 68 (0.00%) | 0 / 71 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Hepatic infection                               |                |                |                |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 68 (0.00%) | 1 / 71 (1.41%) | 0 / 65 (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          |
| Infection                                       |                |                |                |
| subjects affected / exposed                     | 1 / 68 (1.47%) | 0 / 71 (0.00%) | 0 / 65 (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          |
| Lung infection                                  |                |                |                |
| subjects affected / exposed                     | 0 / 68 (0.00%) | 0 / 71 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Tick-borne fever                                |                |                |                |
| subjects affected / exposed                     | 0 / 68 (0.00%) | 0 / 71 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pyelonephritis acute                            |                |                |                |
| subjects affected / exposed                     | 1 / 68 (1.47%) | 0 / 71 (0.00%) | 0 / 65 (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 / 68 (0.00%) | 0 / 71 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Upper respiratory tract infection               |                |                |                |
| subjects affected / exposed                     | 0 / 68 (0.00%) | 1 / 71 (1.41%) | 0 / 65 (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          |
| Metabolism and nutrition disorders              |                |                |                |
| Dehydration                                     |                |                |                |
| subjects affected / exposed                     | 2 / 68 (2.94%) | 3 / 71 (4.23%) | 2 / 65 (3.08%) |
| occurrences causally related to treatment / all | 0 / 2          | 1 / 3          | 1 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Hyponatraemia                                   |                |                |                |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 68 (0.00%) | 0 / 71 (0.00%) | 2 / 65 (3.08%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Food intolerance                                |                |                |                |
| subjects affected / exposed                     | 1 / 68 (1.47%) | 0 / 71 (0.00%) | 0 / 65 (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          |
| Hyperglycaemia                                  |                |                |                |
| subjects affected / exposed                     | 1 / 68 (1.47%) | 0 / 71 (0.00%) | 0 / 65 (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          |
| Hypophosphataemia                               |                |                |                |
| subjects affected / exposed                     | 0 / 68 (0.00%) | 0 / 71 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1          |
| 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>                     | Placebo/placebo   | Demcizumab/placebo | Demcizumab/Demcizumab |
|-------------------------------------------------------|-------------------|--------------------|-----------------------|
| Total subjects affected by non-serious adverse events |                   |                    |                       |
| subjects affected / exposed                           | 68 / 68 (100.00%) | 71 / 71 (100.00%)  | 65 / 65 (100.00%)     |
| Vascular disorders                                    |                   |                    |                       |
| Hypertension                                          |                   |                    |                       |
| subjects affected / exposed                           | 10 / 68 (14.71%)  | 17 / 71 (23.94%)   | 21 / 65 (32.31%)      |
| occurrences (all)                                     | 10                | 17                 | 21                    |
| Hypotension                                           |                   |                    |                       |
| subjects affected / exposed                           | 11 / 68 (16.18%)  | 6 / 71 (8.45%)     | 5 / 65 (7.69%)        |
| occurrences (all)                                     | 11                | 6                  | 5                     |
| Deep vein thrombosis                                  |                   |                    |                       |
| subjects affected / exposed                           | 7 / 68 (10.29%)   | 4 / 71 (5.63%)     | 9 / 65 (13.85%)       |
| occurrences (all)                                     | 7                 | 4                  | 9                     |
| General disorders and administration site conditions  |                   |                    |                       |
| Fatigue                                               |                   |                    |                       |

