



## Clinical trial results:

### A Randomized, Multicenter, Open-Label, Phase 3 Study of Gemcitabine-Cisplatin Chemotherapy Plus Necitumumab (IMC-11F8) Versus Gemcitabine-Cisplatin Chemotherapy Alone in the First-Line Treatment of Patients With Stage IV Squamous Non-Small Cell Lung Cancer (NSCLC)

#### Summary

|                          |                               |
|--------------------------|-------------------------------|
| EudraCT number           | 2009-013838-25                |
| Trial protocol           | BE AT DE HU PT ES GR SK IT GB |
| Global end of trial date | 30 May 2024                   |

#### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 15 June 2025 |
| First version publication date | 15 June 2025 |

#### Trial information

##### Trial identification

|                       |             |
|-----------------------|-------------|
| Sponsor protocol code | I4X-IE-JFCC |
|-----------------------|-------------|

##### Additional study identifiers

|                                    |                                      |
|------------------------------------|--------------------------------------|
| ISRCTN number                      | -                                    |
| ClinicalTrials.gov id (NCT number) | NCT00981058                          |
| WHO universal trial number (UTN)   | -                                    |
| Other trial identifiers            | Additional Identifier: IMCLCP11-0806 |

Notes:

##### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Eli Lilly and Company  |
| Sponsor organisation address | Lilly Corporate Center, Indianapolis, IN, United States, 46285                                       |
| Public contact               | Clinical Trial Information, Eli Lilly and Company, 1 08772854559, EU_Lilly_Clinical_Trials@lilly.com |
| Scientific contact           | Clinical Trial Information, Eli Lilly and Company, 1 877CTLilly, EU_Lilly_Clinical_Trials@lilly.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                       | 30 May 2024 |
| Is this the analysis of the primary completion data? | No          |

|                                  |             |
|----------------------------------|-------------|
| Global end of trial reached?     | Yes         |
| Global end of trial date         | 30 May 2024 |
| Was the trial ended prematurely? | No          |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate the overall survival (OS) in patients with Stage IV squamous NSCLC (per the AJCC Staging Manual, Seventh Edition) treated with IMC-11F8 plus gemcitabine-cisplatin chemotherapy (Arm A) versus gemcitabine-cisplatin chemotherapy alone (Arm B) in the first-line metastatic setting.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonization (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy: -

Evidence for comparator: -

|   |                 |
|---|-----------------|
| Actual start date of recruitment                          | 07 January 2010 |
| Long term follow-up planned                               | No              |
| Independent data monitoring committee (IDMC) involvement? | Yes             |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                         |
|--------------------------------------|-------------------------|
| Country: Number of subjects enrolled | Poland: 128             |
| Country: Number of subjects enrolled | Portugal: 17            |
| Country: Number of subjects enrolled | Romania: 91             |
| Country: Number of subjects enrolled | Slovakia: 19            |
| Country: Number of subjects enrolled | Spain: 58               |
| Country: Number of subjects enrolled | United Kingdom: 19      |
| Country: Number of subjects enrolled | Austria: 8              |
| Country: Number of subjects enrolled | Belgium: 8              |
| Country: Number of subjects enrolled | France: 73              |
| Country: Number of subjects enrolled | Germany: 108            |
| Country: Number of subjects enrolled | Greece: 32              |
| Country: Number of subjects enrolled | Hungary: 84             |
| Country: Number of subjects enrolled | Italy: 25               |
| Country: Number of subjects enrolled | Russian Federation: 195 |
| Country: Number of subjects enrolled | Singapore: 3            |
| Country: Number of subjects enrolled | United States: 36       |
| Country: Number of subjects enrolled | Thailand: 9             |
| Country: Number of subjects enrolled | Brazil: 58              |
| Country: Number of subjects enrolled | Korea, Republic of: 47  |

|                                      |                 |
|--------------------------------------|-----------------|
| Country: Number of subjects enrolled | Serbia: 24      |
| Country: Number of subjects enrolled | Croatia: 6      |
| Country: Number of subjects enrolled | Philippines: 20 |
| Country: Number of subjects enrolled | Canada: 6       |
| Country: Number of subjects enrolled | Taiwan: 5       |
| Country: Number of subjects enrolled | South Africa: 4 |
| Country: Number of subjects enrolled | Australia: 10   |
| Worldwide total number of subjects   | 1093            |
| EEA total number of subjects         | 657             |

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|---|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 0   |
| Adolescents (12-17 years)                 | 0   |
| Adults (18-64 years)                      | 668 |
| From 65 to 84 years                       | 424 |
| 85 years and over                         | 1   |

## Subject disposition

### Recruitment

Recruitment details:

Not applicable.

### Pre-assignment

Screening details:

Completers are defined as those participants who died due to any cause in this study.

### Period 1

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

### Arms

|                              |     |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

|                  |                                       |
|------------------|---------------------------------------|
| <b>Arm title</b> | Necitumumab + Gemcitabine + Cisplatin |
|------------------|---------------------------------------|

Arm description:

Necitumumab + Gemcitabine + Cisplatin

Necitumumab: 800 milligrams (mg) I.V. infusion on Days 1 and 8 of every 3 week cycle.

Continues until progressive disease, toxicity, noncompliance, or withdrawal.

Gemcitabine: 1250 milligrams/square meter (mg/m<sup>2</sup>) on Days 1 and 8 of every 3 week cycle.

Continues for a maximum of six cycles.

Cisplatin: 75 mg/m<sup>2</sup> IV on Day 1 of every 3 week cycle.

Continues for a maximum of six cycles.

|  |                     |
|--|---------------------|
| Arm type                               | Experimental        |
| Investigational medicinal product name | Necitumumab         |
| Investigational medicinal product code |                     |
| Other name                             | LY3012211, IMC-11F8 |
| Pharmaceutical forms                   | Infusion            |
| Routes of administration               | Intravenous use     |

Dosage and administration details:

Administered intravenously.

|  |                 |
|--|-----------------|
| Investigational medicinal product name | Gemcitabine     |
| Investigational medicinal product code |                 |
| Other name                             | LY2334737       |
| Pharmaceutical forms                   | Infusion        |
| Routes of administration               | Intravenous use |

Dosage and administration details:

Administered intravenously.

|  |                 |
|--|-----------------|
| Investigational medicinal product name | Cisplatin       |
| Investigational medicinal product code |                 |
| Other name                             |                 |
| Pharmaceutical forms                   | Infusion        |
| Routes of administration               | Intravenous use |

Dosage and administration details:

Administered intravenously.

|                  |                         |
|------------------|-------------------------|
| <b>Arm title</b> | Gemcitabine + Cisplatin |
|------------------|-------------------------|

Arm description:

Gemcitabine + Cisplatin

Gemcitabine: 1250 mg/m<sup>2</sup> on Days 1 and 8 of every 3 week cycle.

Continues for a maximum of six cycles.

Cisplatin: 75 mg/m<sup>2</sup> IV on Day 1 of every 3 week cycle.  
Continues for a maximum of six cycles.

|  |                   |
|--|-------------------|
| Arm type                               | Active comparator |
| Investigational medicinal product name | Gemcitabine       |
| Investigational medicinal product code |                   |
| Other name                             | LY2334737         |
| Pharmaceutical forms                   | Infusion          |
| Routes of administration               | Intravenous use   |

Dosage and administration details:

Administered intravenously.

|  |                 |
|--|-----------------|
| Investigational medicinal product name | Cisplatin       |
| Investigational medicinal product code |                 |
| Other name                             |                 |
| Pharmaceutical forms                   | Infusion        |
| Routes of administration               | Intravenous use |

Dosage and administration details:

Administered intravenously.

| <b>Number of subjects in period 1</b>  | Necitumumab +<br>Gemcitabine +<br>Cisplatin | Gemcitabine +<br>Cisplatin |
|--|---|----------------------------|
| Started                                | 545   | 548                        |
| Received at Least 1 Dose of Study Drug | 538   | 541                        |
| Completed                              | 476   | 487                        |
| Not completed                          | 69  | 61                         |
| Consent withdrawn by subject           | 24  | 22                         |
| Physician decision                     | 4   | 5                          |
| Progressive Disease                    | 38  | 31                         |
| Lost to follow-up                      | 3   | 2                          |
| Randomization Error                    | -   | 1                          |

## Baseline characteristics

### Reporting groups

|   |                                       |
|---|---------------------------------------|
| Reporting group title   | Necitumumab + Gemcitabine + Cisplatin |
| Reporting group description:  |                                       |
| Necitumumab + Gemcitabine + Cisplatin   |                                       |
| Necitumumab: 800 milligrams (mg) I.V. infusion on Days 1 and 8 of every 3 week cycle.                 |                                       |
| Continues until progressive disease, toxicity, noncompliance, or withdrawal.                          |                                       |
| Gemcitabine: 1250 milligrams/square meter (mg/m <sup>2</sup> ) on Days 1 and 8 of every 3 week cycle. |                                       |
| Continues for a maximum of six cycles.  |                                       |
| Cisplatin: 75 mg/m <sup>2</sup> IV on Day 1 of every 3 week cycle.                                    |                                       |
| Continues for a maximum of six cycles.  |                                       |
| Reporting group title   | Gemcitabine + Cisplatin               |
| Reporting group description:  |                                       |
| Gemcitabine + Cisplatin   |                                       |
| Gemcitabine: 1250 mg/m <sup>2</sup> on Days 1 and 8 of every 3 week cycle.                            |                                       |
| Continues for a maximum of six cycles.  |                                       |
| Cisplatin: 75 mg/m <sup>2</sup> IV on Day 1 of every 3 week cycle.                                    |                                       |
| Continues for a maximum of six cycles.  |                                       |

| Reporting group values                             | Necitumumab + Gemcitabine + Cisplatin | Gemcitabine + Cisplatin | Total |
|--|---------------------------------------|-------------------------|-------|
| Number of subjects                                 | 545                                   | 548                     | 1093  |
| Age categorical                                    |                                       |                         |       |
| 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)                               |                                       |                         | 0     |
| From 65-84 years                                   |                                       |                         | 0     |
| 85 years and over                                  |                                       |                         | 0     |
| Age continuous                                     |                                       |                         |       |
| Units: years                                       |                                       |                         |       |
| median   | 62                                    | 62                      |       |
| full range (min-max)                               | 32 to 84                              | 32 to 86                | -     |
| Gender categorical                                 |                                       |                         |       |
| Units: Subjects                                    |                                       |                         |       |
| Female   | 95                                    | 90                      | 185   |
| Male   | 450                                   | 458                     | 908   |
| Ethnicity (NIH/OMB)                                |                                       |                         |       |
| Units: Subjects                                    |                                       |                         |       |
| Hispanic or Latino                                 | 55                                    | 56                      | 111   |
| Not Hispanic or Latino                             | 489                                   | 490                     | 979   |
| Unknown or Not Reported                            | 1                                     | 2                       | 3     |
| Race/Ethnicity                                     |                                       |                         |       |
| Units: Subjects                                    |                                       |                         |       |
| American Indian or Alaska Native                   | 1                                     | 0                       | 1     |

|   |     |     |     |
|---|-----|-----|-----|
| Asian                                     | 43  | 42  | 85  |
| Native Hawaiian or Other Pacific Islander | 0   | 1   | 1   |
| Black or African American                 | 5   | 6   | 11  |
| White                                     | 457 | 456 | 913 |
| More than one race                        | 1   | 0   | 1   |
| Other                                     | 38  | 43  | 81  |
| Region of Enrollment                      |     |     |     |
| Units: Subjects                           |     |     |     |
| Russian Federation                        | 94  | 101 | 195 |
| Singapore                                 | 1   | 2   | 3   |
| United States                             | 20  | 16  | 36  |
| Thailand                                  | 3   | 6   | 9   |
| Portugal                                  | 8   | 9   | 17  |
| Greece                                    | 18  | 14  | 32  |
| Austria                                   | 4   | 4   | 8   |
| Brazil                                    | 28  | 30  | 58  |
| Republic of Korea                         | 24  | 23  | 47  |
| Poland                                    | 69  | 59  | 128 |
| Slovakia                                  | 9   | 10  | 19  |
| France                                    | 34  | 39  | 73  |
| Serbia                                    | 11  | 13  | 24  |
| Croatia                                   | 2   | 4   | 6   |
| Romania                                   | 46  | 45  | 91  |
| Hungary                                   | 43  | 41  | 84  |
| Philippines                               | 12  | 8   | 20  |
| United Kingdom                            | 9   | 10  | 19  |
| Spain                                     | 33  | 25  | 58  |
| Canada                                    | 2   | 4   | 6   |
| Belgium                                   | 4   | 4   | 8   |
| Taiwan                                    | 3   | 2   | 5   |
| Italy                                     | 13  | 12  | 25  |
| South Africa                              | 2   | 2   | 4   |
| Australia                                 | 4   | 6   | 10  |
| Germany                                   | 49  | 59  | 108 |