|                                                 |                  |                  |                  |
|-------------------------------------------------|------------------|------------------|------------------|
| subjects affected / exposed                     | 34 / 68 (50.00%) | 31 / 71 (43.66%) | 37 / 65 (56.92%) |
| occurrences (all)                               | 34               | 31               | 37               |
| Oedema peripheral                               |                  |                  |                  |
| subjects affected / exposed                     | 29 / 68 (42.65%) | 39 / 71 (54.93%) | 34 / 65 (52.31%) |
| occurrences (all)                               | 29               | 39               | 34               |
| Pyrexia                                         |                  |                  |                  |
| subjects affected / exposed                     | 24 / 68 (35.29%) | 30 / 71 (42.25%) | 23 / 65 (35.38%) |
| occurrences (all)                               | 24               | 30               | 23               |
| Asthenia                                        |                  |                  |                  |
| subjects affected / exposed                     | 18 / 68 (26.47%) | 27 / 71 (38.03%) | 20 / 65 (30.77%) |
| occurrences (all)                               | 18               | 27               | 20               |
| Chills                                          |                  |                  |                  |
| subjects affected / exposed                     | 6 / 68 (8.82%)   | 3 / 71 (4.23%)   | 8 / 65 (12.31%)  |
| occurrences (all)                               | 6                | 3                | 8                |
| Headache                                        |                  |                  |                  |
| subjects affected / exposed                     | 12 / 68 (17.65%) | 13 / 71 (18.31%) | 22 / 65 (33.85%) |
| occurrences (all)                               | 12               | 13               | 22               |
| Respiratory, thoracic and mediastinal disorders |                  |                  |                  |
| Dyspnoea                                        |                  |                  |                  |
| subjects affected / exposed                     | 18 / 68 (26.47%) | 16 / 71 (22.54%) | 10 / 65 (15.38%) |
| occurrences (all)                               | 18               | 16               | 10               |
| Epistaxis                                       |                  |                  |                  |
| subjects affected / exposed                     | 10 / 68 (14.71%) | 13 / 71 (18.31%) | 17 / 65 (26.15%) |
| occurrences (all)                               | 10               | 13               | 17               |
| Cough                                           |                  |                  |                  |
| subjects affected / exposed                     | 10 / 68 (14.71%) | 12 / 71 (16.90%) | 11 / 65 (16.92%) |
| occurrences (all)                               | 10               | 12               | 11               |
| Dyspnoea exertional                             |                  |                  |                  |
| subjects affected / exposed                     | 3 / 68 (4.41%)   | 4 / 71 (5.63%)   | 8 / 65 (12.31%)  |
| occurrences (all)                               | 3                | 4                | 8                |
| Pulmonary hypertension                          |                  |                  |                  |
| subjects affected / exposed                     | 1 / 68 (1.47%)   | 7 / 71 (9.86%)   | 7 / 65 (10.77%)  |
| occurrences (all)                               | 1                | 7                | 7                |
| Rhinorrhoea                                     |                  |                  |                  |

|                                                  |                     |                     |                     |
|--------------------------------------------------|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all) | 5 / 68 (7.35%)<br>5 | 2 / 71 (2.82%)<br>2 | 5 / 65 (7.69%)<br>5 |
| Psychiatric disorders                            |                     |                     |                     |
| Insomnia                                         |                     |                     |                     |
| subjects affected / exposed                      | 9 / 68 (13.24%)     | 8 / 71 (11.27%)     | 9 / 65 (13.85%)     |
| occurrences (all)                                | 9                   | 8                   | 9                   |
| Anxiety                                          |                     |                     |                     |
| subjects affected / exposed                      | 10 / 68 (14.71%)    | 5 / 71 (7.04%)      | 3 / 65 (4.62%)      |
| occurrences (all)                                | 10                  | 5                   | 3                   |
| Depression                                       |                     |                     |                     |
| subjects affected / exposed                      | 6 / 68 (8.82%)      | 3 / 71 (4.23%)      | 7 / 65 (10.77%)     |
| occurrences (all)                                | 6                   | 3                   | 7                   |
| Investigations                                   |                     |                     |                     |
| Platelet count decreased                         |                     |                     |                     |
| subjects affected / exposed                      | 16 / 68 (23.53%)    | 20 / 71 (28.17%)    | 13 / 65 (20.00%)    |
| occurrences (all)                                | 16                  | 20                  | 13                  |
| Alanine aminotransferase increased               |                     |                     |                     |
| subjects affected / exposed                      | 16 / 68 (23.53%)    | 15 / 71 (21.13%)    | 15 / 65 (23.08%)    |
| occurrences (all)                                | 16                  | 15                  | 15                  |
| Neutrophil count decreased                       |                     |                     |                     |
| subjects affected / exposed                      | 16 / 68 (23.53%)    | 12 / 71 (16.90%)    | 12 / 65 (18.46%)    |
| occurrences (all)                                | 16                  | 12                  | 12                  |
| Aspartate aminotransferase increased             |                     |                     |                     |
| subjects affected / exposed                      | 13 / 68 (19.12%)    | 5 / 71 (7.04%)      | 12 / 65 (18.46%)    |
| occurrences (all)                                | 13                  | 5                   | 12                  |
| Brain natriuretic peptide increased              |                     |                     |                     |
| subjects affected / exposed                      | 5 / 68 (7.35%)      | 11 / 71 (15.49%)    | 14 / 65 (21.54%)    |
| occurrences (all)                                | 5                   | 11                  | 14                  |
| White blood cell count decreased                 |                     |                     |                     |
| subjects affected / exposed                      | 9 / 68 (13.24%)     | 4 / 71 (5.63%)      | 10 / 65 (15.38%)    |
| occurrences (all)                                | 9                   | 4                   | 10                  |
| Blood alkaline phosphatase increased             |                     |                     |                     |
| subjects affected / exposed                      | 5 / 68 (7.35%)      | 6 / 71 (8.45%)      | 10 / 65 (15.38%)    |
| occurrences (all)                                | 5                   | 6                   | 10                  |
| Weight decreased                                 |                     |                     |                     |