## End points

### End points reporting groups

|   |                                       |
|---|---------------------------------------|
| Reporting group title   | Necitumumab + Gemcitabine + Cisplatin |
| Reporting group description:<br>Necitumumab + Gemcitabine + Cisplatin<br>Necitumumab: 800 milligrams (mg) I.V. infusion on Days 1 and 8 of every 3 week cycle.<br>Continues until progressive disease, toxicity, noncompliance, or withdrawal.<br>Gemcitabine: 1250 milligrams/square meter (mg/m <sup>2</sup> ) on Days 1 and 8 of every 3 week cycle.<br>Continues for a maximum of six cycles.<br>Cisplatin: 75 mg/m <sup>2</sup> IV on Day 1 of every 3 week cycle.<br>Continues for a maximum of six cycles. |                                       |
| Reporting group title   | Gemcitabine + Cisplatin               |
| Reporting group description:<br>Gemcitabine + Cisplatin<br>Gemcitabine: 1250 mg/m <sup>2</sup> on Days 1 and 8 of every 3 week cycle.<br>Continues for a maximum of six cycles.<br>Cisplatin: 75 mg/m <sup>2</sup> IV on Day 1 of every 3 week cycle.<br>Continues for a maximum of six cycles.   |                                       |

### Primary: Overall Survival Time (OS)

|  |                            |
|--|----------------------------|
| End point title  | Overall Survival Time (OS) |
| End point description:<br>Overall survival is defined as the time from randomization to death from any cause. Participants who do not die at the end of the extended follow-up period, or were lost to follow-up during the study, were censored at the last date they were known to be alive. OS was estimated by the Kaplan-Meier method.<br><br>Analysis Population Description (APD): All randomized participants. Censored participants: Necitumumab + Gemcitabine + Cisplatin = 127, Gemcitabine + Cisplatin = 106 |                            |
| End point type   | Primary                    |
| End point timeframe:<br>Randomization to Death from Any Cause (Up to 31 Months)  |                            |

| End point values                 | Necitumumab + Gemcitabine + Cisplatin | Gemcitabine + Cisplatin |  |  |
|----------------------------------|---------------------------------------|-------------------------|--|--|
| Subject group type               | Reporting group                       | Reporting group         |  |  |
| Number of subjects analysed      | 545                                   | 548                     |  |  |
| Units: Months                    |                                       |                         |  |  |
| median (confidence interval 95%) | 11.5 (10.4 to 12.6)                   | 9.9 (8.9 to 11.1)       |  |  |

### Statistical analyses

|                            |   |
|----------------------------|---|
| Statistical analysis title | Outcome Measure No. 1   |
| Comparison groups          | Necitumumab + Gemcitabine + Cisplatin v Gemcitabine + Cisplatin |



|   |                            |
|---|----------------------------|
| Number of subjects included in analysis | 1093                       |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority <sup>[1]</sup> |
| P-value                                 | = 0.012                    |
| Method                                  | Logrank                    |
| Parameter estimate                      | Hazard ratio (HR)          |
| Point estimate                          | 0.842                      |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | 0.736                      |
| upper limit                             | 0.962                      |

Notes:

[1] - Superiority or Other (legacy)

## Secondary: Progression-Free Survival (PFS)

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

End point description:

PFS is defined as the time from randomization until the first radiographic documentation of objective measured progressive disease as defined by RECIST (Version 1.0), or death from any cause. Progressive Disease (PD) was defined as having at least a 20% increase in the sum of the longest diameter of target lesions. Participants who die without a reported prior progression were considered to have progressed on the day of their death. Participants who did not progress or were lost to follow-up were censored at the day of their last radiographic tumor assessment. If no baseline or postbaseline radiologic assessment was available, the participants were censored at the date of randomization. If death or PD occurs after two or more consecutive missing radiographic visits, censoring occurred at the date of the last radiographic visit prior to the missed visits.

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

End point timeframe:

Randomization to Measured Progressive Disease or Death from Any Cause (Up to 31 Months).

APD: All randomized participants. Censored participants: Necitumumab + Gemcitabine + Cisplatin = 114, Gemcitabine + Cisplatin = 131

| End point values                 | Necitumumab + Gemcitabine + Cisplatin | Gemcitabine + Cisplatin |  |  |
|----------------------------------|---------------------------------------|-------------------------|--|--|
| Subject group type               | Reporting group                       | Reporting group         |  |  |
| Number of subjects analysed      | 545                                   | 548                     |  |  |
| Units: Months                    |                                       |                         |  |  |
| median (confidence interval 95%) | 5.7 (5.6 to 6.0)                      | 5.5 (4.8 to 5.6)        |  |  |

## Statistical analyses

|                            |   |
|----------------------------|---|
| Statistical analysis title | Outcome Measure No. 2   |
| Comparison groups          | Gemcitabine + Cisplatin v Necitumumab + Gemcitabine + Cisplatin |

|   |                            |
|---|----------------------------|
| Number of subjects included in analysis | 1093                       |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority <sup>[2]</sup> |
| P-value                                 | = 0.0201                   |
| Method                                  | Logrank                    |
| Parameter estimate                      | Hazard ratio (HR)          |
| Point estimate                          | 0.851                      |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | 0.743                      |
| upper limit                             | 0.975                      |

Notes:

[2] - Superiority or Other (legacy)

### Secondary: Percentage of Participants Achieving Complete Response (CR) and Partial Response (PR) (Objective Response Rate [ORR])

|                 |   |
|-----------------|---|
| End point title | Percentage of Participants Achieving Complete Response (CR) and Partial Response (PR) (Objective Response Rate [ORR]) |
|-----------------|---|

End point description:

ORR is confirmed best overall tumor response of CR or PR. According to RECIST v1.0, CR was defined as the disappearance of all target and non-target lesions. PR defined as a  $\geq 30\%$  decrease in the sum of the longest diameters (LD) of the target lesions, taking as reference the baseline sum of the LD; Percentage of participants was calculated as: (total number of participants with CR or PR from start of the treatment until disease progression or recurrence)/total number of participants treated) \* 100.

APD: All randomized participants.

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

End point timeframe:

Baseline to Measured Progressive Disease (Up to 31 Months)

| End point values                  | Necitumumab + Gemcitabine + Cisplatin | Gemcitabine + Cisplatin |  |  |
|-----------------------------------|---------------------------------------|-------------------------|--|--|
| Subject group type                | Reporting group                       | Reporting group         |  |  |
| Number of subjects analysed       | 545                                   | 548                     |  |  |
| Units: Percentage of participants |                                       |                         |  |  |
| number (confidence interval 95%)  | 31.2 (27.4 to 35.2)                   | 28.8 (25.2 to 32.8)     |  |  |

### Statistical analyses

|                            |   |
|----------------------------|---|
| Statistical analysis title | Outcome Measure No. 3   |
| Comparison groups          | Necitumumab + Gemcitabine + Cisplatin v Gemcitabine + Cisplatin |

|   |                            |
|---|----------------------------|
| Number of subjects included in analysis | 1093                       |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority <sup>[3]</sup> |
| P-value                                 | = 0.3997                   |
| Method                                  | Cochran-Mantel-Haenszel    |
| Parameter estimate                      | Odds ratio (OR)            |
| Point estimate                          | 1.12                       |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | 0.86                       |
| upper limit                             | 1.45                       |

Notes:

[3] - Superiority or Other (legacy)

### Secondary: Mean Change From Baseline in Patient Reported Outcomes (PRO) Using the European Quality of Life-5 Dimension (EQ-5D)

|                 |   |
|-----------------|---|
| End point title | Mean Change From Baseline in Patient Reported Outcomes (PRO) Using the European Quality of Life-5 Dimension (EQ-5D) |
|-----------------|---|

End point description:

The EQ-5D is a generic, multidimensional, health-related, quality-of-life instrument. The profile allows participants to rate their health state in 5 health domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression using a three level scale 1-3 (no problem, some problems, and major problems). These combinations of attributes were converted into a weighted health-state Index Score according to the United Kingdom (UK) population-based algorithm. The possible values for the Index Score ranged from -0.59 (severe problems in all 5 dimensions) to 1.0 (no problem in any dimension).

APD: All randomized participants who had evaluable baseline and postbaseline EQ-5D data.

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

End point timeframe:

Baseline, Cycle 6 (Cycle = 3 Weeks)

| End point values                     | Necitumumab + Gemcitabine + Cisplatin | Gemcitabine + Cisplatin |  |  |
|--------------------------------------|---------------------------------------|-------------------------|--|--|
| Subject group type                   | Reporting group                       | Reporting group         |  |  |
| Number of subjects analysed          | 305                                   | 245                     |  |  |
| Units: Units on a scale              |                                       |                         |  |  |
| arithmetic mean (standard deviation) | -0.0053 (± 0.23626)                   | -0.0083 (± 0.23866)     |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Time to Treatment Failure (TTF)

|                 |                                 |
|-----------------|---------------------------------|
| End point title | Time to Treatment Failure (TTF) |
|-----------------|---------------------------------|

End point description:

TTF is defined as the time from the date of randomization until the date of the first radiographic documentation of PD, death from any cause, discontinuation of treatment for any reason, or initiation of new cancer therapy. Participants who withdrew from the study for reasons other than progression or death were censored at the date of study withdrawal. Participants who did not meet any of the criteria for treatment failure were censored at their date of last contact in the study.

APD: All randomized participants. Censored participants: Necitumumab + Gemcitabine + Cisplatin = 16, Gemcitabine + Cisplatin = 20

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

End point timeframe:

Randomization to Measured Progressive Disease, Death From Any Cause, Discontinuation of Treatment or Initiation of New Anticancer Therapy (Up to 31 Months)

| End point values                 | Necitumumab + Gemcitabine + Cisplatin | Gemcitabine + Cisplatin |  |  |
|----------------------------------|---------------------------------------|-------------------------|--|--|
| Subject group type               | Reporting group                       | Reporting group         |  |  |
| Number of subjects analysed      | 545                                   | 548                     |  |  |
| Units: Months                    |                                       |                         |  |  |
| median (confidence interval 95%) | 4.3 (4.2 to 4.8)                      | 3.6 (3.3 to 4.1)        |  |  |

## Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Outcome Measure No. 5   |
| Comparison groups                       | Necitumumab + Gemcitabine + Cisplatin v Gemcitabine + Cisplatin |
| Number of subjects included in analysis | 1093  |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority <sup>[4]</sup>                                      |
| P-value                                 | = 0.0061  |
| Method                                  | Logrank   |
| Parameter estimate                      | Hazard ratio (HR)   |
| Point estimate                          | 0.844   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 0.747   |
| upper limit                             | 0.943   |

Notes:

[4] - Superiority or Other (legacy)

## Secondary: Mean Change From Baseline in PRO Using the Outcomes Lung Cancer Symptom Scale (LCSS)

|                 |  |
|-----------------|--|
| End point title | Mean Change From Baseline in PRO Using the Outcomes Lung Cancer Symptom Scale (LCSS) |
|-----------------|--|

End point description:

The LCSS consisted of 9 items: 6 items focused on lung cancer symptoms [loss of appetite, fatigue, cough, dyspnea (shortness of breath), hemoptysis (blood in sputum), and pain] and 3 items were global items (symptom distress, interference with activity level, and global quality of life). Participant

responses to each item were measured using visual analogue scales (VAS) with 100-mm lines. A higher score for any item represented a higher level of symptoms/problems. Scores for each of the reported categories ranged from 0 (for best outcome) to 100 (for worst outcome). The Average Symptom Burden Index (ASBI) was the mean of the 6 symptom items of the LCSS, and the Total LCSS was the mean of all 9 LCSS items. ASBI and Total LCSS were not computed for a participant if he/she had 1 or more missing values for the 6 and 9 items, respectively.

APD: All randomized participants who had evaluable data for LCSS.

|                                     |           |
|-------------------------------------|-----------|
| End point type                      | Secondary |
| End point timeframe:                |           |
| Baseline, Cycle 6 (Cycle = 3 Weeks) |           |

| End point values                                 | Necitumumab + Gemcitabine + Cisplatin | Gemcitabine + Cisplatin |  |  |
|--|---------------------------------------|-------------------------|--|--|
| Subject group type                               | Reporting group                       | Reporting group         |  |  |
| Number of subjects analysed                      | 545                                   | 548                     |  |  |
| Units: millimeter (mm)                           |                                       |                         |  |  |
| arithmetic mean (standard deviation)             |                                       |                         |  |  |
| Loss of Appetite (n=304, 242)                    | 1.8 (± 31.84)                         | 1.5 (± 29.30)           |  |  |
| Fatigue (n=302, 242)                             | 6.3 (± 29.15)                         | 3.5 (± 25.29)           |  |  |
| Cough (n=303, 243)                               | -7.8 (± 28.05)                        | -9.1 (± 25.74)          |  |  |
| Dyspnea (n=305, 244)                             | -2.8 (± 26.52)                        | -1.8 (± 25.27)          |  |  |
| Pain (n=302, 243)                                | -3.3 (± 17.98)                        | -2.2 (± 17.22)          |  |  |
| Overall Symptoms (n=303, 242)                    | -0.3 (± 26.19)                        | -0.6 (± 26.92)          |  |  |
| Interference (n=306,241)                         | 3.8 (± 29.74)                         | 2.2 (± 26.79)           |  |  |
| Quality of Life (n=305, 243)                     | -0.3 (± 27.35)                        | -1.6 (± 24.71)          |  |  |
| Average Symptom Burden Index (ASBI) (n=294, 234) | -1.9 (± 16.55)                        | -1.5 (± 16.52)          |  |  |
| LCSS Total Score (n=290, 228)                    | -0.8 (± 17.03)                        | -0.8 (± 16.17)          |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants With an Epidermal Growth Factor Hormone (EGFR) Protein Expression Measured by Immunohistochemistry (IHC)

|                 |   |
|-----------------|---|
| End point title | Number of Participants With an Epidermal Growth Factor Hormone (EGFR) Protein Expression Measured by Immunohistochemistry (IHC) |
|-----------------|---|

End point description:

EGFR IHC Histoscore H-score = weighted sum of % 1+ cells, twice % 2+ cells, and three times % 3+ cells. IHC H-score criteria was used to assess participants with a low EGFR expression defined by a H-score cutoff value of <200 and participants with a high EGFR expression defined by a H-score of cutoff value of >=200.

APD: All randomized participants who received at least one dose of study drug and had evaluable data for EGFR IHC.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| 31 Months            |           |

| End point values            | Necitumumab + Gemcitabine + Cisplatin | Gemcitabine + Cisplatin |  |  |
|-----------------------------|---------------------------------------|-------------------------|--|--|
| Subject group type          | Reporting group                       | Reporting group         |  |  |
| Number of subjects analysed | 486                                   | 496                     |  |  |
| Units: Participants         |                                       |                         |  |  |
| 00                          | 24                                    | 23                      |  |  |
| >0                          | 462                                   | 473                     |  |  |
| <200                        | 295                                   | 313                     |  |  |
| >=200                       | 191                                   | 183                     |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Pharmacokinetics (PK): Minimum Concentration (Cmin) of Necitumumab

|                 |   |
|-----------------|---|
| End point title | Pharmacokinetics (PK): Minimum Concentration (Cmin) of Necitumumab <sup>[5]</sup> |
|-----------------|---|

End point description:

APD: All randomized participants who received at least one dose of study drug and had evaluable data for PK.

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

End point timeframe:

Day 1 of Cycle 2, 3, 4, 5 and 6 Prior to Necitumumab Drug Infusion, Up to 24 Months

Notes:

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

Justification: All randomized participants who received at least one dose of study drug and had evaluable data for PK were included in this analysis. No inferential statistics was planned for this end point.

| End point values                                    | Necitumumab + Gemcitabine + Cisplatin |  |  |  |
|---|---------------------------------------|--|--|--|
| Subject group type                                  | Reporting group                       |  |  |  |
| Number of subjects analysed                         | 545                                   |  |  |  |
| Units: micrograms/milliliter (ug/mL)                |                                       |  |  |  |
| geometric mean (geometric coefficient of variation) |                                       |  |  |  |
| Predose Cycle 2 Day 1 (n=419)                       | 52.4 (± 95.9)                         |  |  |  |
| Predose Cycle3 Day 1 (n=386)                        | 76.6 (± 80.6)                         |  |  |  |
| Predose Cycle 4 Day 1 (n=344)                       | 94.5 (± 92.2)                         |  |  |  |
| Predose Cycle 5 Day 1 (n=297)                       | 101 (± 90)                            |  |  |  |
| Predose Cycle 6 Day 1 (n=262)                       | 98.5 (± 80)                           |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants With a Serum Anti-Necitumumab Antibody Assessment

|                 |   |
|-----------------|---|
| End point title | Number of Participants With a Serum Anti-Necitumumab Antibody Assessment <sup>[6]</sup> |
|-----------------|---|

End point description:

A participant was considered to have an anti-Necitumumab antibody response if anti-drug antibodies (ADA) were detected at any time point.

APD: All randomized participants who received who received at least 1 dose of drug and had evaluable data for antibodies.

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

End point timeframe:

Baseline through 31 Months

Notes:

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

Justification: All randomized participants who received who received at least 1 dose of drug and had evaluable data for antibodies were included in this analysis. No inferential statistics was planned for this end point.

|   |                                       |  |  |  |
|---|---------------------------------------|--|--|--|
| <b>End point values</b>                     | Necitumumab + Gemcitabine + Cisplatin |  |  |  |
| Subject group type                          | Reporting group                       |  |  |  |
| Number of subjects analysed                 | 528                                   |  |  |  |
| Units: Participants                         |                                       |  |  |  |
| Participants with at least 1 positive titer | 81                                    |  |  |  |
| Neutralizing antibody detected              | 5                                     |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Baseline Up To 156 Months

Adverse event reporting additional description:

All participants who received at least one dose of study drug. The adverse events were analyzed and reported according to the study treatments pre-specified in the statistical analysis plan.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 27.1 |
|--------------------|------|

### Reporting groups

|                       |                         |
|-----------------------|-------------------------|
| Reporting group title | Gemcitabine + Cisplatin |
|-----------------------|-------------------------|

Reporting group description:

Gemcitabine: 1250 mg/m<sup>2</sup> on Days 1 and 8 of every 3 week cycle. Continues for a maximum of six cycles.

Cisplatin: 75 mg/m<sup>2</sup> IV on Day 1 of every 3 week cycle. Continues for a maximum of six cycles.

|                       |                                       |
|-----------------------|---------------------------------------|
| Reporting group title | Necitumumab + Gemcitabine + Cisplatin |
|-----------------------|---------------------------------------|

Reporting group description:

Necitumumab: 800 milligrams (mg) I.V. infusion on Days 1 and 8 of every 3 week cycle.

Continues until progressive disease, toxicity, noncompliance, or withdrawal.

Gemcitabine: 1250 milligrams/square meter (mg/m<sup>2</sup>) on Days 1 and 8 of every 3 week cycle.

Continues for a maximum of six cycles.

Cisplatin: 75 mg/m<sup>2</sup> IV on Day 1 of every 3 week cycle. Continues for a maximum of six cycles.

| Serious adverse events  | Gemcitabine + Cisplatin | Necitumumab + Gemcitabine + Cisplatin |  |
|---|-------------------------|---------------------------------------|--|
| Total subjects affected by serious adverse events                   |                         |                                       |  |
| subjects affected / exposed   | 208 / 541 (38.45%)      | 262 / 538 (48.70%)                    |  |
| number of deaths (all causes)                                       | 487                     | 476                                   |  |
| number of deaths resulting from adverse events                      |                         |                                       |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                         |                                       |  |
| cancer pain   |                         |                                       |  |
| alternative dictionary used: MedDRA 27.1                            |                         |                                       |  |
| subjects affected / exposed   | 3 / 541 (0.55%)         | 1 / 538 (0.19%)                       |  |
| occurrences causally related to treatment / all                     | 0 / 3                   | 0 / 1                                 |  |
| deaths causally related to treatment / all                          | 0 / 0                   | 0 / 0                                 |  |
| metastases to bone  |                         |                                       |  |
| alternative dictionary used: MedDRA 27.1                            |                         |                                       |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 541 (0.18%)  | 0 / 538 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| metastases to central nervous system            |                  |                  |  |
| alternative dictionary used: MedDRA 27.1        |                  |                  |  |
| subjects affected / exposed                     | 2 / 541 (0.37%)  | 1 / 538 (0.19%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| non-small cell lung cancer                      |                  |                  |  |
| alternative dictionary used: MedDRA 27.1        |                  |                  |  |
| subjects affected / exposed                     | 23 / 541 (4.25%) | 26 / 538 (4.83%) |  |
| occurrences causally related to treatment / all | 0 / 23           | 1 / 26           |  |
| deaths causally related to treatment / all      | 0 / 19           | 1 / 24           |  |
| Vascular disorders                              |                  |                  |  |
| deep vein thrombosis                            |                  |                  |  |
| alternative dictionary used: MedDRA 27.1        |                  |                  |  |
| subjects affected / exposed                     | 1 / 541 (0.18%)  | 4 / 538 (0.74%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 3 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| hypertensive crisis                             |                  |                  |  |
| alternative dictionary used: MedDRA 27.1        |                  |                  |  |
| subjects affected / exposed                     | 0 / 541 (0.00%)  | 1 / 538 (0.19%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| hypotension                                     |                  |                  |  |
| alternative dictionary used: MedDRA 27.1        |                  |                  |  |
| subjects affected / exposed                     | 0 / 541 (0.00%)  | 2 / 538 (0.37%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| hypovolaemic shock                              |                  |                  |  |
| alternative dictionary used: MedDRA 27.1        |                  |                  |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed   | 1 / 541 (0.18%) | 0 / 538 (0.00%) |  |
| occurrences causally related to treatment / all                             | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all                                  | 0 / 1           | 0 / 0           |  |
| peripheral artery occlusion<br>alternative dictionary used:<br>MedDRA 27.1  |                 |                 |  |
| subjects affected / exposed   | 1 / 541 (0.18%) | 1 / 538 (0.19%) |  |
| occurrences causally related to treatment / all                             | 0 / 1           | 1 / 1           |  |
| deaths causally related to treatment / all                                  | 0 / 0           | 0 / 0           |  |
| orthostatic hypotension<br>alternative dictionary used:<br>MedDRA 27.1      |                 |                 |  |
| subjects affected / exposed   | 2 / 541 (0.37%) | 0 / 538 (0.00%) |  |
| occurrences causally related to treatment / all                             | 2 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all                                  | 0 / 0           | 0 / 0           |  |
| peripheral venous disease<br>alternative dictionary used:<br>MedDRA 27.1    |                 |                 |  |
| subjects affected / exposed   | 0 / 541 (0.00%) | 1 / 538 (0.19%) |  |
| occurrences causally related to treatment / all                             | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all                                  | 0 / 0           | 0 / 0           |  |
| peripheral embolism<br>alternative dictionary used:<br>MedDRA 27.1          |                 |                 |  |
| subjects affected / exposed   | 0 / 541 (0.00%) | 1 / 538 (0.19%) |  |
| occurrences causally related to treatment / all                             | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all                                  | 0 / 0           | 0 / 0           |  |
| peripheral artery thrombosis<br>alternative dictionary used:<br>MedDRA 27.1 |                 |                 |  |
| subjects affected / exposed   | 1 / 541 (0.18%) | 2 / 538 (0.37%) |  |
| occurrences causally related to treatment / all                             | 1 / 1           | 1 / 2           |  |
| deaths causally related to treatment / all                                  | 0 / 0           | 0 / 0           |  |
| thrombosis<br>alternative dictionary used:<br>MedDRA 27.1                   |                 |                 |  |
| subjects affected / exposed   | 1 / 541 (0.18%) | 1 / 538 (0.19%) |  |
| occurrences causally related to treatment / all                             | 1 / 1           | 1 / 1           |  |
| deaths causally related to treatment / all                                  | 0 / 0           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| superior vena cava syndrome<br>alternative dictionary used:<br>MedDRA 27.1  |                 |                 |  |
| subjects affected / exposed   | 0 / 541 (0.00%) | 1 / 538 (0.19%) |  |
| occurrences causally related to<br>treatment / all                          | 0 / 0           | 0 / 1           |  |
| deaths causally related to<br>treatment / all                               | 0 / 0           | 0 / 0           |  |
| superior vena cava occlusion<br>alternative dictionary used:<br>MedDRA 27.1 |                 |                 |  |
| subjects affected / exposed   | 1 / 541 (0.18%) | 0 / 538 (0.00%) |  |
| occurrences causally related to<br>treatment / all                          | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                               | 0 / 0           | 0 / 0           |  |
| superficial vein thrombosis<br>alternative dictionary used:<br>MedDRA 27.1  |                 |                 |  |
| subjects affected / exposed   | 1 / 541 (0.18%) | 0 / 538 (0.00%) |  |
| occurrences causally related to<br>treatment / all                          | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                               | 0 / 0           | 0 / 0           |  |
| vena cava thrombosis<br>alternative dictionary used:<br>MedDRA 27.1         |                 |                 |  |
| subjects affected / exposed   | 0 / 541 (0.00%) | 1 / 538 (0.19%) |  |
| occurrences causally related to<br>treatment / all                          | 0 / 0           | 1 / 1           |  |
| deaths causally related to<br>treatment / all                               | 0 / 0           | 0 / 0           |  |
| venous thrombosis<br>alternative dictionary used:<br>MedDRA 27.1            |                 |                 |  |
| subjects affected / exposed   | 1 / 541 (0.18%) | 1 / 538 (0.19%) |  |
| occurrences causally related to<br>treatment / all                          | 0 / 1           | 0 / 1           |  |
| deaths causally related to<br>treatment / all                               | 0 / 0           | 0 / 0           |  |
| venous thrombosis limb<br>alternative dictionary used:<br>MedDRA 27.1       |                 |                 |  |
| subjects affected / exposed   | 0 / 541 (0.00%) | 1 / 538 (0.19%) |  |
| occurrences causally related to<br>treatment / all                          | 0 / 0           | 1 / 1           |  |
| deaths causally related to<br>treatment / all                               | 0 / 0           | 0 / 0           |  |
| General disorders and administration<br>site conditions                     |                 |                 |  |
| asthenia<br>alternative dictionary used:<br>MedDRA 27.1                     |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 3 / 541 (0.55%) | 2 / 538 (0.37%) |  |
| occurrences causally related to treatment / all | 3 / 3           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| chills  |                 |                 |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                     | 1 / 541 (0.18%) | 0 / 538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| death   |                 |                 |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                     | 3 / 541 (0.55%) | 8 / 538 (1.49%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 1 / 8           |  |
| deaths causally related to treatment / all      | 0 / 3           | 1 / 8           |  |
| fatigue   |                 |                 |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                     | 4 / 541 (0.74%) | 3 / 538 (0.56%) |  |
| occurrences causally related to treatment / all | 4 / 4           | 3 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| general physical health deterioration           |                 |                 |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                     | 7 / 541 (1.29%) | 8 / 538 (1.49%) |  |
| occurrences causally related to treatment / all | 1 / 7           | 5 / 8           |  |
| deaths causally related to treatment / all      | 0 / 0           | 1 / 1           |  |
| generalised oedema                              |                 |                 |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                     | 1 / 541 (0.18%) | 0 / 538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| non-cardiac chest pain                          |                 |                 |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                     | 0 / 541 (0.00%) | 1 / 538 (0.19%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|  |   |   |  |
|--|---|---|--|
| oedema<br>alternative dictionary used:<br>MedDRA 27.1<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all  | <br><br><br>1 / 541 (0.18%)<br><br>1 / 1<br><br>0 / 0 | <br><br><br>0 / 538 (0.00%)<br><br>0 / 0<br><br>0 / 0 |  |
| oedema peripheral<br>alternative dictionary used:<br>MedDRA 27.1<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all                                   | <br><br><br>1 / 541 (0.18%)<br><br>0 / 1<br><br>0 / 0 | <br><br><br>1 / 538 (0.19%)<br><br>0 / 1<br><br>0 / 0 |  |
| pyrexia<br>alternative dictionary used:<br>MedDRA 27.1<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all   | <br><br><br>4 / 541 (0.74%)<br><br>3 / 4<br><br>0 / 0 | <br><br><br>7 / 538 (1.30%)<br><br>5 / 7<br><br>0 / 0 |  |
| sudden death<br>alternative dictionary used:<br>MedDRA 27.1<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all  | <br><br><br>0 / 541 (0.00%)<br><br>0 / 0<br><br>0 / 0 | <br><br><br>2 / 538 (0.37%)<br><br>0 / 2<br><br>0 / 2 |  |
| Immune system disorders<br>drug hypersensitivity<br>alternative dictionary used:<br>MedDRA 27.1<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all    | <br><br><br>0 / 541 (0.00%)<br><br>0 / 0<br><br>0 / 0 | <br><br><br>2 / 538 (0.37%)<br><br>2 / 2<br><br>0 / 0 |  |
| Social circumstances<br>social stay hospitalisation<br>alternative dictionary used:<br>MedDRA 27.1<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all | <br><br><br>0 / 541 (0.00%)<br><br>0 / 0<br><br>0 / 0 | <br><br><br>1 / 538 (0.19%)<br><br>0 / 1<br><br>0 / 0 |  |
| Reproductive system and breast disorders   |   |   |  |