|                                                                                         |                        |                        |                        |
|-----------------------------------------------------------------------------------------|------------------------|------------------------|------------------------|
| subjects affected / exposed<br>occurrences (all)                                        | 8 / 68 (11.76%)<br>8   | 5 / 71 (7.04%)<br>5    | 8 / 65 (12.31%)<br>8   |
| Blood bilirubin increased<br>subjects affected / exposed<br>occurrences (all)           | 6 / 68 (8.82%)<br>6    | 3 / 71 (4.23%)<br>3    | 3 / 65 (4.62%)<br>3    |
| Gamma-glutamyltransferase increased<br>subjects affected / exposed<br>occurrences (all) | 5 / 68 (7.35%)<br>5    | 2 / 71 (2.82%)<br>2    | 5 / 65 (7.69%)<br>5    |
| Nervous system disorders                                                                |                        |                        |                        |
| Dysgeusia<br>subjects affected / exposed<br>occurrences (all)                           | 18 / 68 (26.47%)<br>18 | 16 / 71 (22.54%)<br>16 | 17 / 65 (26.15%)<br>17 |
| Peripheral sensory neuropathy<br>subjects affected / exposed<br>occurrences (all)       | 16 / 68 (23.53%)<br>16 | 17 / 71 (23.94%)<br>17 | 17 / 65 (26.15%)<br>17 |
| Neuropathy peripheral<br>subjects affected / exposed<br>occurrences (all)               | 11 / 68 (16.18%)<br>11 | 15 / 71 (21.13%)<br>15 | 12 / 65 (18.46%)<br>12 |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)                           | 10 / 68 (14.71%)<br>10 | 5 / 71 (7.04%)<br>5    | 7 / 65 (10.77%)<br>7   |
| Neurotoxicity<br>subjects affected / exposed<br>occurrences (all)                       | 2 / 68 (2.94%)<br>2    | 11 / 71 (15.49%)<br>11 | 4 / 65 (6.15%)<br>4    |
| Blood and lymphatic system disorders                                                    |                        |                        |                        |
| Anaemia<br>subjects affected / exposed<br>occurrences (all)                             | 27 / 68 (39.71%)<br>27 | 43 / 71 (60.56%)<br>43 | 35 / 65 (53.85%)<br>35 |
| Thrombocytopenia<br>subjects affected / exposed<br>occurrences (all)                    | 15 / 68 (22.06%)<br>15 | 14 / 71 (19.72%)<br>14 | 16 / 65 (24.62%)<br>16 |
| Neutropenia<br>subjects affected / exposed<br>occurrences (all)                         | 21 / 68 (30.88%)<br>21 | 24 / 71 (33.80%)<br>24 | 25 / 65 (38.46%)<br>25 |
| Eye disorders                                                                           |                        |                        |                        |