|   |                                   |                                   |  |
|---|-----------------------------------|-----------------------------------|--|
| pelvic pain<br>alternative dictionary used:<br>MedDRA 27.1<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all  | 0 / 541 (0.00%)<br>0 / 0<br>0 / 0 | 1 / 538 (0.19%)<br>0 / 1<br>0 / 0 |  |
| Respiratory, thoracic and mediastinal disorders<br>acute respiratory failure<br>alternative dictionary used:<br>MedDRA 27.1<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all | 1 / 541 (0.18%)<br>1 / 1<br>1 / 1 | 1 / 538 (0.19%)<br>0 / 1<br>0 / 1 |  |
| acute pulmonary oedema<br>alternative dictionary used:<br>MedDRA 27.1<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all   | 1 / 541 (0.18%)<br>0 / 1<br>0 / 0 | 0 / 538 (0.00%)<br>0 / 0<br>0 / 0 |  |
| acute respiratory distress syndrome<br>alternative dictionary used:<br>MedDRA 27.1<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all  | 1 / 541 (0.18%)<br>0 / 1<br>0 / 1 | 0 / 538 (0.00%)<br>0 / 0<br>0 / 0 |  |
| bronchitis chronic<br>alternative dictionary used:<br>MedDRA 27.1<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all   | 1 / 541 (0.18%)<br>0 / 1<br>0 / 0 | 0 / 538 (0.00%)<br>0 / 0<br>0 / 0 |  |
| chronic obstructive pulmonary disease<br>alternative dictionary used:<br>MedDRA 27.1<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all  | 0 / 541 (0.00%)<br>0 / 0<br>0 / 0 | 2 / 538 (0.37%)<br>0 / 2<br>0 / 1 |  |
| cough<br>alternative dictionary used:   |                                   |                                   |  |

|   |                 |                  |  |
|---|-----------------|------------------|--|
| MedDRA 27.1                                     |                 |                  |  |
| subjects affected / exposed                     | 1 / 541 (0.18%) | 0 / 538 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| dyspnoea  |                 |                  |  |
| alternative dictionary used: MedDRA 27.1        |                 |                  |  |
| subjects affected / exposed                     | 4 / 541 (0.74%) | 3 / 538 (0.56%)  |  |
| occurrences causally related to treatment / all | 4 / 4           | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| epistaxis                                       |                 |                  |  |
| alternative dictionary used: MedDRA 27.1        |                 |                  |  |
| subjects affected / exposed                     | 1 / 541 (0.18%) | 0 / 538 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| haemoptysis                                     |                 |                  |  |
| alternative dictionary used: MedDRA 27.1        |                 |                  |  |
| subjects affected / exposed                     | 9 / 541 (1.66%) | 11 / 538 (2.04%) |  |
| occurrences causally related to treatment / all | 2 / 9           | 4 / 11           |  |
| deaths causally related to treatment / all      | 0 / 5           | 1 / 4            |  |
| interstitial lung disease                       |                 |                  |  |
| alternative dictionary used: MedDRA 27.1        |                 |                  |  |
| subjects affected / exposed                     | 0 / 541 (0.00%) | 1 / 538 (0.19%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 1 / 1            |  |
| lung infiltration                               |                 |                  |  |
| alternative dictionary used: MedDRA 27.1        |                 |                  |  |
| subjects affected / exposed                     | 1 / 541 (0.18%) | 0 / 538 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| pulmonary toxicity                              |                 |                  |  |
| alternative dictionary used: MedDRA 27.1        |                 |                  |  |

|  |                 |                  |  |
|--|-----------------|------------------|--|
| subjects affected / exposed  | 1 / 541 (0.18%) | 0 / 538 (0.00%)  |  |
| occurrences causally related to treatment / all                            | 1 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all                                 | 0 / 0           | 0 / 0            |  |
| pharyngeal inflammation<br>alternative dictionary used:<br>MedDRA 27.1     |                 |                  |  |
| subjects affected / exposed  | 0 / 541 (0.00%) | 1 / 538 (0.19%)  |  |
| occurrences causally related to treatment / all                            | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all                                 | 0 / 0           | 0 / 0            |  |
| pneumonitis<br>alternative dictionary used:<br>MedDRA 27.1                 |                 |                  |  |
| subjects affected / exposed  | 1 / 541 (0.18%) | 1 / 538 (0.19%)  |  |
| occurrences causally related to treatment / all                            | 0 / 1           | 0 / 1            |  |
| deaths causally related to treatment / all                                 | 0 / 0           | 0 / 0            |  |
| pneumothorax<br>alternative dictionary used:<br>MedDRA 27.1                |                 |                  |  |
| subjects affected / exposed  | 1 / 541 (0.18%) | 1 / 538 (0.19%)  |  |
| occurrences causally related to treatment / all                            | 0 / 1           | 0 / 1            |  |
| deaths causally related to treatment / all                                 | 0 / 0           | 0 / 0            |  |
| pulmonary artery thrombosis<br>alternative dictionary used:<br>MedDRA 27.1 |                 |                  |  |
| subjects affected / exposed  | 1 / 541 (0.18%) | 0 / 538 (0.00%)  |  |
| occurrences causally related to treatment / all                            | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all                                 | 0 / 0           | 0 / 0            |  |
| pulmonary embolism<br>alternative dictionary used:<br>MedDRA 27.1          |                 |                  |  |
| subjects affected / exposed  | 9 / 541 (1.66%) | 19 / 538 (3.53%) |  |
| occurrences causally related to treatment / all                            | 5 / 9           | 14 / 19          |  |
| deaths causally related to treatment / all                                 | 0 / 0           | 1 / 1            |  |
| pulmonary haemorrhage<br>alternative dictionary used:<br>MedDRA 27.1       |                 |                  |  |
| subjects affected / exposed  | 5 / 541 (0.92%) | 1 / 538 (0.19%)  |  |
| occurrences causally related to treatment / all                            | 0 / 5           | 0 / 1            |  |
| deaths causally related to treatment / all                                 | 0 / 4           | 0 / 1            |  |



|  |                                   |                                   |  |
|--|-----------------------------------|-----------------------------------|--|
| pulmonary hypertension<br>alternative dictionary used:<br>MedDRA 27.1<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all        | 1 / 541 (0.18%)<br>1 / 1<br>1 / 1 | 0 / 538 (0.00%)<br>0 / 0<br>0 / 0 |  |
| pulmonary oedema<br>alternative dictionary used:<br>MedDRA 27.1<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all              | 1 / 541 (0.18%)<br>0 / 1<br>0 / 1 | 1 / 538 (0.19%)<br>0 / 1<br>0 / 0 |  |
| pleural effusion<br>alternative dictionary used:<br>MedDRA 27.1<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all              | 1 / 541 (0.18%)<br>0 / 1<br>0 / 0 | 4 / 538 (0.74%)<br>1 / 4<br>0 / 0 |  |
| pulmonary venous thrombosis<br>alternative dictionary used:<br>MedDRA 27.1<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all   | 0 / 541 (0.00%)<br>0 / 0<br>0 / 0 | 1 / 538 (0.19%)<br>0 / 1<br>0 / 0 |  |
| respiratory tract haemorrhage<br>alternative dictionary used:<br>MedDRA 27.1<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all | 2 / 541 (0.37%)<br>2 / 2<br>2 / 2 | 0 / 538 (0.00%)<br>0 / 0<br>0 / 0 |  |
| respiratory failure<br>alternative dictionary used:<br>MedDRA 27.1<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all           | 2 / 541 (0.37%)<br>0 / 2<br>0 / 1 | 2 / 538 (0.37%)<br>0 / 2<br>0 / 1 |  |
| Psychiatric disorders<br>abnormal behaviour<br>alternative dictionary used:<br>MedDRA 27.1   |                                   |                                   |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 541 (0.18%) | 0 / 538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| alcohol abuse                                   |                 |                 |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                     | 0 / 541 (0.00%) | 1 / 538 (0.19%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| completed suicide                               |                 |                 |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                     | 1 / 541 (0.18%) | 0 / 538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| confusional state                               |                 |                 |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                     | 1 / 541 (0.18%) | 2 / 538 (0.37%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| delirium  |                 |                 |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                     | 1 / 541 (0.18%) | 1 / 538 (0.19%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| depression                                      |                 |                 |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                     | 0 / 541 (0.00%) | 1 / 538 (0.19%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Investigations                                  |                 |                 |  |
| alanine aminotransferase increased              |                 |                 |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |

|   |                 |                 |  |  |
|---|-----------------|-----------------|--|--|
| subjects affected / exposed                     | 0 / 541 (0.00%) | 1 / 538 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |  |
| aspartate aminotransferase increased            |                 |                 |  |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |  |
| subjects affected / exposed                     | 0 / 541 (0.00%) | 1 / 538 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |  |
| blood creatinine increased                      |                 |                 |  |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |  |
| subjects affected / exposed                     | 1 / 541 (0.18%) | 6 / 538 (1.12%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           | 5 / 6           |  |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |  |
| blood phosphorus decreased                      |                 |                 |  |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |  |
| subjects affected / exposed                     | 0 / 541 (0.00%) | 1 / 538 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |  |
| c-reactive protein increased                    |                 |                 |  |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |  |
| subjects affected / exposed                     | 0 / 541 (0.00%) | 1 / 538 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |  |
| ecg signs of myocardial ischaemia               |                 |                 |  |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |  |
| subjects affected / exposed                     | 1 / 541 (0.18%) | 0 / 538 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |  |
| false positive investigation result             |                 |                 |  |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 541 (0.18%) | 0 / 538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| gamma-glutamyltransferase increased             |                 |                 |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                     | 0 / 541 (0.00%) | 1 / 538 (0.19%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| haemoglobin decreased                           |                 |                 |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                     | 1 / 541 (0.18%) | 1 / 538 (0.19%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| platelet count decreased                        |                 |                 |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                     | 1 / 541 (0.18%) | 0 / 538 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Injury, poisoning and procedural complications  |                 |                 |  |
| femoral neck fracture                           |                 |                 |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                     | 0 / 541 (0.00%) | 1 / 538 (0.19%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| femur fracture                                  |                 |                 |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                     | 0 / 541 (0.00%) | 2 / 538 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| head injury                                     |                 |                 |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 541 (0.00%)  | 1 / 538 (0.19%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| incorrect dose administered                     |                  |                  |  |
| alternative dictionary used: MedDRA 27.1        |                  |                  |  |
| subjects affected / exposed                     | 1 / 541 (0.18%)  | 0 / 538 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| medication error                                |                  |                  |  |
| alternative dictionary used: MedDRA 27.1        |                  |                  |  |
| subjects affected / exposed                     | 21 / 541 (3.88%) | 12 / 538 (2.23%) |  |
| occurrences causally related to treatment / all | 1 / 21           | 3 / 12           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| overdose  |                  |                  |  |
| alternative dictionary used: MedDRA 27.1        |                  |                  |  |
| subjects affected / exposed                     | 0 / 541 (0.00%)  | 1 / 538 (0.19%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| toxicity to various agents                      |                  |                  |  |
| alternative dictionary used: MedDRA 27.1        |                  |                  |  |
| subjects affected / exposed                     | 1 / 541 (0.18%)  | 0 / 538 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| spinal compression fracture                     |                  |                  |  |
| alternative dictionary used: MedDRA 27.1        |                  |                  |  |
| subjects affected / exposed                     | 0 / 541 (0.00%)  | 1 / 538 (0.19%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| vascular graft occlusion                        |                  |                  |  |
| alternative dictionary used: MedDRA 27.1        |                  |                  |  |
| subjects affected / exposed                     | 0 / 541 (0.00%)  | 1 / 538 (0.19%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |

|  |   |   |  |
|--|---|---|--|
| underdose<br>alternative dictionary used:<br>MedDRA 27.1<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all   | <br><br><br>0 / 541 (0.00%)<br>0 / 0<br>0 / 0 | <br><br><br>1 / 538 (0.19%)<br>1 / 1<br>0 / 0 |  |
| Congenital, familial and genetic disorders<br>tracheo-oesophageal fistula<br>alternative dictionary used:<br>MedDRA 27.1<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all | <br><br><br>0 / 541 (0.00%)<br>0 / 0<br>0 / 0 | <br><br><br>1 / 538 (0.19%)<br>0 / 1<br>0 / 0 |  |
| Cardiac disorders<br>acute coronary syndrome<br>alternative dictionary used:<br>MedDRA 27.1<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all                              | <br><br><br>1 / 541 (0.18%)<br>0 / 1<br>0 / 0 | <br><br><br>0 / 538 (0.00%)<br>0 / 0<br>0 / 0 |  |
| acute myocardial infarction<br>alternative dictionary used:<br>MedDRA 27.1<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all   | <br><br><br>1 / 541 (0.18%)<br>0 / 1<br>0 / 0 | <br><br><br>2 / 538 (0.37%)<br>1 / 2<br>0 / 0 |  |
| atrial fibrillation<br>alternative dictionary used:<br>MedDRA 27.1<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all   | <br><br><br>4 / 541 (0.74%)<br>2 / 4<br>0 / 0 | <br><br><br>3 / 538 (0.56%)<br>1 / 3<br>0 / 0 |  |
| atrial flutter<br>alternative dictionary used:<br>MedDRA 27.1<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all  | <br><br><br>1 / 541 (0.18%)<br>0 / 1<br>0 / 0 | <br><br><br>0 / 538 (0.00%)<br>0 / 0<br>0 / 0 |  |
| cardiac arrest   |   |   |  |

|  |                 |                 |  |
|--|-----------------|-----------------|--|
| alternative dictionary used:<br>MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                        | 0 / 541 (0.00%) | 2 / 538 (0.37%) |  |
| occurrences causally related to<br>treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 2           |  |
| cardiac failure                                    |                 |                 |  |
| alternative dictionary used:<br>MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                        | 2 / 541 (0.37%) | 0 / 538 (0.00%) |  |
| occurrences causally related to<br>treatment / all | 1 / 2           | 0 / 0           |  |
| deaths causally related to<br>treatment / all      | 1 / 2           | 0 / 0           |  |
| cardiac failure acute                              |                 |                 |  |
| alternative dictionary used:<br>MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                        | 1 / 541 (0.18%) | 0 / 538 (0.00%) |  |
| occurrences causally related to<br>treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all      | 0 / 1           | 0 / 0           |  |
| cardiac failure congestive                         |                 |                 |  |
| alternative dictionary used:<br>MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                        | 1 / 541 (0.18%) | 1 / 538 (0.19%) |  |
| occurrences causally related to<br>treatment / all | 1 / 1           | 0 / 1           |  |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 1           |  |
| cardiac tamponade                                  |                 |                 |  |
| alternative dictionary used:<br>MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                        | 0 / 541 (0.00%) | 1 / 538 (0.19%) |  |
| occurrences causally related to<br>treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           |  |
| cardio-respiratory arrest                          |                 |                 |  |
| alternative dictionary used:<br>MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                        | 1 / 541 (0.18%) | 3 / 538 (0.56%) |  |
| occurrences causally related to<br>treatment / all | 0 / 1           | 0 / 3           |  |
| deaths causally related to<br>treatment / all      | 0 / 1           | 0 / 3           |  |
| coronary artery disease                            |                 |                 |  |
| alternative dictionary used:<br>MedDRA 27.1        |                 |                 |  |

|   |                 |                 |  |  |
|---|-----------------|-----------------|--|--|
| subjects affected / exposed                     | 0 / 541 (0.00%) | 1 / 538 (0.19%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |  |
| myocardial ischaemia                            |                 |                 |  |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |  |
| subjects affected / exposed                     | 1 / 541 (0.18%) | 0 / 538 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |  |
| myocardial infarction                           |                 |                 |  |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |  |
| subjects affected / exposed                     | 2 / 541 (0.37%) | 2 / 538 (0.37%) |  |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 2           |  |  |
| pericarditis                                    |                 |                 |  |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |  |
| subjects affected / exposed                     | 1 / 541 (0.18%) | 0 / 538 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |  |
| pericardial effusion malignant                  |                 |                 |  |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |  |
| subjects affected / exposed                     | 1 / 541 (0.18%) | 0 / 538 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |  |
| pericardial effusion                            |                 |                 |  |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |  |
| subjects affected / exposed                     | 1 / 541 (0.18%) | 0 / 538 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |  |
| supraventricular tachycardia                    |                 |                 |  |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |  |
| subjects affected / exposed                     | 0 / 541 (0.00%) | 2 / 538 (0.37%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |  |



|  |                 |                 |  |
|--|-----------------|-----------------|--|
| Nervous system disorders                           |                 |                 |  |
| ataxia   |                 |                 |  |
| alternative dictionary used:<br>MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                        | 0 / 541 (0.00%) | 1 / 538 (0.19%) |  |
| occurrences causally related to<br>treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           |  |
| brain oedema                                       |                 |                 |  |
| alternative dictionary used:<br>MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                        | 0 / 541 (0.00%) | 1 / 538 (0.19%) |  |
| occurrences causally related to<br>treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to<br>treatment / all      | 0 / 0           | 1 / 1           |  |
| cerebral haemorrhage                               |                 |                 |  |
| alternative dictionary used:<br>MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                        | 0 / 541 (0.00%) | 1 / 538 (0.19%) |  |
| occurrences causally related to<br>treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           |  |
| cerebral infarction                                |                 |                 |  |
| alternative dictionary used:<br>MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                        | 0 / 541 (0.00%) | 1 / 538 (0.19%) |  |
| occurrences causally related to<br>treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           |  |
| cerebral ischaemia                                 |                 |                 |  |
| alternative dictionary used:<br>MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                        | 0 / 541 (0.00%) | 2 / 538 (0.37%) |  |
| occurrences causally related to<br>treatment / all | 0 / 0           | 1 / 2           |  |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           |  |
| dizziness  |                 |                 |  |
| alternative dictionary used:<br>MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                        | 0 / 541 (0.00%) | 4 / 538 (0.74%) |  |
| occurrences causally related to<br>treatment / all | 0 / 0           | 1 / 4           |  |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           |  |
| encephalopathy                                     |                 |                 |  |
| alternative dictionary used:<br>MedDRA 27.1        |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 541 (0.37%) | 0 / 538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 2           | 0 / 0           |  |
| epilepsy  |                 |                 |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                     | 0 / 541 (0.00%) | 1 / 538 (0.19%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| hydrocephalus                                   |                 |                 |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                     | 0 / 541 (0.00%) | 1 / 538 (0.19%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| headache  |                 |                 |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                     | 1 / 541 (0.18%) | 1 / 538 (0.19%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| hemiplegia                                      |                 |                 |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                     | 0 / 541 (0.00%) | 1 / 538 (0.19%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| loss of consciousness                           |                 |                 |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                     | 1 / 541 (0.18%) | 0 / 538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| ischaemic stroke                                |                 |                 |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                     | 0 / 541 (0.00%) | 4 / 538 (0.74%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 2 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |

|  |                 |                 |  |  |
|--|-----------------|-----------------|--|--|
| paraesthesia                                       |                 |                 |  |  |
| alternative dictionary used:<br>MedDRA 27.1        |                 |                 |  |  |
| subjects affected / exposed                        | 0 / 541 (0.00%) | 1 / 538 (0.19%) |  |  |
| occurrences causally related to<br>treatment / all | 0 / 0           | 1 / 1           |  |  |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           |  |  |
| peripheral motor neuropathy                        |                 |                 |  |  |
| alternative dictionary used:<br>MedDRA 27.1        |                 |                 |  |  |
| subjects affected / exposed                        | 0 / 541 (0.00%) | 1 / 538 (0.19%) |  |  |
| occurrences causally related to<br>treatment / all | 0 / 0           | 1 / 1           |  |  |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           |  |  |
| presyncope   |                 |                 |  |  |
| alternative dictionary used:<br>MedDRA 27.1        |                 |                 |  |  |
| subjects affected / exposed                        | 1 / 541 (0.18%) | 0 / 538 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all | 1 / 1           | 0 / 0           |  |  |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           |  |  |
| radiculopathy                                      |                 |                 |  |  |
| alternative dictionary used:<br>MedDRA 27.1        |                 |                 |  |  |
| subjects affected / exposed                        | 1 / 541 (0.18%) | 0 / 538 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all | 0 / 1           | 0 / 0           |  |  |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           |  |  |
| radial nerve palsy                                 |                 |                 |  |  |
| alternative dictionary used:<br>MedDRA 27.1        |                 |                 |  |  |
| subjects affected / exposed                        | 0 / 541 (0.00%) | 1 / 538 (0.19%) |  |  |
| occurrences causally related to<br>treatment / all | 0 / 0           | 0 / 1           |  |  |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           |  |  |
| seizure  |                 |                 |  |  |
| alternative dictionary used:<br>MedDRA 27.1        |                 |                 |  |  |
| subjects affected / exposed                        | 0 / 541 (0.00%) | 3 / 538 (0.56%) |  |  |
| occurrences causally related to<br>treatment / all | 0 / 0           | 1 / 3           |  |  |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           |  |  |
| sciatica   |                 |                 |  |  |
| alternative dictionary used:<br>MedDRA 27.1        |                 |                 |  |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 541 (0.18%) | 1 / 538 (0.19%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| spinal cord compression                         |                 |                 |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                     | 1 / 541 (0.18%) | 1 / 538 (0.19%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| syncope   |                 |                 |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                     | 3 / 541 (0.55%) | 4 / 538 (0.74%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 1 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| vocal cord paralysis                            |                 |                 |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                     | 2 / 541 (0.37%) | 0 / 538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| transient ischaemic attack                      |                 |                 |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                     | 1 / 541 (0.18%) | 2 / 538 (0.37%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Blood and lymphatic system disorders            |                 |                 |  |
| agranulocytosis                                 |                 |                 |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                     | 0 / 541 (0.00%) | 1 / 538 (0.19%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| anaemia   |                 |                 |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 17 / 541 (3.14%) | 22 / 538 (4.09%) |  |
| occurrences causally related to treatment / all | 15 / 17          | 21 / 22          |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| febrile neutropenia                             |                  |                  |  |
| alternative dictionary used: MedDRA 27.1        |                  |                  |  |
| subjects affected / exposed                     | 7 / 541 (1.29%)  | 6 / 538 (1.12%)  |  |
| occurrences causally related to treatment / all | 7 / 7            | 5 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| leukopenia                                      |                  |                  |  |
| alternative dictionary used: MedDRA 27.1        |                  |                  |  |
| subjects affected / exposed                     | 4 / 541 (0.74%)  | 6 / 538 (1.12%)  |  |
| occurrences causally related to treatment / all | 4 / 4            | 6 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| neutropenia                                     |                  |                  |  |
| alternative dictionary used: MedDRA 27.1        |                  |                  |  |
| subjects affected / exposed                     | 33 / 541 (6.10%) | 20 / 538 (3.72%) |  |
| occurrences causally related to treatment / all | 31 / 33          | 20 / 20          |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| myelosuppression                                |                  |                  |  |
| alternative dictionary used: MedDRA 27.1        |                  |                  |  |
| subjects affected / exposed                     | 1 / 541 (0.18%)  | 0 / 538 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| pancytopenia                                    |                  |                  |  |
| alternative dictionary used: MedDRA 27.1        |                  |                  |  |
| subjects affected / exposed                     | 3 / 541 (0.55%)  | 6 / 538 (1.12%)  |  |
| occurrences causally related to treatment / all | 3 / 3            | 6 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0            | 1 / 1            |  |
| thrombocytosis                                  |                  |                  |  |
| alternative dictionary used: MedDRA 27.1        |                  |                  |  |
| subjects affected / exposed                     | 0 / 541 (0.00%)  | 1 / 538 (0.19%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |

|  |                                      |                                      |  |
|--|--------------------------------------|--------------------------------------|--|
| thrombocytopenia<br>alternative dictionary used:<br>MedDRA 27.1<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all                                  | 20 / 541 (3.70%)<br>20 / 20<br>0 / 0 | 17 / 538 (3.16%)<br>16 / 17<br>0 / 0 |  |
| Ear and labyrinth disorders<br>deafness bilateral<br>alternative dictionary used:<br>MedDRA 27.1<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all | 1 / 541 (0.18%)<br>1 / 1<br>0 / 0    | 0 / 538 (0.00%)<br>0 / 0<br>0 / 0    |  |
| ototoxicity<br>alternative dictionary used:<br>MedDRA 27.1<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all                                       | 0 / 541 (0.00%)<br>0 / 0<br>0 / 0    | 1 / 538 (0.19%)<br>1 / 1<br>0 / 0    |  |
| Gastrointestinal disorders<br>abdominal pain<br>alternative dictionary used:<br>MedDRA 27.1<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all      | 1 / 541 (0.18%)<br>0 / 1<br>0 / 0    | 2 / 538 (0.37%)<br>0 / 2<br>0 / 0    |  |
| abdominal pain upper<br>alternative dictionary used:<br>MedDRA 27.1<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all                              | 0 / 541 (0.00%)<br>0 / 0<br>0 / 0    | 1 / 538 (0.19%)<br>0 / 1<br>0 / 0    |  |
| constipation<br>alternative dictionary used:<br>MedDRA 27.1<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all                                      | 1 / 541 (0.18%)<br>1 / 1<br>0 / 0    | 1 / 538 (0.19%)<br>0 / 1<br>0 / 0    |  |
| colitis ischaemic<br>alternative dictionary used:<br>MedDRA 27.1   |                                      |                                      |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 541 (0.00%) | 1 / 538 (0.19%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| duodenal ulcer                                  |                 |                 |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                     | 1 / 541 (0.18%) | 0 / 538 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| duodenal ulcer perforation                      |                 |                 |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                     | 1 / 541 (0.18%) | 0 / 538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| dysphagia                                       |                 |                 |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                     | 1 / 541 (0.18%) | 3 / 538 (0.56%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| enteritis                                       |                 |                 |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                     | 1 / 541 (0.18%) | 0 / 538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| diarrhoea                                       |                 |                 |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                     | 5 / 541 (0.92%) | 8 / 538 (1.49%) |  |
| occurrences causally related to treatment / all | 3 / 5           | 7 / 8           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| gastric haemorrhage                             |                 |                 |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                     | 0 / 541 (0.00%) | 1 / 538 (0.19%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |

|  |                 |                 |  |
|--|-----------------|-----------------|--|
| gastric ulcer                                      |                 |                 |  |
| alternative dictionary used:<br>MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                        | 1 / 541 (0.18%) | 0 / 538 (0.00%) |  |
| occurrences causally related to<br>treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           |  |
| gastroduodenal ulcer                               |                 |                 |  |
| alternative dictionary used:<br>MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                        | 0 / 541 (0.00%) | 1 / 538 (0.19%) |  |
| occurrences causally related to<br>treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           |  |
| gastrointestinal disorder                          |                 |                 |  |
| alternative dictionary used:<br>MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                        | 0 / 541 (0.00%) | 1 / 538 (0.19%) |  |
| occurrences causally related to<br>treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           |  |
| haematemesis                                       |                 |                 |  |
| alternative dictionary used:<br>MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                        | 1 / 541 (0.18%) | 0 / 538 (0.00%) |  |
| occurrences causally related to<br>treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           |  |
| haematochezia                                      |                 |                 |  |
| alternative dictionary used:<br>MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                        | 0 / 541 (0.00%) | 2 / 538 (0.37%) |  |
| occurrences causally related to<br>treatment / all | 0 / 0           | 2 / 2           |  |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           |  |
| ileus  |                 |                 |  |
| alternative dictionary used:<br>MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                        | 1 / 541 (0.18%) | 0 / 538 (0.00%) |  |
| occurrences causally related to<br>treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           |  |
| mesenteric vein thrombosis                         |                 |                 |  |
| alternative dictionary used:<br>MedDRA 27.1        |                 |                 |  |



|   |                 |                  |  |
|---|-----------------|------------------|--|
| subjects affected / exposed                     | 1 / 541 (0.18%) | 1 / 538 (0.19%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0            |  |
| intestinal obstruction                          |                 |                  |  |
| alternative dictionary used: MedDRA 27.1        |                 |                  |  |
| subjects affected / exposed                     | 2 / 541 (0.37%) | 1 / 538 (0.19%)  |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| nausea  |                 |                  |  |
| alternative dictionary used: MedDRA 27.1        |                 |                  |  |
| subjects affected / exposed                     | 2 / 541 (0.37%) | 4 / 538 (0.74%)  |  |
| occurrences causally related to treatment / all | 2 / 2           | 3 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| pancreatitis acute                              |                 |                  |  |
| alternative dictionary used: MedDRA 27.1        |                 |                  |  |
| subjects affected / exposed                     | 1 / 541 (0.18%) | 1 / 538 (0.19%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0            |  |
| small intestinal obstruction                    |                 |                  |  |
| alternative dictionary used: MedDRA 27.1        |                 |                  |  |
| subjects affected / exposed                     | 0 / 541 (0.00%) | 1 / 538 (0.19%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| stomatitis                                      |                 |                  |  |
| alternative dictionary used: MedDRA 27.1        |                 |                  |  |
| subjects affected / exposed                     | 3 / 541 (0.55%) | 2 / 538 (0.37%)  |  |
| occurrences causally related to treatment / all | 3 / 3           | 1 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| vomiting  |                 |                  |  |
| alternative dictionary used: MedDRA 27.1        |                 |                  |  |
| subjects affected / exposed                     | 2 / 541 (0.37%) | 12 / 538 (2.23%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 12 / 12          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |

|   |   |   |  |
|---|---|---|--|
| upper gastrointestinal haemorrhage<br>alternative dictionary used:<br>MedDRA 27.1<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all                             | <br><br><br>1 / 541 (0.18%)<br><br>1 / 1<br><br>0 / 0 | <br><br><br>0 / 538 (0.00%)<br><br>0 / 0<br><br>0 / 0 |  |
| Hepatobiliary disorders<br>bile duct stenosis<br>alternative dictionary used:<br>MedDRA 27.1<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all                  | <br><br><br>1 / 541 (0.18%)<br><br>0 / 1<br><br>0 / 0 | <br><br><br>0 / 538 (0.00%)<br><br>0 / 0<br><br>0 / 0 |  |
| cholelithiasis<br>alternative dictionary used:<br>MedDRA 27.1<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all   | <br><br><br>0 / 541 (0.00%)<br><br>0 / 0<br><br>0 / 0 | <br><br><br>1 / 538 (0.19%)<br><br>0 / 1<br><br>0 / 0 |  |
| hepatorenal syndrome<br>alternative dictionary used:<br>MedDRA 27.1<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all   | <br><br><br>0 / 541 (0.00%)<br><br>0 / 0<br><br>0 / 0 | <br><br><br>1 / 538 (0.19%)<br><br>1 / 1<br><br>0 / 0 |  |
| Skin and subcutaneous tissue disorders<br>dermatitis acneiform<br>alternative dictionary used:<br>MedDRA 27.1<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all | <br><br><br>0 / 541 (0.00%)<br><br>0 / 0<br><br>0 / 0 | <br><br><br>1 / 538 (0.19%)<br><br>1 / 1<br><br>0 / 0 |  |
| dermatitis allergic<br>alternative dictionary used:<br>MedDRA 27.1<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all  | <br><br><br>1 / 541 (0.18%)<br><br>0 / 1<br><br>0 / 0 | <br><br><br>0 / 538 (0.00%)<br><br>0 / 0<br><br>0 / 0 |  |
| rash maculo-papular<br>alternative dictionary used:<br>MedDRA 27.1  |   |   |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 541 (0.00%) | 1 / 538 (0.19%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| skin fissures                                   |                 |                 |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                     | 0 / 541 (0.00%) | 1 / 538 (0.19%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| skin toxicity                                   |                 |                 |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                     | 0 / 541 (0.00%) | 1 / 538 (0.19%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| skin ulcer                                      |                 |                 |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                     | 0 / 541 (0.00%) | 1 / 538 (0.19%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal and urinary disorders                     |                 |                 |  |
| acute kidney injury                             |                 |                 |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                     | 5 / 541 (0.92%) | 4 / 538 (0.74%) |  |
| occurrences causally related to treatment / all | 4 / 5           | 4 / 4           |  |
| deaths causally related to treatment / all      | 1 / 1           | 0 / 0           |  |
| nephrotic syndrome                              |                 |                 |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                     | 0 / 541 (0.00%) | 1 / 538 (0.19%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| nephropathy toxic                               |                 |                 |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 541 (0.18%) | 1 / 538 (0.19%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| renal failure                                   |                 |                 |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                     | 6 / 541 (1.11%) | 8 / 538 (1.49%) |  |
| occurrences causally related to treatment / all | 6 / 6           | 7 / 8           |  |
| deaths causally related to treatment / all      | 1 / 1           | 0 / 0           |  |
| renal infarct                                   |                 |                 |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                     | 0 / 541 (0.00%) | 1 / 538 (0.19%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| renal tubular necrosis                          |                 |                 |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                     | 1 / 541 (0.18%) | 0 / 538 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| urinary retention                               |                 |                 |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                     | 1 / 541 (0.18%) | 0 / 538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |                 |                 |  |
| arthralgia                                      |                 |                 |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                     | 0 / 541 (0.00%) | 1 / 538 (0.19%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| back pain                                       |                 |                 |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed   | 1 / 541 (0.18%) | 5 / 538 (0.93%) |  |
| occurrences causally related to treatment / all                               | 0 / 1           | 0 / 5           |  |
| deaths causally related to treatment / all                                    | 0 / 0           | 0 / 0           |  |
| intervertebral disc protrusion<br>alternative dictionary used:<br>MedDRA 27.1 |                 |                 |  |
| subjects affected / exposed   | 0 / 541 (0.00%) | 1 / 538 (0.19%) |  |
| occurrences causally related to treatment / all                               | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all                                    | 0 / 0           | 0 / 0           |  |
| osteolysis<br>alternative dictionary used:<br>MedDRA 27.1                     |                 |                 |  |
| subjects affected / exposed   | 1 / 541 (0.18%) | 0 / 538 (0.00%) |  |
| occurrences causally related to treatment / all                               | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all                                    | 0 / 0           | 0 / 0           |  |
| pathological fracture<br>alternative dictionary used:<br>MedDRA 27.1          |                 |                 |  |
| subjects affected / exposed   | 0 / 541 (0.00%) | 1 / 538 (0.19%) |  |
| occurrences causally related to treatment / all                               | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all                                    | 0 / 0           | 0 / 0           |  |
| pain in extremity<br>alternative dictionary used:<br>MedDRA 27.1              |                 |                 |  |
| subjects affected / exposed   | 1 / 541 (0.18%) | 1 / 538 (0.19%) |  |
| occurrences causally related to treatment / all                               | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all                                    | 0 / 0           | 0 / 0           |  |
| Infections and infestations   |                 |                 |  |
| appendicitis<br>alternative dictionary used:<br>MedDRA 27.1                   |                 |                 |  |
| subjects affected / exposed   | 1 / 541 (0.18%) | 0 / 538 (0.00%) |  |
| occurrences causally related to treatment / all                               | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all                                    | 0 / 0           | 0 / 0           |  |
| bacterial infection<br>alternative dictionary used:<br>MedDRA 27.1            |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 541 (0.18%) | 0 / 538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| bronchitis                                      |                 |                 |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                     | 3 / 541 (0.55%) | 6 / 538 (1.12%) |  |
| occurrences causally related to treatment / all | 2 / 3           | 2 / 6           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| cystitis  |                 |                 |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                     | 0 / 541 (0.00%) | 1 / 538 (0.19%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| device related infection                        |                 |                 |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                     | 0 / 541 (0.00%) | 1 / 538 (0.19%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| dental gangrene                                 |                 |                 |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                     | 1 / 541 (0.18%) | 0 / 538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| escherichia urinary tract infection             |                 |                 |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                     | 0 / 541 (0.00%) | 1 / 538 (0.19%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| gastroenteritis                                 |                 |                 |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                     | 1 / 541 (0.18%) | 1 / 538 (0.19%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|  |                  |                  |  |
|--|------------------|------------------|--|
| infectious pleural effusion<br>alternative dictionary used:<br>MedDRA 27.1       |                  |                  |  |
| subjects affected / exposed  | 1 / 541 (0.18%)  | 0 / 538 (0.00%)  |  |
| occurrences causally related to<br>treatment / all                               | 0 / 1            | 0 / 0            |  |
| deaths causally related to<br>treatment / all                                    | 0 / 0            | 0 / 0            |  |
| injection site abscess<br>alternative dictionary used:<br>MedDRA 27.1            |                  |                  |  |
| subjects affected / exposed  | 0 / 541 (0.00%)  | 1 / 538 (0.19%)  |  |
| occurrences causally related to<br>treatment / all                               | 0 / 0            | 0 / 1            |  |
| deaths causally related to<br>treatment / all                                    | 0 / 0            | 0 / 0            |  |
| lower respiratory tract infection<br>alternative dictionary used:<br>MedDRA 27.1 |                  |                  |  |
| subjects affected / exposed  | 4 / 541 (0.74%)  | 4 / 538 (0.74%)  |  |
| occurrences causally related to<br>treatment / all                               | 1 / 4            | 1 / 4            |  |
| deaths causally related to<br>treatment / all                                    | 0 / 0            | 0 / 0            |  |
| neutropenic sepsis<br>alternative dictionary used:<br>MedDRA 27.1                |                  |                  |  |
| subjects affected / exposed  | 2 / 541 (0.37%)  | 0 / 538 (0.00%)  |  |
| occurrences causally related to<br>treatment / all                               | 2 / 2            | 0 / 0            |  |
| deaths causally related to<br>treatment / all                                    | 1 / 1            | 0 / 0            |  |
| oral fungal infection<br>alternative dictionary used:<br>MedDRA 27.1             |                  |                  |  |
| subjects affected / exposed  | 0 / 541 (0.00%)  | 1 / 538 (0.19%)  |  |
| occurrences causally related to<br>treatment / all                               | 0 / 0            | 1 / 1            |  |
| deaths causally related to<br>treatment / all                                    | 0 / 0            | 0 / 0            |  |
| pneumonia<br>alternative dictionary used:<br>MedDRA 27.1                         |                  |                  |  |
| subjects affected / exposed  | 20 / 541 (3.70%) | 13 / 538 (2.42%) |  |
| occurrences causally related to<br>treatment / all                               | 6 / 20           | 2 / 13           |  |
| deaths causally related to<br>treatment / all                                    | 0 / 3            | 2 / 6            |  |
| pneumonia bacterial<br>alternative dictionary used:<br>MedDRA 27.1               |                  |                  |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 541 (0.00%) | 1 / 538 (0.19%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| pneumonia necrotising                           |                 |                 |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                     | 0 / 541 (0.00%) | 2 / 538 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| pyelonephritis acute                            |                 |                 |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                     | 1 / 541 (0.18%) | 0 / 538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| pulmonary tuberculosis                          |                 |                 |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                     | 1 / 541 (0.18%) | 0 / 538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| septic shock                                    |                 |                 |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                     | 3 / 541 (0.55%) | 0 / 538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 2           | 0 / 0           |  |
| sepsis  |                 |                 |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                     | 5 / 541 (0.92%) | 2 / 538 (0.37%) |  |
| occurrences causally related to treatment / all | 3 / 5           | 1 / 2           |  |
| deaths causally related to treatment / all      | 1 / 1           | 0 / 1           |  |
| respiratory tract infection bacterial           |                 |                 |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                     | 0 / 541 (0.00%) | 1 / 538 (0.19%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |



|  |                 |                 |  |
|--|-----------------|-----------------|--|
| respiratory tract infection<br>alternative dictionary used:<br>MedDRA 27.1<br>subjects affected / exposed                              | 1 / 541 (0.18%) | 0 / 538 (0.00%) |  |
| occurrences causally related to<br>treatment / all   | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all  | 0 / 0           | 0 / 0           |  |
| upper respiratory tract infection<br>alternative dictionary used:<br>MedDRA 27.1<br>subjects affected / exposed                        | 0 / 541 (0.00%) | 1 / 538 (0.19%) |  |
| occurrences causally related to<br>treatment / all   | 0 / 0           | 0 / 1           |  |
| deaths causally related to<br>treatment / all  | 0 / 0           | 0 / 0           |  |
| upper respiratory tract infection<br>bacterial<br>alternative dictionary used:<br>MedDRA 27.1<br>subjects affected / exposed           | 0 / 541 (0.00%) | 2 / 538 (0.37%) |  |
| occurrences causally related to<br>treatment / all   | 0 / 0           | 1 / 2           |  |
| deaths causally related to<br>treatment / all  | 0 / 0           | 1 / 2           |  |
| urinary tract infection<br>alternative dictionary used:<br>MedDRA 27.1<br>subjects affected / exposed                                  | 1 / 541 (0.18%) | 2 / 538 (0.37%) |  |
| occurrences causally related to<br>treatment / all   | 0 / 1           | 0 / 2           |  |
| deaths causally related to<br>treatment / all  | 0 / 0           | 0 / 0           |  |
| urosepsis<br>alternative dictionary used:<br>MedDRA 27.1<br>subjects affected / exposed  | 1 / 541 (0.18%) | 0 / 538 (0.00%) |  |
| occurrences causally related to<br>treatment / all   | 1 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all  | 1 / 1           | 0 / 0           |  |
| Metabolism and nutrition disorders<br>decreased appetite<br>alternative dictionary used:<br>MedDRA 27.1<br>subjects affected / exposed | 1 / 541 (0.18%) | 1 / 538 (0.19%) |  |
| occurrences causally related to<br>treatment / all   | 0 / 1           | 1 / 1           |  |
| deaths causally related to<br>treatment / all  | 0 / 0           | 0 / 0           |  |
| dehydration<br>alternative dictionary used:<br>MedDRA 27.1   |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 8 / 541 (1.48%) | 5 / 538 (0.93%) |  |
| occurrences causally related to treatment / all | 7 / 8           | 5 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| diabetic ketoacidosis                           |                 |                 |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                     | 1 / 541 (0.18%) | 0 / 538 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| electrolyte imbalance                           |                 |                 |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                     | 0 / 541 (0.00%) | 1 / 538 (0.19%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| hypomagnesaemia                                 |                 |                 |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                     | 1 / 541 (0.18%) | 3 / 538 (0.56%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 3 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| hypocalcaemia                                   |                 |                 |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                     | 0 / 541 (0.00%) | 2 / 538 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| hyperuricaemia                                  |                 |                 |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                     | 0 / 541 (0.00%) | 1 / 538 (0.19%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| hyperkalaemia                                   |                 |                 |  |
| alternative dictionary used: MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                     | 0 / 541 (0.00%) | 1 / 538 (0.19%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|  |                 |                 |  |
|--|-----------------|-----------------|--|
| hyperglycaemia                                     |                 |                 |  |
| alternative dictionary used:<br>MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                        | 3 / 541 (0.55%) | 1 / 538 (0.19%) |  |
| occurrences causally related to<br>treatment / all | 1 / 3           | 1 / 1           |  |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           |  |
| hypercreatininaemia                                |                 |                 |  |
| alternative dictionary used:<br>MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                        | 1 / 541 (0.18%) | 0 / 538 (0.00%) |  |
| occurrences causally related to<br>treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           |  |
| hypercalcaemia                                     |                 |                 |  |
| alternative dictionary used:<br>MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                        | 2 / 541 (0.37%) | 3 / 538 (0.56%) |  |
| occurrences causally related to<br>treatment / all | 0 / 2           | 0 / 3           |  |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           |  |
| hyponatraemia                                      |                 |                 |  |
| alternative dictionary used:<br>MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                        | 6 / 541 (1.11%) | 4 / 538 (0.74%) |  |
| occurrences causally related to<br>treatment / all | 5 / 6           | 3 / 4           |  |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           |  |
| hypophosphataemia                                  |                 |                 |  |
| alternative dictionary used:<br>MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                        | 0 / 541 (0.00%) | 1 / 538 (0.19%) |  |
| occurrences causally related to<br>treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           |  |
| hypokalaemia                                       |                 |                 |  |
| alternative dictionary used:<br>MedDRA 27.1        |                 |                 |  |
| subjects affected / exposed                        | 2 / 541 (0.37%) | 3 / 538 (0.56%) |  |
| occurrences causally related to<br>treatment / all | 1 / 2           | 2 / 3           |  |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           |  |