|                                                                                      |                        |                        |                        |
|--------------------------------------------------------------------------------------|------------------------|------------------------|------------------------|
| Vision blurred<br>subjects affected / exposed<br>occurrences (all)                   | 3 / 68 (4.41%)<br>3    | 3 / 71 (4.23%)<br>3    | 5 / 65 (7.69%)<br>5    |
| Gastrointestinal disorders                                                           |                        |                        |                        |
| Nausea<br>subjects affected / exposed<br>occurrences (all)                           | 42 / 68 (61.76%)<br>42 | 38 / 71 (53.52%)<br>38 | 41 / 65 (63.08%)<br>41 |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)                        | 34 / 68 (50.00%)<br>34 | 41 / 71 (57.75%)<br>41 | 45 / 65 (69.23%)<br>45 |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)                         | 27 / 68 (39.71%)<br>27 | 32 / 71 (45.07%)<br>32 | 25 / 65 (38.46%)<br>25 |
| Constipation<br>subjects affected / exposed<br>occurrences (all)                     | 20 / 68 (29.41%)<br>20 | 21 / 71 (29.58%)<br>21 | 28 / 65 (43.08%)<br>28 |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)                   | 24 / 68 (35.29%)<br>24 | 16 / 71 (22.54%)<br>16 | 27 / 65 (41.54%)<br>27 |
| Stomatitis<br>subjects affected / exposed<br>occurrences (all)                       | 13 / 68 (19.12%)<br>13 | 12 / 71 (16.90%)<br>12 | 15 / 65 (23.08%)<br>15 |
| Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all)             | 13 / 68 (19.12%)<br>13 | 6 / 71 (8.45%)<br>6    | 8 / 65 (12.31%)<br>8   |
| Dry mouth<br>subjects affected / exposed<br>occurrences (all)                        | 7 / 68 (10.29%)<br>7   | 9 / 71 (12.68%)<br>9   | 6 / 65 (9.23%)<br>6    |
| Ascites<br>subjects affected / exposed<br>occurrences (all)                          | 9 / 68 (13.24%)<br>9   | 6 / 71 (8.45%)<br>6    | 3 / 65 (4.62%)<br>3    |
| Gastrooesophageal reflux disease<br>subjects affected / exposed<br>occurrences (all) | 6 / 68 (8.82%)<br>6    | 7 / 71 (9.86%)<br>7    | 5 / 65 (7.69%)<br>5    |
| Abdominal distension                                                                 |                        |                        |                        |

|                                                  |                     |                     |                     |
|--------------------------------------------------|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all) | 5 / 68 (7.35%)<br>5 | 4 / 71 (5.63%)<br>4 | 4 / 65 (6.15%)<br>4 |
| Skin and subcutaneous tissue disorders           |                     |                     |                     |
| Alopecia                                         |                     |                     |                     |
| subjects affected / exposed                      | 30 / 68 (44.12%)    | 33 / 71 (46.48%)    | 28 / 65 (43.08%)    |
| occurrences (all)                                | 30                  | 33                  | 28                  |
| Rash                                             |                     |                     |                     |
| subjects affected / exposed                      | 18 / 68 (26.47%)    | 14 / 71 (19.72%)    | 17 / 65 (26.15%)    |
| occurrences (all)                                | 18                  | 14                  | 17                  |
| Dry skin                                         |                     |                     |                     |
| subjects affected / exposed                      | 4 / 68 (5.88%)      | 5 / 71 (7.04%)      | 5 / 65 (7.69%)      |
| occurrences (all)                                | 4                   | 5                   | 5                   |
| Rash maculo-papular                              |                     |                     |                     |
| subjects affected / exposed                      | 6 / 68 (8.82%)      | 3 / 71 (4.23%)      | 5 / 65 (7.69%)      |
| occurrences (all)                                | 6                   | 3                   | 5                   |
| Erythema                                         |                     |                     |                     |
| subjects affected / exposed                      | 3 / 68 (4.41%)      | 7 / 71 (9.86%)      | 3 / 65 (4.62%)      |
| occurrences (all)                                | 3                   | 7                   | 3                   |
| Hypokalaemia                                     |                     |                     |                     |
| subjects affected / exposed                      | 7 / 68 (10.29%)     | 7 / 71 (9.86%)      | 6 / 65 (9.23%)      |
| occurrences (all)                                | 7                   | 7                   | 6                   |
| Musculoskeletal and connective tissue disorders  |                     |                     |                     |
| Back pain                                        |                     |                     |                     |
| subjects affected / exposed                      | 16 / 68 (23.53%)    | 10 / 71 (14.08%)    | 13 / 65 (20.00%)    |
| occurrences (all)                                | 16                  | 10                  | 13                  |
| Myalgia                                          |                     |                     |                     |
| subjects affected / exposed                      | 6 / 68 (8.82%)      | 10 / 71 (14.08%)    | 15 / 65 (23.08%)    |
| occurrences (all)                                | 6                   | 10                  | 15                  |
| Arthralgia                                       |                     |                     |                     |
| subjects affected / exposed                      | 8 / 68 (11.76%)     | 9 / 71 (12.68%)     | 10 / 65 (15.38%)    |
| occurrences (all)                                | 8                   | 9                   | 10                  |
| Pain in extremity                                |                     |                     |                     |
| subjects affected / exposed                      | 8 / 68 (11.76%)     | 5 / 71 (7.04%)      | 7 / 65 (10.77%)     |
| occurrences (all)                                | 8                   | 5                   | 7                   |
| Musculoskeletal pain                             |                     |                     |                     |

|                                                                                       |                        |                        |                        |
|---------------------------------------------------------------------------------------|------------------------|------------------------|------------------------|
| subjects affected / exposed<br>occurrences (all)                                      | 3 / 68 (4.41%)<br>3    | 3 / 71 (4.23%)<br>3    | 6 / 65 (9.23%)<br>6    |
| Muscular weakness<br>subjects affected / exposed<br>occurrences (all)                 | 5 / 68 (7.35%)<br>5    | 2 / 71 (2.82%)<br>2    | 4 / 65 (6.15%)<br>4    |
| Infections and infestations                                                           |                        |                        |                        |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)           | 7 / 68 (10.29%)<br>7   | 5 / 71 (7.04%)<br>5    | 7 / 65 (10.77%)<br>7   |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 6 / 68 (8.82%)<br>6    | 6 / 71 (8.45%)<br>6    | 6 / 65 (9.23%)<br>6    |
| Oral candidiasis<br>subjects affected / exposed<br>occurrences (all)                  | 8 / 68 (11.76%)<br>8   | 2 / 71 (2.82%)<br>2    | 4 / 65 (6.15%)<br>4    |
| Cellulitis<br>subjects affected / exposed<br>occurrences (all)                        | 6 / 68 (8.82%)<br>6    | 5 / 71 (7.04%)<br>5    | 1 / 65 (1.54%)<br>1    |
| Sepsis<br>subjects affected / exposed<br>occurrences (all)                            | 3 / 68 (4.41%)<br>3    | 5 / 71 (7.04%)<br>5    | 4 / 65 (6.15%)<br>4    |
| Metabolism and nutrition disorders                                                    |                        |                        |                        |
| Decreased appetite<br>subjects affected / exposed<br>occurrences (all)                | 19 / 68 (27.94%)<br>19 | 30 / 71 (42.25%)<br>30 | 27 / 65 (41.54%)<br>27 |
| Hypoalbuminaemia<br>subjects affected / exposed<br>occurrences (all)                  | 8 / 68 (11.76%)<br>8   | 10 / 71 (14.08%)<br>10 | 9 / 65 (13.85%)<br>9   |
| Dehydration<br>subjects affected / exposed<br>occurrences (all)                       | 6 / 68 (8.82%)<br>6    | 10 / 71 (14.08%)<br>10 | 6 / 65 (9.23%)<br>6    |
| Hyperglycaemia<br>subjects affected / exposed<br>occurrences (all)                    | 11 / 68 (16.18%)<br>11 | 5 / 71 (7.04%)<br>5    | 4 / 65 (6.15%)<br>4    |
| Hyponatraemia                                                                         |                        |                        |                        |

|                             |                |                |                 |
|-----------------------------|----------------|----------------|-----------------|
| subjects affected / exposed | 6 / 68 (8.82%) | 4 / 71 (5.63%) | 8 / 65 (12.31%) |
| occurrences (all)           | 6              | 4              | 8               |
| Hypophosphataemia           |                |                |                 |
| subjects affected / exposed | 5 / 68 (7.35%) | 5 / 71 (7.04%) | 6 / 65 (9.23%)  |
| occurrences (all)           | 5              | 5              | 6               |
| Hypocalcaemia               |                |                |                 |
| subjects affected / exposed | 6 / 68 (8.82%) | 7 / 71 (9.86%) | 2 / 65 (3.08%)  |
| occurrences (all)           | 6              | 7              | 2               |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 24 November 2014 | The following changes were made at the request of the USA Food and Drug Administration: the inclusion criteria for bilirubin was reduced to $1 \times \text{ULN}$ , $>\text{Grade 2}$ pulmonary hypertension was added as a treatment termination criteria, a section was added regarding the role of the DSMB and clarifying the data that they would review and the sample informed consent was revised to clarify that subjects received 6 doses of demcizumab or placebo during each of the two 70-day truncated courses of therapy and that subjects might receive less intensive gemcitabine/Abraxane therapy than if they were not on the study due to demcizumab toxicity.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 10 February 2015 | The requirement for mandatory FFPE (either from archival tissue or from a fresh core biopsy) was removed and instead FFPE was only to be collected if available, i.e., subjects who did not have archival tissue were not undergo a core biopsy to obtain fresh tumor tissue. In addition, the requirement for subjects who had 2 BNP values $> 100 \text{ pg/mL}$ or 1 value $> 200 \text{ pg/mL}$ to be referred to a cardiologist changed to state that such subjects would be referred to a cardiologist if appropriate. Definitions were added to the protocol for "women of child-bearing potential" and "adequate contraception". Additional serum pregnancy tests were added every 56 days while on study, at the termination visit and at 56 and 112 days following the termination visit for women of child-bearing potential.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| 28 May 2015      | The primary purpose of this amendment was to make the following modifications to the inclusion/exclusion criteria. Inclusion criterion #1 was modified to allow subjects with a cytologic diagnosis to be eligible. Exclusion criterion #6 was modified to provide a definition of clinically significant ascites. The previous exclusion criterion #7 was removed so that subjects with plastic biliary stents are eligible. The previous exclusion criterion #10 (now exclusion criterion #9) was modified to clarify that subjects with prior chest wall radiotherapy are excluded only if the radiation field involved the heart. The previous exclusion criterion #16 (now exclusion criterion #15) was modified to state that subjects on prophylactic doses of heparin, warfarin, factor Xa inhibitors, or other similar anticoagulants are eligible. In addition, Section 13 of the protocol was modified to clarify that the BNP measurement must be obtained on the Day of the demcizumab dosing and the result reviewed prior to dosing and the sample informed consent was modified to clarify the objectives of the study. In addition, modifications were made to clarify the appropriate radiologic assessments to be obtained.                                                                                               |
| 31 March 2016    | The primary purpose of this amendment was to change the method for analyzing the primary endpoint of PFS. The previous approach for the primary endpoint analysis involved comparing placebo/placebo arm to demcizumab/placebo arm and placebo/placebo arm to demcizumab/demcizumab arm, separately. This approach required that 80% of subjects achieve the PFS endpoint (i.e., either progress or died). However, a blinded review of the data to date suggests that only about 69% of the subjects are having a PFS event. Thus, it appears that there may not be an adequate number of events at the end of the study to conduct the PFS analysis initially described in the protocol. Thus, the method for this analysis has been modified to compare the placebo/placebo arm to a pooled dataset of the demcizumab/placebo arm and demcizumab/demcizumab arm, which requires a lower percentage of subjects to achieve a PFS endpoint. In addition, the wording of the study objectives and endpoints were modified to account for this modification. A statement that standard of tests performed prior to the informed consent date may be used for screening purposes if they were done within 28 days of Day 0. Also, wording was added to allow the BNP to be drawn the day prior to dosing at a site if approved by the sponsor. |

|                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 19 December 2016 | <p>The primary purpose of this amendment was to add 2 additional analyses of overall survival to be conducted on all deaths through 01 June 2017 and 01 November 2017, respectively. In addition, the protocol was modified to state that subjects in long-term follow-up would have their survival status updated every 3 months or sooner at the request of the Sponsor. In addition, changes were made to the Abraxane/gemcitabine dosage modification section to:</p> <ul style="list-style-type: none"> <li>- Delete the statement that subjects having their gemcitabine/Abraxane therapy held for 21 days due to drug related toxicity should have their gemcitabine and Abraxane stopped</li> <li>- To add a statement that subjects who had undergone 2 dose reductions of gemcitabine/Abraxane and still were unable to tolerate that treatment could receive gemcitabine/Abraxane on Days 1 and 15 (i.e., omit Day 8) of each 28-day cycle</li> </ul> |
|------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

Notes:

---

## **Interruptions (globally)**

Were there any global interruptions to the trial? No

## **Limitations and caveats**

None reported