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

| <b>Non-serious adverse events</b>                     | <b>Gemcitabine +<br/>Cisplatin</b> | <b>Necitumumab +<br/>Gemcitabine +<br/>Cisplatin</b> |  |
|---|------------------------------------|--|--|
| Total subjects affected by non-serious adverse events |                                    |  |  |
| subjects affected / exposed                           | 512 / 541 (94.64%)                 | 518 / 538 (96.28%)                                   |  |
| Investigations  |                                    |  |  |
| blood creatinine increased                            |                                    |  |  |
| alternative dictionary used:<br>MedDRA 27.1           |                                    |  |  |
| subjects affected / exposed                           | 41 / 541 (7.58%)                   | 49 / 538 (9.11%)                                     |  |
| occurrences (all)                                     | 41                                 | 49   |  |
| weight decreased                                      |                                    |  |  |
| alternative dictionary used:<br>MedDRA 27.1           |                                    |  |  |
| subjects affected / exposed                           | 36 / 541 (6.65%)                   | 73 / 538 (13.57%)                                    |  |
| occurrences (all)                                     | 36                                 | 73   |  |
| Nervous system disorders                              |                                    |  |  |
| dizziness   |                                    |  |  |
| alternative dictionary used:<br>MedDRA 27.1           |                                    |  |  |
| subjects affected / exposed                           | 42 / 541 (7.76%)                   | 55 / 538 (10.22%)                                    |  |
| occurrences (all)                                     | 42                                 | 55   |  |
| headache  |                                    |  |  |
| alternative dictionary used:<br>MedDRA 27.1           |                                    |  |  |
| subjects affected / exposed                           | 32 / 541 (5.91%)                   | 57 / 538 (10.59%)                                    |  |
| occurrences (all)                                     | 32                                 | 57   |  |
| Blood and lymphatic system disorders                  |                                    |  |  |
| anaemia   |                                    |  |  |
| alternative dictionary used:<br>MedDRA 27.1           |                                    |  |  |
| subjects affected / exposed                           | 246 / 541 (45.47%)                 | 221 / 538 (41.08%)                                   |  |
| occurrences (all)                                     | 246                                | 221  |  |
| leukopenia  |                                    |  |  |
| alternative dictionary used:<br>MedDRA 27.1           |                                    |  |  |
| subjects affected / exposed                           | 85 / 541 (15.71%)                  | 71 / 538 (13.20%)                                    |  |
| occurrences (all)                                     | 85                                 | 71   |  |
| neutropenia   |                                    |  |  |
| alternative dictionary used:<br>MedDRA 27.1           |                                    |  |  |
| subjects affected / exposed                           | 229 / 541 (42.33%)                 | 220 / 538 (40.89%)                                   |  |
| occurrences (all)                                     | 229                                | 220  |  |
| thrombocytopenia                                      |                                    |  |  |

|  |                           |                           |  |
|--|---------------------------|---------------------------|--|
| alternative dictionary used:<br>MedDRA 27.1<br>subjects affected / exposed<br>occurrences (all)  | 124 / 541 (22.92%)<br>124 | 103 / 538 (19.14%)<br>103 |  |
| General disorders and administration<br>site conditions<br>asthenia<br>alternative dictionary used:<br>MedDRA 27.1<br>subjects affected / exposed<br>occurrences (all) | 112 / 541 (20.70%)<br>112 | 125 / 538 (23.23%)<br>125 |  |
| fatigue<br>alternative dictionary used:<br>MedDRA 27.1<br>subjects affected / exposed<br>occurrences (all)   | 121 / 541 (22.37%)<br>121 | 117 / 538 (21.75%)<br>117 |  |
| oedema peripheral<br>alternative dictionary used:<br>MedDRA 27.1<br>subjects affected / exposed<br>occurrences (all)   | 42 / 541 (7.76%)<br>42    | 44 / 538 (8.18%)<br>44    |  |
| pyrexia<br>alternative dictionary used:<br>MedDRA 27.1<br>subjects affected / exposed<br>occurrences (all)   | 61 / 541 (11.28%)<br>61   | 70 / 538 (13.01%)<br>70   |  |
| Gastrointestinal disorders<br>abdominal pain upper<br>alternative dictionary used:<br>MedDRA 27.1<br>subjects affected / exposed<br>occurrences (all)                  | 29 / 541 (5.36%)<br>29    | 31 / 538 (5.76%)<br>31    |  |
| constipation<br>alternative dictionary used:<br>MedDRA 27.1<br>subjects affected / exposed<br>occurrences (all)  | 101 / 541 (18.67%)<br>101 | 111 / 538 (20.63%)<br>111 |  |
| diarrhoea<br>alternative dictionary used:<br>MedDRA 27.1<br>subjects affected / exposed<br>occurrences (all)   | 60 / 541 (11.09%)<br>60   | 84 / 538 (15.61%)<br>84   |  |
| dyspepsia<br>alternative dictionary used:  |                           |                           |  |

|   |                    |                    |  |
|---|--------------------|--------------------|--|
| MedDRA 27.1                                     |                    |                    |  |
| subjects affected / exposed                     | 22 / 541 (4.07%)   | 27 / 538 (5.02%)   |  |
| occurrences (all)                               | 22                 | 27                 |  |
| nausea  |                    |                    |  |
| alternative dictionary used:<br>MedDRA 27.1     |                    |                    |  |
| subjects affected / exposed                     | 284 / 541 (52.50%) | 265 / 538 (49.26%) |  |
| occurrences (all)                               | 284                | 265                |  |
| stomatitis                                      |                    |                    |  |
| alternative dictionary used:<br>MedDRA 27.1     |                    |                    |  |
| subjects affected / exposed                     | 32 / 541 (5.91%)   | 58 / 538 (10.78%)  |  |
| occurrences (all)                               | 32                 | 58                 |  |
| vomiting  |                    |                    |  |
| alternative dictionary used:<br>MedDRA 27.1     |                    |                    |  |
| subjects affected / exposed                     | 134 / 541 (24.77%) | 153 / 538 (28.44%) |  |
| occurrences (all)                               | 134                | 153                |  |
| Respiratory, thoracic and mediastinal disorders |                    |                    |  |
| cough   |                    |                    |  |
| alternative dictionary used:<br>MedDRA 27.1     |                    |                    |  |
| subjects affected / exposed                     | 72 / 541 (13.31%)  | 93 / 538 (17.29%)  |  |
| occurrences (all)                               | 72                 | 93                 |  |
| dyspnoea  |                    |                    |  |
| alternative dictionary used:<br>MedDRA 27.1     |                    |                    |  |
| subjects affected / exposed                     | 79 / 541 (14.60%)  | 93 / 538 (17.29%)  |  |
| occurrences (all)                               | 79                 | 93                 |  |
| epistaxis                                       |                    |                    |  |
| alternative dictionary used:<br>MedDRA 27.1     |                    |                    |  |
| subjects affected / exposed                     | 16 / 541 (2.96%)   | 40 / 538 (7.43%)   |  |
| occurrences (all)                               | 16                 | 40                 |  |
| haemoptysis                                     |                    |                    |  |
| alternative dictionary used:<br>MedDRA 27.1     |                    |                    |  |
| subjects affected / exposed                     | 22 / 541 (4.07%)   | 49 / 538 (9.11%)   |  |
| occurrences (all)                               | 22                 | 49                 |  |
| productive cough                                |                    |                    |  |
| alternative dictionary used:<br>MedDRA 27.1     |                    |                    |  |

|   |                         |                           |  |
|---|-------------------------|---------------------------|--|
| subjects affected / exposed<br>occurrences (all)  | 12 / 541 (2.22%)<br>12  | 29 / 538 (5.39%)<br>29    |  |
| Skin and subcutaneous tissue disorders  |                         |                           |  |
| alopecia<br>alternative dictionary used:<br>MedDRA 27.1<br>subjects affected / exposed<br>occurrences (all)             | 70 / 541 (12.94%)<br>70 | 76 / 538 (14.13%)<br>76   |  |
| dermatitis acneiform<br>alternative dictionary used:<br>MedDRA 27.1<br>subjects affected / exposed<br>occurrences (all) | 3 / 541 (0.55%)<br>3    | 80 / 538 (14.87%)<br>80   |  |
| dry skin<br>alternative dictionary used:<br>MedDRA 27.1<br>subjects affected / exposed<br>occurrences (all)             | 8 / 541 (1.48%)<br>8    | 35 / 538 (6.51%)<br>35    |  |
| acne<br>alternative dictionary used:<br>MedDRA 27.1<br>subjects affected / exposed<br>occurrences (all)                 | 3 / 541 (0.55%)<br>3    | 47 / 538 (8.74%)<br>47    |  |
| pruritus<br>alternative dictionary used:<br>MedDRA 27.1<br>subjects affected / exposed<br>occurrences (all)             | 5 / 541 (0.92%)<br>5    | 39 / 538 (7.25%)<br>39    |  |
| rash<br>alternative dictionary used:<br>MedDRA 27.1<br>subjects affected / exposed<br>occurrences (all)                 | 32 / 541 (5.91%)<br>32  | 252 / 538 (46.84%)<br>252 |  |
| skin fissures<br>alternative dictionary used:<br>MedDRA 27.1<br>subjects affected / exposed<br>occurrences (all)        | 0 / 541 (0.00%)<br>0    | 27 / 538 (5.02%)<br>27    |  |
| Psychiatric disorders   |                         |                           |  |
| insomnia<br>alternative dictionary used:<br>MedDRA 27.1   |                         |                           |  |

|  |                           |                           |  |
|--|---------------------------|---------------------------|--|
| subjects affected / exposed<br>occurrences (all)   | 30 / 541 (5.55%)<br>30    | 29 / 538 (5.39%)<br>29    |  |
| Musculoskeletal and connective tissue disorders  |                           |                           |  |
| arthralgia<br>alternative dictionary used:<br>MedDRA 27.1<br>subjects affected / exposed<br>occurrences (all)              | 31 / 541 (5.73%)<br>31    | 31 / 538 (5.76%)<br>31    |  |
| back pain<br>alternative dictionary used:<br>MedDRA 27.1<br>subjects affected / exposed<br>occurrences (all)               | 30 / 541 (5.55%)<br>30    | 38 / 538 (7.06%)<br>38    |  |
| pain in extremity<br>alternative dictionary used:<br>MedDRA 27.1<br>subjects affected / exposed<br>occurrences (all)       | 21 / 541 (3.88%)<br>21    | 27 / 538 (5.02%)<br>27    |  |
| Infections and infestations  |                           |                           |  |
| paronychia<br>alternative dictionary used:<br>MedDRA 27.1<br>subjects affected / exposed<br>occurrences (all)              | 1 / 541 (0.18%)<br>1      | 36 / 538 (6.69%)<br>36    |  |
| urinary tract infection<br>alternative dictionary used:<br>MedDRA 27.1<br>subjects affected / exposed<br>occurrences (all) | 13 / 541 (2.40%)<br>13    | 31 / 538 (5.76%)<br>31    |  |
| Metabolism and nutrition disorders   |                           |                           |  |
| decreased appetite<br>alternative dictionary used:<br>MedDRA 27.1<br>subjects affected / exposed<br>occurrences (all)      | 153 / 541 (28.28%)<br>153 | 162 / 538 (30.11%)<br>162 |  |
| hyperglycaemia<br>alternative dictionary used:<br>MedDRA 27.1<br>subjects affected / exposed<br>occurrences (all)          | 16 / 541 (2.96%)<br>16    | 28 / 538 (5.20%)<br>28    |  |
| hyperkalaemia<br>alternative dictionary used:<br>MedDRA 27.1   |                           |                           |  |



|   |                   |                    |  |
|---|-------------------|--------------------|--|
| subjects affected / exposed                 | 19 / 541 (3.51%)  | 27 / 538 (5.02%)   |  |
| occurrences (all)                           | 19                | 27                 |  |
| hypokalaemia                                |                   |                    |  |
| alternative dictionary used:<br>MedDRA 27.1 |                   |                    |  |
| subjects affected / exposed                 | 27 / 541 (4.99%)  | 37 / 538 (6.88%)   |  |
| occurrences (all)                           | 27                | 37                 |  |
| hypomagnesaemia                             |                   |                    |  |
| alternative dictionary used:<br>MedDRA 27.1 |                   |                    |  |
| subjects affected / exposed                 | 82 / 541 (15.16%) | 159 / 538 (29.55%) |  |
| occurrences (all)                           | 82                | 159                |  |
| hyponatraemia                               |                   |                    |  |
| alternative dictionary used:<br>MedDRA 27.1 |                   |                    |  |
| subjects affected / exposed                 | 29 / 541 (5.36%)  | 23 / 538 (4.28%)   |  |
| occurrences (all)                           | 29                | 23                 |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date          | Amendment   |
|---------------|---|
| 20 April 2010 | - Updated secondary and exploratory objectives to reflect modification in the biomarker program; - Updated inclusion criteria for more clarity; - Updated efficacy and pharmacokinetic assessment data to reflect change in medical processes.  |
| 09 June 2011  | -Serious adverse events reporting information was updated; - Thromboembolic events section was added;   |
| 28 May 2013   | - A secondary objective was deleted, and some exploratory objectives were amended to reflect prioritization of biomarker analyses on current scientific data. - Changes made to tumor tissue collection and blood sampling collection to be consistent with changes made to objectives. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported