



## Clinical trial results:

### A Phase 3, Multicenter, Randomized, Double-blind, Placebo Controlled Study of Rilotumumab (AMG 102) with Epirubicin, Cisplatin, and Capecitabine (ECX) as First-line Therapy in Advanced MET-positive Gastric or Gastroesophageal Junction Adenocarcinoma

#### Summary

|                          |                                                 |
|--------------------------|-------------------------------------------------|
| EudraCT number           | 2011-004923-11                                  |
| Trial protocol           | GR IT CZ BE PT AT GB DE SE HU ES DK BG PL SK RO |
| Global end of trial date | 07 August 2015                                  |

#### Results information

|                                |                |
|--------------------------------|----------------|
| Result version number          | v1 (current)   |
| This version publication date  | 13 August 2016 |
| First version publication date | 13 August 2016 |

#### Trial information

##### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | 20070622 |
|-----------------------|----------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01697072 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |                                                                                       |
|------------------------------|---------------------------------------------------------------------------------------|
| Sponsor organisation name    | Amgen, Inc                                                                            |
| Sponsor organisation address | One Amgen Center Drive, Thousand Oaks, CA, United States, 91320                       |
| Public contact               | IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com |
| Scientific contact           | IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.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                       | 10 September 2015 |
| Is this the analysis of the primary completion data? | No                |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 07 August 2015    |
| Was the trial ended prematurely?                     | Yes               |

Notes:

## General information about the trial

Main objective of the trial:

To determine if the treatment of rilotumumab in combination with ECX significantly improves overall survival (OS) as compared with rilotumumab-placebo in combination with ECX in subjects with unresectable, locally advanced or metastatic, mesenchymal epithelial transition factor (MET)-positive, gastric, or gastroesophageal junction (GEJ).

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) and country-specific regulations/guidelines.

The investigator was responsible for obtaining written informed consent from the subject or legally acceptable representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol specified screening procedures or any investigational products are administered.

The study protocol, amendments, and the informed consent form (ICF) were reviewed by the Institutional Review Boards (IRBs) and Independent Ethics Committees (IECs). No subjects were recruited into the study and no investigational product (IP) was shipped until the IRB/IEC gave written approval of the protocol and ICF and Amgen received copies of these approvals.

An independent Data Monitoring Committee (DMC) external to Amgen conducted planned safety reviews and one interim efficacy review.

Background therapy: -

Evidence for comparator: -

|                                                           |                  |
|-----------------------------------------------------------|------------------|
| Actual start date of recruitment                          | 07 November 2012 |
| Long term follow-up planned                               | Yes              |
| Long term follow-up rationale                             | Safety, Efficacy |
| Long term follow-up duration                              | 6 Months         |
| Independent data monitoring committee (IDMC) involvement? | Yes              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Australia: 30      |
| Country: Number of subjects enrolled | Austria: 8         |
| Country: Number of subjects enrolled | Belgium: 6         |
| Country: Number of subjects enrolled | Brazil: 21         |
| Country: Number of subjects enrolled | Bulgaria: 16       |
| Country: Number of subjects enrolled | Canada: 12         |
| Country: Number of subjects enrolled | Czech Republic: 16 |
| Country: Number of subjects enrolled | Denmark: 9         |
| Country: Number of subjects enrolled | France: 20         |
| Country: Number of subjects enrolled | Germany: 34        |

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | United Kingdom: 56     |
| Country: Number of subjects enrolled | Greece: 10             |
| Country: Number of subjects enrolled | Hungary: 16            |
| Country: Number of subjects enrolled | Italy: 36              |
| Country: Number of subjects enrolled | Mexico: 14             |
| Country: Number of subjects enrolled | Poland: 47             |
| Country: Number of subjects enrolled | Portugal: 17           |
| Country: Number of subjects enrolled | Romania: 39            |
| Country: Number of subjects enrolled | Russian Federation: 63 |
| Country: Number of subjects enrolled | Slovakia: 7            |
| Country: Number of subjects enrolled | South Africa: 4        |
| Country: Number of subjects enrolled | Spain: 22              |
| Country: Number of subjects enrolled | Sweden: 1              |
| Country: Number of subjects enrolled | Switzerland: 7         |
| Country: Number of subjects enrolled | Turkey: 14             |
| Country: Number of subjects enrolled | Ukraine: 43            |
| Country: Number of subjects enrolled | United States: 41      |
| Worldwide total number of subjects   | 609                    |
| EEA total number of subjects         | 360                    |

Notes:

### Subjects enrolled per age group

|                                           |     |
|-------------------------------------------|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 0   |
| Adolescents (12-17 years)                 | 0   |
| Adults (18-64 years)                      | 404 |
| From 65 to 84 years                       | 205 |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

This study was conducted at 152 centers across Australia, Europe, South Africa, North America, and South America.

### Pre-assignment

Screening details:

Eligible subjects were randomized in a 1:1 ratio to either of 2 treatment arms. Randomization was stratified by 2 factors; extent of the disease (locally advanced vs metastatic disease) and the Eastern Cooperative Oncology Group (ECOG) status (0 vs 1).

### Period 1

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

### Arms

|                              |               |
|------------------------------|---------------|
| Are arms mutually exclusive? | Yes           |
| <b>Arm title</b>             | Placebo + ECX |

Arm description:

Participants received placebo to rilotumumab administered as an intravenous (IV) infusion on day 1 of each 21-day cycle until documented disease progression, intolerable adverse event, withdrawal of consent, or study termination by the sponsor. Participants also received chemotherapy with epirubicin (E) 50 mg/m<sup>2</sup> IV on day 1, cisplatin (C) 60 mg/m<sup>2</sup> IV on day 1, and capecitabine (X) 625 mg/m<sup>2</sup> orally twice a day on days 1 to 21 for a maximum of 10 cycles.

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

Dosage and administration details:

Administered as an intravenous (IV) infusion through a peripheral line or indwelling catheter on day 1 of each cycle before dosing of ECX.

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

Dosage and administration details:

50 mg/m<sup>2</sup> IV on day 1 of every 21 day cycle.

|                                        |                                       |
|----------------------------------------|---------------------------------------|
| Investigational medicinal product name | Cisplatin                             |
| Investigational medicinal product code |                                       |
| Other name                             |                                       |
| Pharmaceutical forms                   | Concentrate for solution for infusion |
| Routes of administration               | Intravenous use                       |

Dosage and administration details:

60 mg/m<sup>2</sup> IV on day 1 of every 21-day cycle

|                                        |                    |
|----------------------------------------|--------------------|
| Investigational medicinal product name | Capecitabine       |
| Investigational medicinal product code |                    |
| Other name                             | Xeloda             |
| Pharmaceutical forms                   | Film-coated tablet |
| Routes of administration               | Oral use           |

Dosage and administration details:

625 mg/m<sup>2</sup> orally twice a day on days 1-21 of every 21 day cycle

|                  |                   |
|------------------|-------------------|
| <b>Arm title</b> | Rilotumumab + ECX |
|------------------|-------------------|

Arm description:

Participants received rilotumumab 15 mg/kg administered as an IV infusion on day 1 of each 21-day cycle until documented disease progression, intolerable adverse event, withdrawal of consent, or study termination by the sponsor. Participants also received chemotherapy with epirubicin (E) 50 mg/m<sup>2</sup> IV on day 1, cisplatin (C) 60 mg/m<sup>2</sup> IV on day 1, and capecitabine (X) 625 mg/m<sup>2</sup> orally twice a day on days 1 to 21 for a maximum of 10 cycles.

|                                        |                       |
|----------------------------------------|-----------------------|
| Arm type                               | Experimental          |
| Investigational medicinal product name | Rilotumumab           |
| Investigational medicinal product code | AMG 102               |
| Other name                             |                       |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

Dosage and administration details:

Administered as an intravenous (IV) infusion through a peripheral line or indwelling catheter on day 1 of each cycle before dosing of ECX.

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

Dosage and administration details:

50 mg/m<sup>2</sup> IV on day 1 of every 21 day cycle.

|                                        |                                       |
|----------------------------------------|---------------------------------------|
| Investigational medicinal product name | Cisplatin                             |
| Investigational medicinal product code |                                       |
| Other name                             |                                       |
| Pharmaceutical forms                   | Concentrate for solution for infusion |
| Routes of administration               | Intravenous use                       |

Dosage and administration details:

60 mg/m<sup>2</sup> IV on day 1 of every 21-day cycle

|                                        |                    |
|----------------------------------------|--------------------|
| Investigational medicinal product name | Capecitabine       |
| Investigational medicinal product code |                    |
| Other name                             | Xeloda             |
| Pharmaceutical forms                   | Film-coated tablet |
| Routes of administration               | Oral use           |

Dosage and administration details:

625 mg/m<sup>2</sup> orally twice a day on days 1-21 of every 21 day cycle

| <b>Number of subjects in period 1</b> | Placebo + ECX | Rilotumumab + ECX |
|---------------------------------------|---------------|-------------------|
| Started                               | 305           | 304               |
| Received Study Drug                   | 300           | 297               |
| Completed                             | 0             | 0                 |
| Not completed                         | 305           | 304               |
| Consent withdrawn by subject          | 8             | 16                |
| Death                                 | 196           | 217               |
| Lost to follow-up                     | 10            | 7                 |
| Subjects continuing study             | 2             | 1                 |
| Decision by sponsor                   | 89            | 63                |

## Baseline characteristics

### Reporting groups

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                   |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Placebo + ECX     |
| Reporting group description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                   |
| Participants received placebo to rilotumumab administered as an intravenous (IV) infusion on day 1 of each 21-day cycle until documented disease progression, intolerable adverse event, withdrawal of consent, or study termination by the sponsor. Participants also received chemotherapy with epirubicin (E) 50 mg/m <sup>2</sup> IV on day 1, cisplatin (C) 60 mg/m <sup>2</sup> IV on day 1, and capecitabine (X) 625 mg/m <sup>2</sup> orally twice a day on days 1 to 21 for a maximum of 10 cycles. |                   |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Rilotumumab + ECX |
| Reporting group description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                   |
| Participants received rilotumumab 15 mg/kg administered as an IV infusion on day 1 of each 21-day cycle until documented disease progression, intolerable adverse event, withdrawal of consent, or study termination by the sponsor. Participants also received chemotherapy with epirubicin (E) 50 mg/m <sup>2</sup> IV on day 1, cisplatin (C) 60 mg/m <sup>2</sup> IV on day 1, and capecitabine (X) 625 mg/m <sup>2</sup> orally twice a day on days 1 to 21 for a maximum of 10 cycles.                 |                   |

| Reporting group values                                                                                                                                                                                                                                                                                                                                                                                                                 | Placebo + ECX | Rilotumumab + ECX | Total |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------|-------------------|-------|
| Number of subjects                                                                                                                                                                                                                                                                                                                                                                                                                     | 305           | 304               | 609   |
| Age Categorical                                                                                                                                                                                                                                                                                                                                                                                                                        |               |                   |       |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                        |               |                   |       |
| < 65 years                                                                                                                                                                                                                                                                                                                                                                                                                             | 211           | 193               | 404   |
| ≥ 65 years                                                                                                                                                                                                                                                                                                                                                                                                                             | 94            | 111               | 205   |
| Age Continuous                                                                                                                                                                                                                                                                                                                                                                                                                         |               |                   |       |
| Units: years                                                                                                                                                                                                                                                                                                                                                                                                                           |               |                   |       |
| arithmetic mean                                                                                                                                                                                                                                                                                                                                                                                                                        | 58.4          | 59.5              | -     |
| standard deviation                                                                                                                                                                                                                                                                                                                                                                                                                     | ± 11.2        | ± 11.3            | -     |
| Gender Categorical                                                                                                                                                                                                                                                                                                                                                                                                                     |               |                   |       |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                        |               |                   |       |
| Female                                                                                                                                                                                                                                                                                                                                                                                                                                 | 85            | 99                | 184   |
| Male                                                                                                                                                                                                                                                                                                                                                                                                                                   | 220           | 205               | 425   |
| Race                                                                                                                                                                                                                                                                                                                                                                                                                                   |               |                   |       |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                        |               |                   |       |
| Asian                                                                                                                                                                                                                                                                                                                                                                                                                                  | 2             | 4                 | 6     |
| Black or African American                                                                                                                                                                                                                                                                                                                                                                                                              | 5             | 3                 | 8     |
| Native Hawaiian or Other Pacific Islander                                                                                                                                                                                                                                                                                                                                                                                              | 0             | 1                 | 1     |
| Other                                                                                                                                                                                                                                                                                                                                                                                                                                  | 10            | 6                 | 16    |
| White                                                                                                                                                                                                                                                                                                                                                                                                                                  | 288           | 290               | 578   |
| Region                                                                                                                                                                                                                                                                                                                                                                                                                                 |               |                   |       |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                        |               |                   |       |
| Western Europe, South Africa and Australia                                                                                                                                                                                                                                                                                                                                                                                             | 129           | 121               | 250   |
| Eastern Europe (Including Turkey)                                                                                                                                                                                                                                                                                                                                                                                                      | 130           | 141               | 271   |
| North America                                                                                                                                                                                                                                                                                                                                                                                                                          | 27            | 26                | 53    |
| South America                                                                                                                                                                                                                                                                                                                                                                                                                          | 19            | 16                | 35    |
| Eastern Cooperative Oncology Group (ECOG) Performance Status                                                                                                                                                                                                                                                                                                                                                                           |               |                   |       |
| Scale used to assess how a patient's disease is progressing, how the disease affects the daily living abilities of the patient: 0 = Fully active, able to carry on all pre-disease performance without restriction; 1 = Restricted in physically strenuous activity, ambulatory, able to carry out work of a light nature; 2 = Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about > 50% |               |                   |       |

|                                                                                                                                                                        |     |     |     |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|-----|-----|
| of waking hours; 3 = Capable of only limited self care, confined to a bed or chair > 50% of waking hours; 4 = Completely disabled, confined to bed or chair; 5 = Dead. |     |     |     |
| Units: Subjects                                                                                                                                                        |     |     |     |
| Grade 0                                                                                                                                                                | 122 | 122 | 244 |
| Grade 1                                                                                                                                                                | 183 | 182 | 365 |
| Disease Extent                                                                                                                                                         |     |     |     |
| Units: Subjects                                                                                                                                                        |     |     |     |
| Locally advanced                                                                                                                                                       | 31  | 30  | 61  |
| Metastatic disease                                                                                                                                                     | 274 | 274 | 548 |



## End points

### End points reporting groups

|                       |               |
|-----------------------|---------------|
| Reporting group title | Placebo + ECX |
|-----------------------|---------------|

Reporting group description:

Participants received placebo to rilotumumab administered as an intravenous (IV) infusion on day 1 of each 21-day cycle until documented disease progression, intolerable adverse event, withdrawal of consent, or study termination by the sponsor. Participants also received chemotherapy with epirubicin (E) 50 mg/m<sup>2</sup> IV on day 1, cisplatin (C) 60 mg/m<sup>2</sup> IV on day 1, and capecitabine (X) 625 mg/m<sup>2</sup> orally twice a day on days 1 to 21 for a maximum of 10 cycles.

|                       |                   |
|-----------------------|-------------------|
| Reporting group title | Rilotumumab + ECX |
|-----------------------|-------------------|

Reporting group description:

Participants received rilotumumab 15 mg/kg administered as an IV infusion on day 1 of each 21-day cycle until documented disease progression, intolerable adverse event, withdrawal of consent, or study termination by the sponsor. Participants also received chemotherapy with epirubicin (E) 50 mg/m<sup>2</sup> IV on day 1, cisplatin (C) 60 mg/m<sup>2</sup> IV on day 1, and capecitabine (X) 625 mg/m<sup>2</sup> orally twice a day on days 1 to 21 for a maximum of 10 cycles.

### Primary: Overall Survival

|                 |                  |
|-----------------|------------------|
| End point title | Overall Survival |
|-----------------|------------------|

End point description:

Overall survival (OS) is defined as the time from randomization to death due to any cause. Subjects who had not died by the analysis data cut-off or were lost to follow-up were censored at their last contact date, subjects who withdrew consent were censored at the date of withdrawal. OS was analyzed using Kaplan-Meier methods.

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

End point timeframe:

From randomization until the data cut-off date of 10 September 2015; median (min, max) follow-up time was 7.74 months (0.07, 32.69) in the rilotumumab arm and 9.36 months (0.13, 28.78) in the placebo arm.

| End point values                 | Placebo + ECX         | Rilotumumab + ECX    |  |  |
|----------------------------------|-----------------------|----------------------|--|--|
| Subject group type               | Reporting group       | Reporting group      |  |  |
| Number of subjects analysed      | 305                   | 304                  |  |  |
| Units: months                    |                       |                      |  |  |
| median (confidence interval 95%) | 10.74 (9.63 to 12.35) | 8.84 (7.72 to 10.15) |  |  |

### Statistical analyses

|                            |                                      |
|----------------------------|--------------------------------------|
| Statistical analysis title | Primary Analysis of Overall Survival |
|----------------------------|--------------------------------------|

Statistical analysis description:

A log-rank test stratified by the randomization factors was used for the primary comparison.

|                   |                                   |
|-------------------|-----------------------------------|
| Comparison groups | Placebo + ECX v Rilotumumab + ECX |
|-------------------|-----------------------------------|

|                                         |                    |
|-----------------------------------------|--------------------|
| Number of subjects included in analysis | 609                |
| Analysis specification                  | Pre-specified      |
| Analysis type                           | superiority        |
| P-value                                 | = 1 <sup>[1]</sup> |
| Method                                  | Logrank            |

Notes:

[1] - 1-sided p-value stratified by disease extent and ECOG performance status.

|                                   |                                         |
|-----------------------------------|-----------------------------------------|
| <b>Statistical analysis title</b> | Additional Analysis of Overall Survival |
|-----------------------------------|-----------------------------------------|

Statistical analysis description:

A Cox proportional hazards regression model was used to provide the hazard ratio and 2-sided 95% CI for rilotumumab + ECX relative to placebo + ECX, stratified by disease extent and ECOG performance status. A hazard ratio < 1.0 indicates a lower average event rate and a longer overall survival for Rilotumumab + ECX relative to Placebo + ECX.

|                                         |                                   |
|-----------------------------------------|-----------------------------------|
| Comparison groups                       | Placebo + ECX v Rilotumumab + ECX |
| Number of subjects included in analysis | 609                               |
| Analysis specification                  | Pre-specified                     |
| Analysis type                           | superiority                       |
| P-value                                 | = 0.003 <sup>[2]</sup>            |
| Method                                  | Regression, Cox                   |
| Parameter estimate                      | Hazard ratio (HR)                 |
| Point estimate                          | 1.339                             |
| Confidence interval                     |                                   |
| level                                   | 95 %                              |
| sides                                   | 2-sided                           |
| lower limit                             | 1.103                             |
| upper limit                             | 1.627                             |

Notes:

[2] - 2-sided p-value stratified by disease extent and ECOG performance status.

## Secondary: Progression-free Survival

|                 |                           |
|-----------------|---------------------------|
| End point title | Progression-free Survival |
|-----------------|---------------------------|

End point description:

Progression-free survival (PFS) was defined as the time from the date of randomization to either disease progression or death. PFS was based upon the investigators assessment of disease progression, per Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1. If a subject's disease did not progress and the subject was alive, PFS was censored at the last evaluable radiological assessment. If a subject had no tumor evaluation in the study, the PFS time was censored at the date of randomization. PFS was analyzed using Kaplan-Meier methods.

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

End point timeframe:

From randomization until the data cut-off date of 10 September 2015; median (min, max) follow-up time was 7.74 months (0.07, 32.69) in the rilotumumab arm and 9.36 months (0.13, 28.78) in the placebo arm.

| End point values                 | Placebo + ECX      | Rilotumumab + ECX   |  |  |
|----------------------------------|--------------------|---------------------|--|--|
| Subject group type               | Reporting group    | Reporting group     |  |  |
| Number of subjects analysed      | 305                | 304                 |  |  |
| Units: months                    |                    |                     |  |  |
| median (confidence interval 95%) | 5.98 (5.65 to 7.2) | 5.62 (5.32 to 5.91) |  |  |

## Statistical analyses

| Statistical analysis title                                                                                                        | Primary Analysis of Progression-free Survival |
|-----------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|
| Statistical analysis description:<br>A log-rank test stratified by the randomization factors was used for the primary comparison. |                                               |
| Comparison groups                                                                                                                 | Placebo + ECX v Rilotumumab + ECX             |
| Number of subjects included in analysis                                                                                           | 609                                           |
| Analysis specification                                                                                                            | Pre-specified                                 |
| Analysis type                                                                                                                     | superiority                                   |
| P-value                                                                                                                           | = 0.99 <sup>[3]</sup>                         |
| Method                                                                                                                            | Logrank                                       |

Notes:

[3] - 1-sided p-value stratified by disease extent and ECOG performance status

| Statistical analysis title                                                                                                                                                                                                                                                                                            | Additional Analysis of Progression-free Survival |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------|
| Statistical analysis description:<br>The hazard ratio estimates were from a Cox proportional hazard model stratified by disease extent and ECOG performance status. A hazard ratio < 1.0 indicates a lower average event rate and a longer progression-free survival for Rilotumumab + ECX relative to Placebo + ECX. |                                                  |
| Comparison groups                                                                                                                                                                                                                                                                                                     | Placebo + ECX v Rilotumumab + ECX                |
| Number of subjects included in analysis                                                                                                                                                                                                                                                                               | 609                                              |
| Analysis specification                                                                                                                                                                                                                                                                                                | Pre-specified                                    |
| Analysis type                                                                                                                                                                                                                                                                                                         | superiority                                      |
| P-value                                                                                                                                                                                                                                                                                                               | = 0.016 <sup>[4]</sup>                           |
| Method                                                                                                                                                                                                                                                                                                                | Regression, Cox                                  |
| Parameter estimate                                                                                                                                                                                                                                                                                                    | Hazard ratio (HR)                                |
| Point estimate                                                                                                                                                                                                                                                                                                        | 1.256                                            |
| Confidence interval                                                                                                                                                                                                                                                                                                   |                                                  |
| level                                                                                                                                                                                                                                                                                                                 | 95 %                                             |
| sides                                                                                                                                                                                                                                                                                                                 | 2-sided                                          |
| lower limit                                                                                                                                                                                                                                                                                                           | 1.043                                            |
| upper limit                                                                                                                                                                                                                                                                                                           | 1.512                                            |

Notes:

[4] - 2-sided

## Secondary: Survival Rate at 12 Months

| End point title                                                                                                                                                  | Survival Rate at 12 Months |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------|
| End point description:<br>Survival rate at 12 months was defined as the stratified Kaplan-Meier (K-M) estimate of the percentage of subjects alive at 12 months. |                            |
| End point type                                                                                                                                                   | Secondary                  |

End point timeframe:

12 months

| End point values                  | Placebo + ECX       | Rilotumumab + ECX |  |  |
|-----------------------------------|---------------------|-------------------|--|--|
| Subject group type                | Reporting group     | Reporting group   |  |  |
| Number of subjects analysed       | 305                 | 304               |  |  |
| Units: percentage of participants |                     |                   |  |  |
| number (confidence interval 95%)  | 45.1 (39.2 to 50.8) | 36 (30.3 to 41.7) |  |  |

### Statistical analyses

|                                         |                                                |
|-----------------------------------------|------------------------------------------------|
| <b>Statistical analysis title</b>       | Primary Analysis of Survival Rate at 12 Months |
| Comparison groups                       | Placebo + ECX v Rilotumumab + ECX              |
| Number of subjects included in analysis | 609                                            |
| Analysis specification                  | Pre-specified                                  |
| Analysis type                           | superiority                                    |
| P-value                                 | = 0.032 <sup>[5]</sup>                         |
| Method                                  | Cochran-Mantel-Haenszel                        |
| Parameter estimate                      | Treatment difference                           |
| Point estimate                          | -8.9                                           |
| Confidence interval                     |                                                |
| level                                   | 95 %                                           |
| sides                                   | 2-sided                                        |
| lower limit                             | -17                                            |
| upper limit                             | -0.7                                           |

Notes:

[5] - Stratified by disease extent and ECOG performance status.

### Secondary: Time to Progression

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                     |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Time to Progression |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                     |
| Time to progression (TTP) was defined as the time from the date of randomization to disease progression (per RECIST 1.1). If a subject's disease did not progress, TTP was censored at the last evaluable radiological assessment, surgical resection date or the start of new anti-cancer therapy (if available) date. If a subject had no tumor evaluation in the study, the TTP time was censored at the date of randomization. If a subject died without radiological progression, TTP was censored at the last evaluable radiological assessment date. TTP was analyzed using Kaplan-Meier methods. |                     |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Secondary           |

End point timeframe:

From randomization until the data cut-off date of 10 September 2015; median (min, max) follow-up time was 7.74 months (0.07, 32.69) in the rilotumumab arm and 9.36 months (0.13, 28.78) in the placebo arm.

| End point values                 | Placebo + ECX       | Rilotumumab + ECX   |  |  |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type               | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed      | 305                 | 304                 |  |  |
| Units: months                    |                     |                     |  |  |
| median (confidence interval 95%) | 7.06 (5.88 to 7.85) | 6.05 (5.68 to 7.95) |  |  |

## Statistical analyses

| Statistical analysis title              | Primary Analysis of Time to Progression |
|-----------------------------------------|-----------------------------------------|
| Comparison groups                       | Placebo + ECX v Rilotumumab + ECX       |
| Number of subjects included in analysis | 609                                     |
| Analysis specification                  | Pre-specified                           |
| Analysis type                           | superiority                             |
| P-value                                 | = 0.95 <sup>[6]</sup>                   |
| Method                                  | Logrank                                 |

Notes:

[6] - 1-sided p-value stratified by disease extent and ECOG performance status

| Statistical analysis title              | Additional Analysis of Time to Progression |
|-----------------------------------------|--------------------------------------------|
| Comparison groups                       | Placebo + ECX v Rilotumumab + ECX          |
| Number of subjects included in analysis | 609                                        |
| Analysis specification                  | Pre-specified                              |
| Analysis type                           | superiority <sup>[7]</sup>                 |
| P-value                                 | = 0.097 <sup>[8]</sup>                     |
| Method                                  | Regression, Cox                            |
| Parameter estimate                      | Hazard ratio (HR)                          |
| Point estimate                          | 1.237                                      |
| Confidence interval                     |                                            |
| level                                   | 95 %                                       |
| sides                                   | 2-sided                                    |
| lower limit                             | 0.961                                      |
| upper limit                             | 1.591                                      |

Notes:

[7] - The hazard ratio estimates were obtained from the Cox Proportional Hazard Model. A hazard ratio < 1.0 indicates a lower average event rate and a longer time to progression for Rilotumumab + ECX relative to Placebo + ECX.

[8] - 2-sided

## Secondary: Objective Response Rate

| End point title        | Objective Response Rate                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point description: | Objective response rate was defined as the incidence rate of either complete response (CR) or partial response (PR) per RECIST 1.1 criteria. Best Overall Response for a subject is the best observed disease response per RECIST 1.1, excluding tumor assessments after initiation of new anti-cancer therapy, surgical resection or an assessment of disease progression. Overall response was analyzed in the Response Analysis Set, defined as the subset of subjects in the Full Analysis Set with at least 1 uni-dimensionally measurable lesion at baseline, per RECIST 1.1. |
| End point type         | Secondary                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |

End point timeframe:

From randomization until the data cut-off date of 10 September 2015; median (min, max) follow-up time was 7.74 months (0.07, 32.69) in the rilotumumab arm and 9.36 months (0.13, 28.78) in the placebo arm.

| End point values                  | Placebo + ECX       | Rilotumumab + ECX   |  |  |
|-----------------------------------|---------------------|---------------------|--|--|
| Subject group type                | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed       | 267 <sup>[9]</sup>  | 262 <sup>[10]</sup> |  |  |
| Units: percentage of participants |                     |                     |  |  |
| number (confidence interval 95%)  | 44.6 (38.5 to 50.8) | 29.8 (24.3 to 35.7) |  |  |

Notes:

[9] - Response Analysis Set

[10] - Response Analysis Set

## Statistical analyses

| Statistical analysis title                                                                                                                                                          | Analysis of Best Overall Response |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|
| Statistical analysis description:<br>A Cochran-Mantel-Haenszel test stratified by extent of disease and ECOG performance status was used to provide the adjusted common odds ratio. |                                   |
| Comparison groups                                                                                                                                                                   | Placebo + ECX v Rilotumumab + ECX |
| Number of subjects included in analysis                                                                                                                                             | 529                               |
| Analysis specification                                                                                                                                                              | Pre-specified                     |
| Analysis type                                                                                                                                                                       | superiority                       |
| P-value                                                                                                                                                                             | < 0.001                           |
| Method                                                                                                                                                                              | Cochran-Mantel-Haenszel           |
| Parameter estimate                                                                                                                                                                  | Odds ratio (OR)                   |
| Point estimate                                                                                                                                                                      | 0.53                              |
| Confidence interval                                                                                                                                                                 |                                   |
| level                                                                                                                                                                               | 95 %                              |
| sides                                                                                                                                                                               | 2-sided                           |
| lower limit                                                                                                                                                                         | 0.37                              |
| upper limit                                                                                                                                                                         | 0.76                              |

## Secondary: Disease Control Rate

| End point title                                                                                                                                                                                                                                                              | Disease Control Rate |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|
| End point description:<br>Disease control rate was defined as the incidence rate of either a CR, PR or stable disease (SD) per RECIST 1.1. The SD classification required subjects to have a response of SD $\geq$ 11 weeks after the date of the first dose of rilotumumab. |                      |
| End point type                                                                                                                                                                                                                                                               | Secondary            |
| End point timeframe:<br>From randomization until the data cut-off date of 10 September 2015; median (min, max) follow-up time was 7.74 months (0.07, 32.69) in the rilotumumab arm and 9.36 months (0.13, 28.78) in the placebo arm.                                         |                      |

| <b>End point values</b>           | Placebo + ECX       | Rilotumumab + ECX   |  |  |
|-----------------------------------|---------------------|---------------------|--|--|
| Subject group type                | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed       | 267 <sup>[11]</sup> | 262 <sup>[12]</sup> |  |  |
| Units: percentage of participants |                     |                     |  |  |
| number (confidence interval 95%)  | 70.8 (64.9 to 76.2) | 53.4 (47.2 to 59.6) |  |  |

Notes:

[11] - Response Analysis Set

[12] - Response Analysis Set

## Statistical analyses

| <b>Statistical analysis title</b> | Analysis of Disease Control Rate |
|-----------------------------------|----------------------------------|
|-----------------------------------|----------------------------------|

Statistical analysis description:

A Cochran-Mantel-Haenszel test stratified by extent of disease and ECOG performance status was used to provide the adjusted common odds ratio.

|                                         |                                   |
|-----------------------------------------|-----------------------------------|
| Comparison groups                       | Placebo + ECX v Rilotumumab + ECX |
| Number of subjects included in analysis | 529                               |
| Analysis specification                  | Pre-specified                     |
| Analysis type                           | superiority                       |
| P-value                                 | < 0.001                           |
| Method                                  | Cochran-Mantel-Haenszel           |
| Parameter estimate                      | Odds ratio (OR)                   |
| Point estimate                          | 0.47                              |
| Confidence interval                     |                                   |
| level                                   | 95 %                              |
| sides                                   | 2-sided                           |
| lower limit                             | 0.33                              |
| upper limit                             | 0.68                              |

## Secondary: Duration of Response

|                 |                      |
|-----------------|----------------------|
| End point title | Duration of Response |
|-----------------|----------------------|

End point description:

Duration of response (DOR) was defined as time from the date of first response (PR or CR) to disease progression (per RECIST 1.1) or death. If a subject's disease did not progress and the subject was alive, DOR was censored at the last evaluable radiological assessment. DOR was analyzed using Kaplan-Meier methods.

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

End point timeframe:

From randomization until the data cut-off date of 10 September 2015; median (min, max) follow-up time was 7.74 months (0.07, 32.69) in the rilotumumab arm and 9.36 months (0.13, 28.78) in the placebo arm.

| End point values                 | Placebo + ECX       | Rilotumumab + ECX  |  |  |
|----------------------------------|---------------------|--------------------|--|--|
| Subject group type               | Reporting group     | Reporting group    |  |  |
| Number of subjects analysed      | 119 <sup>[13]</sup> | 78 <sup>[14]</sup> |  |  |
| Units: months                    |                     |                    |  |  |
| median (confidence interval 95%) | 5.29 (4.5 to 6.08)  | 5.65 (4.6 to 6.51) |  |  |

Notes:

[13] - Response Analysis Set with CR or PR

[14] - Response Analysis Set with CR or PR

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to Initial Objective Response

|                 |                                    |
|-----------------|------------------------------------|
| End point title | Time to Initial Objective Response |
|-----------------|------------------------------------|

End point description:

Time to initial response is calculated as the time from randomization to the first tumor response assessment with an outcome indicating an objective response (CR or PR) as classified by RECIST 1.1 criteria.

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

End point timeframe:

From randomization until the data cut-off date of 10 September 2015; median (min, max) follow-up time was 7.74 months (0.07, 32.69) in the rilotumumab arm and 9.36 months (0.13, 28.78) in the placebo arm.

| End point values                      | Placebo + ECX         | Rilotumumab + ECX     |  |  |
|---------------------------------------|-----------------------|-----------------------|--|--|
| Subject group type                    | Reporting group       | Reporting group       |  |  |
| Number of subjects analysed           | 119 <sup>[15]</sup>   | 78 <sup>[16]</sup>    |  |  |
| Units: months                         |                       |                       |  |  |
| median (inter-quartile range (Q1-Q3)) | 2.76 (2.628 to 2.957) | 2.793 (2.694 to 2.99) |  |  |

Notes:

[15] - Response Analysis Set with CR or PR

[16] - Response Analysis Set with CR or PR

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants with Adverse Events

|                 |                                            |
|-----------------|--------------------------------------------|
| End point title | Number of Participants with Adverse Events |
|-----------------|--------------------------------------------|

End point description:

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

End point timeframe:

From the date of first administration of protocol specified treatment through 30 days after the last administration of protocol specified treatment.



| End point values                             | Placebo + ECX       | Rilotumumab + ECX   |  |  |
|----------------------------------------------|---------------------|---------------------|--|--|
| Subject group type                           | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed                  | 299 <sup>[17]</sup> | 298 <sup>[18]</sup> |  |  |
| Units: participants                          |                     |                     |  |  |
| Any adverse event                            | 288                 | 283                 |  |  |
| Serious adverse events                       | 149                 | 142                 |  |  |
| Leading to discontinuation of study drug     | 30                  | 41                  |  |  |
| Leading to discontinuation of Epirubicin     | 53                  | 57                  |  |  |
| Leading to discontinuation of Cisplatin      | 48                  | 52                  |  |  |
| Leading to discontinuation of Capecitabine   | 48                  | 57                  |  |  |
| Leading to discontinuation of all treatments | 21                  | 30                  |  |  |
| Fatal adverse events                         | 31                  | 42                  |  |  |

Notes:

[17] - Subjects who received at least 1 dose of study drug, analyzed according to the treatment received.

[18] - Subjects who received at least 1 dose of study drug, analyzed according to the treatment received.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants who Developed Antibodies to Rilotumumab

|                 |                                                                |
|-----------------|----------------------------------------------------------------|
| End point title | Number of Participants who Developed Antibodies to Rilotumumab |
|-----------------|----------------------------------------------------------------|

End point description:

participants who were binding antibody positive post baseline with a negative or no result at baseline. The analysis was performed using the Antibody Analysis Set which includes all randomized subjects with evaluable antibody data.

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

End point timeframe:

Day 1 of cycles 1, 3 & 7, and every 8 cycles thereafter (prior to study drug administration).

| End point values            | Placebo + ECX       | Rilotumumab + ECX   |  |  |
|-----------------------------|---------------------|---------------------|--|--|
| Subject group type          | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed | 259 <sup>[19]</sup> | 228 <sup>[20]</sup> |  |  |
| Units: participants         | 0                   | 0                   |  |  |

Notes:

[19] - Subjects with a postbaseline result

[20] - Subjects with a postbaseline result

### Statistical analyses

No statistical analyses for this end point

**Secondary: Duration of Treatment**

|                 |                       |
|-----------------|-----------------------|
| End point title | Duration of Treatment |
|-----------------|-----------------------|

End point description:

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

End point timeframe:

Day 1 until end of treatment

| End point values                      | Placebo + ECX    | Rilotumumab + ECX |  |  |
|---------------------------------------|------------------|-------------------|--|--|
| Subject group type                    | Reporting group  | Reporting group   |  |  |
| Number of subjects analysed           | 299              | 298               |  |  |
| Units: months                         |                  |                   |  |  |
| median (inter-quartile range (Q1-Q3)) |                  |                   |  |  |
| Placebo to Rilotumumab/Rilotumumab    | 3.7 (1.6 to 6.4) | 2.5 (1 to 5.1)    |  |  |
| Epirubicin                            | 4.1 (2.1 to 6.2) | 2.4 (1 to 4.8)    |  |  |
| Cisplatin                             | 4.2 (2.1 to 6.2) | 2.6 (1 to 4.9)    |  |  |
| Capecitabine                          | 4.8 (2.8 to 6.9) | 2.9 (1.4 to 5.3)  |  |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Maximum Observed Serum Concentration of Rilotumumab in Cycle 1**

|                 |                                                                                |
|-----------------|--------------------------------------------------------------------------------|
| End point title | Maximum Observed Serum Concentration of Rilotumumab in Cycle 1 <sup>[21]</sup> |
|-----------------|--------------------------------------------------------------------------------|

End point description:

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

End point timeframe:

Cycle 1: Pre-dose, and within 5 min before end of infusion , 2 hours, 24 hours, 168 hours, and 336 hours after start of infusion and predose on day 1 of cycle 2

Notes:

[21] - 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: Rilotumumab pharmacokinetic (PK) parameters were only analyzed for subjects in the Rilotumumab + ECX treatment arm.

| End point values                     | Rilotumumab + ECX  |  |  |  |
|--------------------------------------|--------------------|--|--|--|
| Subject group type                   | Reporting group    |  |  |  |
| Number of subjects analysed          | 48 <sup>[22]</sup> |  |  |  |
| Units: µg/mL                         |                    |  |  |  |
| arithmetic mean (standard deviation) | 227 (± 59.1)       |  |  |  |

Notes:

[22] - Subjects who participated in the intensive PK assessment with available data

## Statistical analyses

No statistical analyses for this end point

### Secondary: Area Under the Concentration-time Curve From Time Zero to Time of Last Quantifiable Concentration (AUClast) of Rilotumumab in Cycle 1

|                 |                                                                                                                                                       |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Area Under the Concentration-time Curve From Time Zero to Time of Last Quantifiable Concentration (AUClast) of Rilotumumab in Cycle 1 <sup>[23]</sup> |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

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

End point timeframe:

Cycle 1 predose and within 5 minutes before end of infusion, 2 hours, 24 hours, 168 hours, and 336 hours after start of infusion and Cycle 2, predose on day 1

Notes:

[23] - 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: Rilotumumab pharmacokinetic (PK) parameters were only analyzed for subjects in the Rilotumumab + ECX treatment arm.

| End point values                     | Rilotumumab + ECX  |  |  |  |
|--------------------------------------|--------------------|--|--|--|
| Subject group type                   | Reporting group    |  |  |  |
| Number of subjects analysed          | 43 <sup>[24]</sup> |  |  |  |
| Units: hr*µg/mL                      |                    |  |  |  |
| arithmetic mean (standard deviation) | 54200 (± 12200)    |  |  |  |

Notes:

[24] - Subjects who participated in the intensive PK assessment with available data

## Statistical analyses

No statistical analyses for this end point

### Secondary: Maximum Observed Concentration of ECX in Cycle 3

|                 |                                                  |
|-----------------|--------------------------------------------------|
| End point title | Maximum Observed Concentration of ECX in Cycle 3 |
|-----------------|--------------------------------------------------|

End point description:

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

End point timeframe:

Cycle 3 (week 7) day 1 predose to 24 hours post infusion

| End point values                     | Placebo + ECX      | Rilotumumab + ECX  |  |  |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type                   | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed          | 38 <sup>[25]</sup> | 37 <sup>[26]</sup> |  |  |
| Units: µg/mL                         |                    |                    |  |  |
| arithmetic mean (standard deviation) |                    |                    |  |  |
| Epirubicin (N = 21, 23)              | 1.15 (± 0.948)     | 0.973 (± 0.799)    |  |  |

|                               |                   |                 |  |  |
|-------------------------------|-------------------|-----------------|--|--|
| Total Platinum (N = 26, 19)   | 2.39 (± 0.531)    | 2.42 (± 0.508)  |  |  |
| Unbound Platinum (N = 26, 19) | 0.636 (± 0.41)    | 0.814 (± 0.458) |  |  |
| Capecitabine (N = 21, 14)     | 2.82 (± 4.01)     | 2.37 (± 2.56)   |  |  |
| 5-Fluorouracil (N = 21, 12)   | 0.0765 (± 0.0479) | 0.1 (± 0.0513)  |  |  |

Notes:

[25] - Subjects who participated in the intensive PK assessment with ECX samples

[26] - Subjects who participated in the intensive PK assessment with ECX samples

### Statistical analyses

No statistical analyses for this end point

### Secondary: Area Under the Concentration-time Curve From Time Zero to Time of Last Quantifiable Concentration (AUClast) of ECX in Cycle 3

|                 |                                                                                                                               |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------|
| End point title | Area Under the Concentration-time Curve From Time Zero to Time of Last Quantifiable Concentration (AUClast) of ECX in Cycle 3 |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------|

End point description:

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

End point timeframe:

Cycle 3

| End point values                     | Placebo + ECX      | Rilotumumab + ECX  |  |  |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type                   | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed          | 38 <sup>[27]</sup> | 37 <sup>[28]</sup> |  |  |
| Units: hr*µg/mL                      |                    |                    |  |  |
| arithmetic mean (standard deviation) |                    |                    |  |  |
| Epirubicin (N = 19, 18)              | 0.777 (± 0.322)    | 0.66 (± 0.372)     |  |  |
| Total Platinum (N = 26, 14)          | 38.3 (± 8.35)      | 39.6 (± 5.18)      |  |  |
| Unbound Platinum (N = 26, 14)        | 4.11 (± 3.21)      | 4.11 (± 1.79)      |  |  |
| Capecitabine (N = 21, 13)            | 4.29 (± 5.37)      | 4.47 (± 4.92)      |  |  |
| 5-Fluorouracil (N = 21, 12)          | 0.13 (± 0.0558)    | 0.205 (± 0.0975)   |  |  |

Notes:

[27] - Subjects who participated in the intensive PK assessment with ECX samples

[28] - Subjects who participated in the intensive PK assessment with ECX samples

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Median duration of exposure to study treatment was 3.7 months and 2.5 months for the placebo and rilotumumab arms respectively.

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

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 18.0   |

### Reporting groups

|                       |               |
|-----------------------|---------------|
| Reporting group title | Placebo + ECX |
|-----------------------|---------------|

Reporting group description:

Participants received placebo to rilotumumab administered as an intravenous (IV) infusion on day 1 of each 21-day cycle until documented disease progression, intolerable adverse event, withdrawal of consent, or study termination by the sponsor. Participants also received chemotherapy with epirubicin (E) 50 mg/m<sup>2</sup> IV on day 1, cisplatin (C) 60 mg/m<sup>2</sup> IV on day 1, and capecitabine (X) 625 mg/m<sup>2</sup> orally twice a day on days 1 to 21 for a maximum of 10 cycles.

|                       |                   |
|-----------------------|-------------------|
| Reporting group title | Rilotumumab + ECX |
|-----------------------|-------------------|

Reporting group description:

Participants received rilotumumab 15 mg/kg administered as an IV infusion on day 1 of each 21-day cycle until documented disease progression, intolerable adverse event, withdrawal of consent, or study termination by the sponsor. Participants also received chemotherapy with epirubicin (E) 50 mg/m<sup>2</sup> IV on day 1, cisplatin (C) 60 mg/m<sup>2</sup> IV on day 1, and capecitabine (X) 625 mg/m<sup>2</sup> orally twice a day on days 1 to 21 for a maximum of 10 cycles.

| Serious adverse events                                              | Placebo + ECX      | Rilotumumab + ECX  |  |
|---------------------------------------------------------------------|--------------------|--------------------|--|
| Total subjects affected by serious adverse events                   |                    |                    |  |
| subjects affected / exposed                                         | 149 / 299 (49.83%) | 142 / 298 (47.65%) |  |
| number of deaths (all causes)                                       | 194                | 213                |  |
| number of deaths resulting from adverse events                      |                    |                    |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                    |                    |  |
| Adenocarcinoma                                                      |                    |                    |  |
| subjects affected / exposed                                         | 0 / 299 (0.00%)    | 2 / 298 (0.67%)    |  |
| occurrences causally related to treatment / all                     | 0 / 0              | 0 / 2              |  |
| deaths causally related to treatment / all                          | 0 / 0              | 0 / 2              |  |
| Adenocarcinoma gastric                                              |                    |                    |  |
| subjects affected / exposed                                         | 3 / 299 (1.00%)    | 1 / 298 (0.34%)    |  |
| occurrences causally related to treatment / all                     | 0 / 3              | 0 / 1              |  |
| deaths causally related to treatment / all                          | 0 / 2              | 0 / 1              |  |
| Cancer pain                                                         |                    |                    |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastric cancer                                  |                 |                 |  |
| subjects affected / exposed                     | 2 / 299 (0.67%) | 8 / 298 (2.68%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 8           |  |
| deaths causally related to treatment / all      | 0 / 2           | 0 / 7           |  |
| Gastric cancer stage IV                         |                 |                 |  |
| subjects affected / exposed                     | 4 / 299 (1.34%) | 1 / 298 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 4           | 0 / 1           |  |
| Lymphangiosis carcinomatosa                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) | 1 / 298 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Malignant ascites                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (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            |                 |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metastases to lymph nodes                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) | 1 / 298 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metastases to meninges                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metastatic pain                                 |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Oesophageal adenocarcinoma                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 1 / 298 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Oesophageal cancer metastatic                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Signet-ring cell carcinoma                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 1 / 298 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           |  |
| Tumour haemorrhage                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 1 / 298 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vascular disorders                              |                 |                 |  |
| Arterial thrombosis                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Deep vein thrombosis                            |                 |                 |  |
| subjects affected / exposed                     | 2 / 299 (0.67%) | 8 / 298 (2.68%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 6 / 8           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Embolism                                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 1 / 298 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Embolism venous                                 |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 299 (0.33%) | 1 / 298 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypotension                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) | 3 / 298 (1.01%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Peripheral arterial occlusive disease           |                 |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Peripheral artery thrombosis                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 1 / 298 (0.34%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Shock haemorrhagic                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Thrombophlebitis                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) | 1 / 298 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Thrombophlebitis superficial                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) | 1 / 298 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Thrombosis                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) | 1 / 298 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Venous thrombosis limb                          |                 |                 |  |



|                                                      |                 |                 |  |
|------------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                          | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| General disorders and administration site conditions |                 |                 |  |
| Asthenia                                             |                 |                 |  |
| subjects affected / exposed                          | 7 / 299 (2.34%) | 8 / 298 (2.68%) |  |
| occurrences causally related to treatment / all      | 5 / 8           | 1 / 8           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Brain death                                          |                 |                 |  |
| subjects affected / exposed                          | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 1           | 0 / 0           |  |
| Chest pain                                           |                 |                 |  |
| subjects affected / exposed                          | 0 / 299 (0.00%) | 1 / 298 (0.34%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Death                                                |                 |                 |  |
| subjects affected / exposed                          | 2 / 299 (0.67%) | 3 / 298 (1.01%) |  |
| occurrences causally related to treatment / all      | 0 / 2           | 0 / 3           |  |
| deaths causally related to treatment / all           | 0 / 2           | 0 / 3           |  |
| Device dislocation                                   |                 |                 |  |
| subjects affected / exposed                          | 1 / 299 (0.33%) | 1 / 298 (0.34%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Extravasation                                        |                 |                 |  |
| subjects affected / exposed                          | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Fatigue                                              |                 |                 |  |
| subjects affected / exposed                          | 4 / 299 (1.34%) | 5 / 298 (1.68%) |  |
| occurrences causally related to treatment / all      | 1 / 6           | 3 / 5           |  |
| deaths causally related to treatment / all           | 0 / 1           | 0 / 0           |  |
| General physical health deterioration                |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 3 / 299 (1.00%) | 4 / 298 (1.34%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 1 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Generalised oedema                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) | 1 / 298 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Local swelling                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) | 1 / 298 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Malaise                                         |                 |                 |  |
| subjects affected / exposed                     | 2 / 299 (0.67%) | 0 / 298 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Multi-organ failure                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 4 / 298 (1.34%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 1 / 4           |  |
| deaths causally related to treatment / all      | 0 / 1           | 1 / 4           |  |
| Non-cardiac chest pain                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) | 1 / 298 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Oedema peripheral                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 4 / 298 (1.34%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 1 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Organ failure                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Pain                                            |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 299 (0.00%) | 1 / 298 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pyrexia                                         |                 |                 |  |
| subjects affected / exposed                     | 8 / 299 (2.68%) | 4 / 298 (1.34%) |  |
| occurrences causally related to treatment / all | 2 / 10          | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sudden death                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 2 / 298 (0.67%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 1 / 1           | 0 / 2           |  |
| Immune system disorders                         |                 |                 |  |
| Hypersensitivity                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) | 1 / 298 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Reproductive system and breast disorders        |                 |                 |  |
| Balanoposthitis                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Female genital tract fistula                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) | 1 / 298 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory, thoracic and mediastinal disorders |                 |                 |  |
| Acute respiratory distress syndrome             |                 |                 |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) | 1 / 298 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cough                                           |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dyspnoea                                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 4 / 298 (1.34%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Haemoptysis                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hydrothorax                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) | 1 / 298 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypoxia                                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) | 1 / 298 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Oropharyngeal pain                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pleural effusion                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) | 2 / 298 (0.67%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary artery thrombosis                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary embolism                              |                 |                 |  |

|                                                 |                 |                  |  |
|-------------------------------------------------|-----------------|------------------|--|
| subjects affected / exposed                     | 4 / 299 (1.34%) | 12 / 298 (4.03%) |  |
| occurrences causally related to treatment / all | 3 / 4           | 6 / 12           |  |
| deaths causally related to treatment / all      | 0 / 0           | 1 / 1            |  |
| Pulmonary oedema                                |                 |                  |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) | 1 / 298 (0.34%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Respiratory failure                             |                 |                  |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0            |  |
| Psychiatric disorders                           |                 |                  |  |
| Acute psychosis                                 |                 |                  |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Anxiety                                         |                 |                  |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 2 / 298 (0.67%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Confusional state                               |                 |                  |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) | 1 / 298 (0.34%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Mood altered                                    |                 |                  |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Investigations                                  |                 |                  |  |
| Blood bilirubin increased                       |                 |                  |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Blood sodium increased                          |                 |                  |  |

|                                                                |                 |                 |  |
|----------------------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                                    | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences causally related to treatment / all                | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all                     | 0 / 0           | 0 / 0           |  |
| Creatinine renal clearance decreased                           |                 |                 |  |
| subjects affected / exposed                                    | 0 / 299 (0.00%) | 1 / 298 (0.34%) |  |
| occurrences causally related to treatment / all                | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all                     | 0 / 0           | 0 / 0           |  |
| Eastern Cooperative Oncology Group performance status worsened |                 |                 |  |
| subjects affected / exposed                                    | 0 / 299 (0.00%) | 1 / 298 (0.34%) |  |
| occurrences causally related to treatment / all                | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all                     | 0 / 0           | 0 / 1           |  |
| Gamma-glutamyltransferase increased                            |                 |                 |  |
| subjects affected / exposed                                    | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences causally related to treatment / all                | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all                     | 0 / 0           | 0 / 0           |  |
| Lipase increased                                               |                 |                 |  |
| subjects affected / exposed                                    | 0 / 299 (0.00%) | 1 / 298 (0.34%) |  |
| occurrences causally related to treatment / all                | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all                     | 0 / 0           | 0 / 0           |  |
| Neutrophil count decreased                                     |                 |                 |  |
| subjects affected / exposed                                    | 0 / 299 (0.00%) | 2 / 298 (0.67%) |  |
| occurrences causally related to treatment / all                | 0 / 0           | 2 / 2           |  |
| deaths causally related to treatment / all                     | 0 / 0           | 0 / 0           |  |
| Platelet count decreased                                       |                 |                 |  |
| subjects affected / exposed                                    | 2 / 299 (0.67%) | 0 / 298 (0.00%) |  |
| occurrences causally related to treatment / all                | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all                     | 0 / 0           | 0 / 0           |  |
| Weight decreased                                               |                 |                 |  |
| subjects affected / exposed                                    | 1 / 299 (0.33%) | 1 / 298 (0.34%) |  |
| occurrences causally related to treatment / all                | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all                     | 0 / 0           | 0 / 0           |  |
| Injury, poisoning and procedural complications                 |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| Cervical vertebral fracture                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Fall                                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Feeding tube complication                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Femoral neck fracture                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Femur fracture                                  |                 |                 |  |
| subjects affected / exposed                     | 2 / 299 (0.67%) | 0 / 298 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Humerus fracture                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac disorders                               |                 |                 |  |
| Acute myocardial infarction                     |                 |                 |  |
| subjects affected / exposed                     | 2 / 299 (0.67%) | 1 / 298 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Angina pectoris                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac arrest                                  |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 3 / 299 (1.00%) | 1 / 298 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           |  |
| Cardiac failure                                 |                 |                 |  |
| subjects affected / exposed                     | 3 / 299 (1.00%) | 0 / 298 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 2 / 3           | 0 / 0           |  |
| Cardiac failure acute                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardio-respiratory arrest                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 2 / 298 (0.67%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 2           |  |
| Myocardial infarction                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ventricular tachycardia                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nervous system disorders                        |                 |                 |  |
| Brain oedema                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) | 1 / 298 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cerebral haemorrhage                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 1 / 298 (0.34%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cerebral infarction                             |                 |                 |  |



|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 299 (0.67%) | 0 / 298 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cerebral venous thrombosis                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Cerebrovascular accident                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Coma                                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) | 2 / 298 (0.67%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Coma hepatic                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) | 1 / 298 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Dizziness                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dysarthria                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) | 1 / 298 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Epilepsy                                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) | 1 / 298 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Generalised tonic-clonic seizure                |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 299 (0.00%) | 1 / 298 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Headache                                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hemiparesis                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ischaemic stroke                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) | 1 / 298 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Polyneuropathy                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) | 1 / 298 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Loss of consciousness                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) | 1 / 298 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Presyncope                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Seizure                                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) | 1 / 298 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Speech disorder                                 |                 |                 |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 299 (0.33%)  | 0 / 298 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Syncope                                         |                  |                  |  |
| subjects affected / exposed                     | 2 / 299 (0.67%)  | 2 / 298 (0.67%)  |  |
| occurrences causally related to treatment / all | 1 / 2            | 1 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Transient ischaemic attack                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 299 (0.33%)  | 0 / 298 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Blood and lymphatic system disorders            |                  |                  |  |
| Anaemia                                         |                  |                  |  |
| subjects affected / exposed                     | 21 / 299 (7.02%) | 7 / 298 (2.35%)  |  |
| occurrences causally related to treatment / all | 13 / 29          | 1 / 10           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Disseminated intravascular coagulation          |                  |                  |  |
| subjects affected / exposed                     | 1 / 299 (0.33%)  | 0 / 298 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Febrile bone marrow aplasia                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 299 (0.00%)  | 1 / 298 (0.34%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Febrile neutropenia                             |                  |                  |  |
| subjects affected / exposed                     | 11 / 299 (3.68%) | 12 / 298 (4.03%) |  |
| occurrences causally related to treatment / all | 6 / 12           | 6 / 12           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haematotoxicity                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 299 (0.33%)  | 0 / 298 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Iron deficiency anaemia                         |                  |                  |  |

|                                                 |                 |                  |  |
|-------------------------------------------------|-----------------|------------------|--|
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Microangiopathic haemolytic anaemia             |                 |                  |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Neutropenia                                     |                 |                  |  |
| subjects affected / exposed                     | 6 / 299 (2.01%) | 10 / 298 (3.36%) |  |
| occurrences causally related to treatment / all | 2 / 6           | 4 / 15           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Pancytopenia                                    |                 |                  |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) | 3 / 298 (1.01%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 3 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Thrombocytopenia                                |                 |                  |  |
| subjects affected / exposed                     | 5 / 299 (1.67%) | 1 / 298 (0.34%)  |  |
| occurrences causally related to treatment / all | 1 / 6           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Gastrointestinal disorders                      |                 |                  |  |
| Abdominal pain                                  |                 |                  |  |
| subjects affected / exposed                     | 8 / 299 (2.68%) | 7 / 298 (2.35%)  |  |
| occurrences causally related to treatment / all | 1 / 9           | 0 / 7            |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0            |  |
| Abdominal pain lower                            |                 |                  |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) | 1 / 298 (0.34%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Abdominal pain upper                            |                 |                  |  |
| subjects affected / exposed                     | 2 / 299 (0.67%) | 2 / 298 (0.67%)  |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Ascites                                         |                 |                  |  |

|                                                 |                  |                 |  |
|-------------------------------------------------|------------------|-----------------|--|
| subjects affected / exposed                     | 1 / 299 (0.33%)  | 2 / 298 (0.67%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Colitis                                         |                  |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%)  | 0 / 298 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Constipation                                    |                  |                 |  |
| subjects affected / exposed                     | 2 / 299 (0.67%)  | 1 / 298 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Diarrhoea                                       |                  |                 |  |
| subjects affected / exposed                     | 11 / 299 (3.68%) | 7 / 298 (2.35%) |  |
| occurrences causally related to treatment / all | 2 / 11           | 2 / 7           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Duodenal obstruction                            |                  |                 |  |
| subjects affected / exposed                     | 2 / 299 (0.67%)  | 0 / 298 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| Dysphagia                                       |                  |                 |  |
| subjects affected / exposed                     | 7 / 299 (2.34%)  | 7 / 298 (2.35%) |  |
| occurrences causally related to treatment / all | 0 / 8            | 0 / 8           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Gastric haemorrhage                             |                  |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%)  | 4 / 298 (1.34%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 2           |  |
| Gastric perforation                             |                  |                 |  |
| subjects affected / exposed                     | 0 / 299 (0.00%)  | 1 / 298 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Gastritis                                       |                  |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal haemorrhage                    |                 |                 |  |
| subjects affected / exposed                     | 3 / 299 (1.00%) | 3 / 298 (1.01%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 1 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 1 / 2           |  |
| Gastrointestinal inflammation                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal perforation                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haematemesis                                    |                 |                 |  |
| subjects affected / exposed                     | 5 / 299 (1.67%) | 0 / 298 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Ileus                                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 1 / 298 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ileus paralytic                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) | 1 / 298 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intestinal obstruction                          |                 |                 |  |
| subjects affected / exposed                     | 3 / 299 (1.00%) | 5 / 298 (1.68%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 1 / 7           |  |
| deaths causally related to treatment / all      | 0 / 0           | 1 / 3           |  |
| Jejunal perforation                             |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Melaena                                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nausea                                          |                 |                 |  |
| subjects affected / exposed                     | 5 / 299 (1.67%) | 7 / 298 (2.35%) |  |
| occurrences causally related to treatment / all | 3 / 5           | 2 / 7           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Obstruction gastric                             |                 |                 |  |
| subjects affected / exposed                     | 3 / 299 (1.00%) | 2 / 298 (0.67%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Oesophageal obstruction                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Oesophageal perforation                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) | 1 / 298 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Oesophageal stenosis                            |                 |                 |  |
| subjects affected / exposed                     | 2 / 299 (0.67%) | 2 / 298 (0.67%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Oesophagitis                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) | 1 / 298 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pancreatitis acute                              |                 |                 |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 299 (0.33%)  | 0 / 298 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Small intestinal obstruction                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 299 (0.00%)  | 2 / 298 (0.67%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Stomatitis                                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 299 (0.00%)  | 3 / 298 (1.01%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Subileus                                        |                  |                  |  |
| subjects affected / exposed                     | 2 / 299 (0.67%)  | 0 / 298 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vomiting                                        |                  |                  |  |
| subjects affected / exposed                     | 12 / 299 (4.01%) | 14 / 298 (4.70%) |  |
| occurrences causally related to treatment / all | 8 / 15           | 2 / 15           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hepatobiliary disorders                         |                  |                  |  |
| Bile duct obstruction                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 299 (0.00%)  | 1 / 298 (0.34%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hepatitis                                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 299 (0.00%)  | 1 / 298 (0.34%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hepatotoxicity                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 299 (0.00%)  | 1 / 298 (0.34%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hyperbilirubinaemia                             |                  |                  |  |



|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 3 / 299 (1.00%) | 3 / 298 (1.01%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 1 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Perforation bile duct                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) | 1 / 298 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Portal hypertension                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Skin and subcutaneous tissue disorders          |                 |                 |  |
| Palmar-plantar erythrodysesthesia syndrome      |                 |                 |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) | 1 / 298 (0.34%) |  |
| 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                             |                 |                 |  |
| subjects affected / exposed                     | 3 / 299 (1.00%) | 1 / 298 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Chronic kidney disease                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haematuria                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) | 1 / 298 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hydronephrosis                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) | 1 / 298 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| Nephropathy toxic                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal colic                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal infarct                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) | 1 / 298 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 2 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urinary incontinence                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urinary retention                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) | 2 / 298 (0.67%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |                 |                 |  |
| Back pain                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 1 / 298 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Muscular weakness                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) | 1 / 298 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Myalgia                                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| Pain in extremity                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infections and infestations                     |                 |                 |  |
| Appendicitis perforated                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) | 1 / 298 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bacteraemia                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) | 1 / 298 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bacterial infection                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) | 2 / 298 (0.67%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bronchitis                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Campylobacter infection                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) | 1 / 298 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cellulitis                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) | 1 / 298 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Device related infection                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 3 / 298 (1.01%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 1 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Device related sepsis                           |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Enteritis infectious                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastroenteritis                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) | 1 / 298 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Influenza                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lower respiratory tract infection               |                 |                 |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) | 1 / 298 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lung abscess                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) | 1 / 298 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lung infection                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lymph gland infection                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) | 1 / 298 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Meningitis bacterial                            |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 299 (0.00%) | 1 / 298 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Neutropenic sepsis                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) | 3 / 298 (1.01%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Peritonitis bacterial                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) | 1 / 298 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia                                       |                 |                 |  |
| subjects affected / exposed                     | 3 / 299 (1.00%) | 5 / 298 (1.68%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 1 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 2           |  |
| Pneumonia bacterial                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) | 1 / 298 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory tract infection                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) | 1 / 298 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sepsis                                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 4 / 298 (1.34%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Staphylococcal sepsis                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Systemic mycosis                                |                 |                 |  |

|                                                 |                 |                  |  |
|-------------------------------------------------|-----------------|------------------|--|
| subjects affected / exposed                     | 0 / 299 (0.00%) | 1 / 298 (0.34%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Urinary tract infection                         |                 |                  |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Metabolism and nutrition disorders              |                 |                  |  |
| Cachexia                                        |                 |                  |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0            |  |
| Decreased appetite                              |                 |                  |  |
| subjects affected / exposed                     | 2 / 299 (0.67%) | 2 / 298 (0.67%)  |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Dehydration                                     |                 |                  |  |
| subjects affected / exposed                     | 6 / 299 (2.01%) | 10 / 298 (3.36%) |  |
| occurrences causally related to treatment / all | 3 / 8           | 2 / 12           |  |
| deaths causally related to treatment / all      | 0 / 2           | 0 / 0            |  |
| Electrolyte imbalance                           |                 |                  |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Fluid retention                                 |                 |                  |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) | 1 / 298 (0.34%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Hyperglycaemia                                  |                 |                  |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Hyperosmolar hyperglycaemic state               |                 |                  |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypocalcaemia                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypokalaemia                                    |                 |                 |  |
| subjects affected / exposed                     | 4 / 299 (1.34%) | 2 / 298 (0.67%) |  |
| occurrences causally related to treatment / all | 1 / 4           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypomagnesaemia                                 |                 |                 |  |
| subjects affected / exposed                     | 5 / 299 (1.67%) | 2 / 298 (0.67%) |  |
| occurrences causally related to treatment / all | 8 / 11          | 2 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyponatraemia                                   |                 |                 |  |
| subjects affected / exposed                     | 4 / 299 (1.34%) | 1 / 298 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypophagia                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) | 1 / 298 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypophosphataemia                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) | 1 / 298 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Malnutrition                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) | 2 / 298 (0.67%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metabolic acidosis                              |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 299 (0.00%) | 1 / 298 (0.34%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

Frequency threshold for reporting non-serious adverse events: 0 %

| <b>Non-serious adverse events</b>                                   | Placebo + ECX      | Rilotumumab + ECX  |  |
|---------------------------------------------------------------------|--------------------|--------------------|--|
| Total subjects affected by non-serious adverse events               |                    |                    |  |
| subjects affected / exposed                                         | 281 / 299 (93.98%) | 268 / 298 (89.93%) |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                    |                    |  |
| Cancer pain                                                         |                    |                    |  |
| subjects affected / exposed                                         | 0 / 299 (0.00%)    | 1 / 298 (0.34%)    |  |
| occurrences (all)                                                   | 0                  | 1                  |  |
| Lip and/or oral cavity cancer                                       |                    |                    |  |
| subjects affected / exposed                                         | 0 / 299 (0.00%)    | 1 / 298 (0.34%)    |  |
| occurrences (all)                                                   | 0                  | 1                  |  |
| Mycosis fungoides                                                   |                    |                    |  |
| subjects affected / exposed                                         | 0 / 299 (0.00%)    | 1 / 298 (0.34%)    |  |
| occurrences (all)                                                   | 0                  | 1                  |  |
| Myelodysplastic syndrome                                            |                    |                    |  |
| subjects affected / exposed                                         | 0 / 299 (0.00%)    | 1 / 298 (0.34%)    |  |
| occurrences (all)                                                   | 0                  | 1                  |  |
| Vascular disorders                                                  |                    |                    |  |
| Aortic thrombosis                                                   |                    |                    |  |
| subjects affected / exposed                                         | 1 / 299 (0.33%)    | 0 / 298 (0.00%)    |  |
| occurrences (all)                                                   | 1                  | 0                  |  |
| Axillary vein thrombosis                                            |                    |                    |  |
| subjects affected / exposed                                         | 0 / 299 (0.00%)    | 1 / 298 (0.34%)    |  |
| occurrences (all)                                                   | 0                  | 1                  |  |
| Deep vein thrombosis                                                |                    |                    |  |
| subjects affected / exposed                                         | 10 / 299 (3.34%)   | 21 / 298 (7.05%)   |  |
| occurrences (all)                                                   | 11                 | 21                 |  |
| Embolism                                                            |                    |                    |  |
| subjects affected / exposed                                         | 1 / 299 (0.33%)    | 1 / 298 (0.34%)    |  |
| occurrences (all)                                                   | 1                  | 1                  |  |
| Hot flush                                                           |                    |                    |  |



|                                       |                  |                  |
|---------------------------------------|------------------|------------------|
| subjects affected / exposed           | 2 / 299 (0.67%)  | 2 / 298 (0.67%)  |
| occurrences (all)                     | 2                | 2                |
| Hypertension                          |                  |                  |
| subjects affected / exposed           | 12 / 299 (4.01%) | 1 / 298 (0.34%)  |
| occurrences (all)                     | 14               | 2                |
| Hypotension                           |                  |                  |
| subjects affected / exposed           | 7 / 299 (2.34%)  | 18 / 298 (6.04%) |
| occurrences (all)                     | 9                | 22               |
| Intermittent claudication             |                  |                  |
| subjects affected / exposed           | 1 / 299 (0.33%)  | 0 / 298 (0.00%)  |
| occurrences (all)                     | 1                | 0                |
| Lymphoedema                           |                  |                  |
| subjects affected / exposed           | 1 / 299 (0.33%)  | 2 / 298 (0.67%)  |
| occurrences (all)                     | 1                | 3                |
| Orthostatic hypotension               |                  |                  |
| subjects affected / exposed           | 2 / 299 (0.67%)  | 2 / 298 (0.67%)  |
| occurrences (all)                     | 2                | 2                |
| Pallor                                |                  |                  |
| subjects affected / exposed           | 1 / 299 (0.33%)  | 0 / 298 (0.00%)  |
| occurrences (all)                     | 1                | 0                |
| Peripheral arterial occlusive disease |                  |                  |
| subjects affected / exposed           | 0 / 299 (0.00%)  | 1 / 298 (0.34%)  |
| occurrences (all)                     | 0                | 1                |
| Peripheral venous disease             |                  |                  |
| subjects affected / exposed           | 1 / 299 (0.33%)  | 0 / 298 (0.00%)  |
| occurrences (all)                     | 1                | 0                |
| Phlebitis                             |                  |                  |
| subjects affected / exposed           | 2 / 299 (0.67%)  | 5 / 298 (1.68%)  |
| occurrences (all)                     | 2                | 7                |
| Phlebitis superficial                 |                  |                  |
| subjects affected / exposed           | 2 / 299 (0.67%)  | 1 / 298 (0.34%)  |
| occurrences (all)                     | 2                | 1                |
| Subclavian vein thrombosis            |                  |                  |
| subjects affected / exposed           | 0 / 299 (0.00%)  | 2 / 298 (0.67%)  |
| occurrences (all)                     | 0                | 2                |
| Thrombophlebitis                      |                  |                  |

|                                                      |                   |                   |  |
|------------------------------------------------------|-------------------|-------------------|--|
| subjects affected / exposed                          | 1 / 299 (0.33%)   | 6 / 298 (2.01%)   |  |
| occurrences (all)                                    | 1                 | 7                 |  |
| Thrombophlebitis superficial                         |                   |                   |  |
| subjects affected / exposed                          | 3 / 299 (1.00%)   | 1 / 298 (0.34%)   |  |
| occurrences (all)                                    | 3                 | 1                 |  |
| Thrombosis                                           |                   |                   |  |
| subjects affected / exposed                          | 2 / 299 (0.67%)   | 5 / 298 (1.68%)   |  |
| occurrences (all)                                    | 2                 | 5                 |  |
| Vascular insufficiency                               |                   |                   |  |
| subjects affected / exposed                          | 1 / 299 (0.33%)   | 0 / 298 (0.00%)   |  |
| occurrences (all)                                    | 1                 | 0                 |  |
| Vena cava thrombosis                                 |                   |                   |  |
| subjects affected / exposed                          | 0 / 299 (0.00%)   | 1 / 298 (0.34%)   |  |
| occurrences (all)                                    | 0                 | 1                 |  |
| Venous thrombosis                                    |                   |                   |  |
| subjects affected / exposed                          | 2 / 299 (0.67%)   | 5 / 298 (1.68%)   |  |
| occurrences (all)                                    | 2                 | 5                 |  |
| Venous thrombosis limb                               |                   |                   |  |
| subjects affected / exposed                          | 0 / 299 (0.00%)   | 5 / 298 (1.68%)   |  |
| occurrences (all)                                    | 0                 | 6                 |  |
| Surgical and medical procedures                      |                   |                   |  |
| Abdominal cavity drainage                            |                   |                   |  |
| subjects affected / exposed                          | 0 / 299 (0.00%)   | 1 / 298 (0.34%)   |  |
| occurrences (all)                                    | 0                 | 1                 |  |
| Dental operation                                     |                   |                   |  |
| subjects affected / exposed                          | 0 / 299 (0.00%)   | 1 / 298 (0.34%)   |  |
| occurrences (all)                                    | 0                 | 1                 |  |
| Tooth extraction                                     |                   |                   |  |
| subjects affected / exposed                          | 1 / 299 (0.33%)   | 0 / 298 (0.00%)   |  |
| occurrences (all)                                    | 1                 | 0                 |  |
| General disorders and administration site conditions |                   |                   |  |
| Asthenia                                             |                   |                   |  |
| subjects affected / exposed                          | 52 / 299 (17.39%) | 52 / 298 (17.45%) |  |
| occurrences (all)                                    | 107               | 112               |  |
| Catheter site related reaction                       |                   |                   |  |

|                                       |                   |                    |
|---------------------------------------|-------------------|--------------------|
| subjects affected / exposed           | 0 / 299 (0.00%)   | 1 / 298 (0.34%)    |
| occurrences (all)                     | 0                 | 1                  |
| Chest discomfort                      |                   |                    |
| subjects affected / exposed           | 0 / 299 (0.00%)   | 4 / 298 (1.34%)    |
| occurrences (all)                     | 0                 | 4                  |
| Chest pain                            |                   |                    |
| subjects affected / exposed           | 4 / 299 (1.34%)   | 8 / 298 (2.68%)    |
| occurrences (all)                     | 5                 | 9                  |
| Chills                                |                   |                    |
| subjects affected / exposed           | 4 / 299 (1.34%)   | 8 / 298 (2.68%)    |
| occurrences (all)                     | 4                 | 8                  |
| Device issue                          |                   |                    |
| subjects affected / exposed           | 0 / 299 (0.00%)   | 1 / 298 (0.34%)    |
| occurrences (all)                     | 0                 | 1                  |
| Device occlusion                      |                   |                    |
| subjects affected / exposed           | 1 / 299 (0.33%)   | 0 / 298 (0.00%)    |
| occurrences (all)                     | 1                 | 0                  |
| Extravasation                         |                   |                    |
| subjects affected / exposed           | 2 / 299 (0.67%)   | 0 / 298 (0.00%)    |
| occurrences (all)                     | 2                 | 0                  |
| Face oedema                           |                   |                    |
| subjects affected / exposed           | 2 / 299 (0.67%)   | 0 / 298 (0.00%)    |
| occurrences (all)                     | 2                 | 0                  |
| Fatigue                               |                   |                    |
| subjects affected / exposed           | 98 / 299 (32.78%) | 103 / 298 (34.56%) |
| occurrences (all)                     | 218               | 199                |
| Feeling abnormal                      |                   |                    |
| subjects affected / exposed           | 0 / 299 (0.00%)   | 1 / 298 (0.34%)    |
| occurrences (all)                     | 0                 | 1                  |
| Feeling hot                           |                   |                    |
| subjects affected / exposed           | 0 / 299 (0.00%)   | 1 / 298 (0.34%)    |
| occurrences (all)                     | 0                 | 1                  |
| General physical health deterioration |                   |                    |
| subjects affected / exposed           | 1 / 299 (0.33%)   | 1 / 298 (0.34%)    |
| occurrences (all)                     | 1                 | 1                  |
| Generalised oedema                    |                   |                    |

|                             |                 |                 |
|-----------------------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 299 (0.00%) | 1 / 298 (0.34%) |
| occurrences (all)           | 0               | 1               |
| Hyperpyrexia                |                 |                 |
| subjects affected / exposed | 0 / 299 (0.00%) | 1 / 298 (0.34%) |
| occurrences (all)           | 0               | 2               |
| Hyperthermia                |                 |                 |
| subjects affected / exposed | 2 / 299 (0.67%) | 0 / 298 (0.00%) |
| occurrences (all)           | 2               | 0               |
| Hypothermia                 |                 |                 |
| subjects affected / exposed | 1 / 299 (0.33%) | 2 / 298 (0.67%) |
| occurrences (all)           | 1               | 2               |
| Inflammation                |                 |                 |
| subjects affected / exposed | 1 / 299 (0.33%) | 0 / 298 (0.00%) |
| occurrences (all)           | 1               | 0               |
| Influenza like illness      |                 |                 |
| subjects affected / exposed | 3 / 299 (1.00%) | 1 / 298 (0.34%) |
| occurrences (all)           | 3               | 1               |
| Injection site bruising     |                 |                 |
| subjects affected / exposed | 1 / 299 (0.33%) | 0 / 298 (0.00%) |
| occurrences (all)           | 1               | 0               |
| Injection site phlebitis    |                 |                 |
| subjects affected / exposed | 0 / 299 (0.00%) | 2 / 298 (0.67%) |
| occurrences (all)           | 0               | 2               |
| Injection site reaction     |                 |                 |
| subjects affected / exposed | 0 / 299 (0.00%) | 1 / 298 (0.34%) |
| occurrences (all)           | 0               | 1               |
| Localised oedema            |                 |                 |
| subjects affected / exposed | 0 / 299 (0.00%) | 6 / 298 (2.01%) |
| occurrences (all)           | 0               | 13              |
| Malaise                     |                 |                 |
| subjects affected / exposed | 4 / 299 (1.34%) | 1 / 298 (0.34%) |
| occurrences (all)           | 7               | 1               |
| Medical device pain         |                 |                 |
| subjects affected / exposed | 1 / 299 (0.33%) | 0 / 298 (0.00%) |
| occurrences (all)           | 1               | 0               |
| Mucosal inflammation        |                 |                 |

|                             |                   |                   |  |
|-----------------------------|-------------------|-------------------|--|
| subjects affected / exposed | 15 / 299 (5.02%)  | 21 / 298 (7.05%)  |  |
| occurrences (all)           | 22                | 30                |  |
| Non-cardiac chest pain      |                   |                   |  |
| subjects affected / exposed | 0 / 299 (0.00%)   | 2 / 298 (0.67%)   |  |
| occurrences (all)           | 0                 | 3                 |  |
| Oedema                      |                   |                   |  |
| subjects affected / exposed | 13 / 299 (4.35%)  | 19 / 298 (6.38%)  |  |
| occurrences (all)           | 15                | 26                |  |
| Oedema peripheral           |                   |                   |  |
| subjects affected / exposed | 38 / 299 (12.71%) | 86 / 298 (28.86%) |  |
| occurrences (all)           | 54                | 130               |  |
| Pain                        |                   |                   |  |
| subjects affected / exposed | 8 / 299 (2.68%)   | 14 / 298 (4.70%)  |  |
| occurrences (all)           | 9                 | 17                |  |
| Peripheral swelling         |                   |                   |  |
| subjects affected / exposed | 1 / 299 (0.33%)   | 4 / 298 (1.34%)   |  |
| occurrences (all)           | 1                 | 4                 |  |
| Pyrexia                     |                   |                   |  |
| subjects affected / exposed | 17 / 299 (5.69%)  | 20 / 298 (6.71%)  |  |
| occurrences (all)           | 23                | 21                |  |
| Swelling                    |                   |                   |  |
| subjects affected / exposed | 1 / 299 (0.33%)   | 0 / 298 (0.00%)   |  |
| occurrences (all)           | 2                 | 0                 |  |
| Thrombosis in device        |                   |                   |  |
| subjects affected / exposed | 2 / 299 (0.67%)   | 2 / 298 (0.67%)   |  |
| occurrences (all)           | 2                 | 2                 |  |
| Xerosis                     |                   |                   |  |
| subjects affected / exposed | 2 / 299 (0.67%)   | 1 / 298 (0.34%)   |  |
| occurrences (all)           | 2                 | 1                 |  |
| Immune system disorders     |                   |                   |  |
| Hypersensitivity            |                   |                   |  |
| subjects affected / exposed | 1 / 299 (0.33%)   | 0 / 298 (0.00%)   |  |
| occurrences (all)           | 1                 | 0                 |  |
| Multiple allergies          |                   |                   |  |
| subjects affected / exposed | 0 / 299 (0.00%)   | 1 / 298 (0.34%)   |  |
| occurrences (all)           | 0                 | 1                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| Social circumstances                            |                 |                 |  |
| Sight disability                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences (all)                               | 1               | 0               |  |
| Reproductive system and breast disorders        |                 |                 |  |
| Genital erythema                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 299 (0.00%) | 1 / 298 (0.34%) |  |
| occurrences (all)                               | 0               | 1               |  |
| Haematospermia                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences (all)                               | 1               | 0               |  |
| Oedema genital                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences (all)                               | 1               | 0               |  |
| Pelvic pain                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences (all)                               | 1               | 0               |  |
| Penile oedema                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences (all)                               | 1               | 0               |  |
| Penile pain                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences (all)                               | 1               | 0               |  |
| Prostatomegaly                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences (all)                               | 1               | 0               |  |
| Vaginal haemorrhage                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 1 / 298 (0.34%) |  |
| occurrences (all)                               | 1               | 1               |  |
| Vulvovaginal rash                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences (all)                               | 1               | 0               |  |
| Respiratory, thoracic and mediastinal disorders |                 |                 |  |
| Atelectasis                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences (all)                               | 1               | 0               |  |

|                                       |                  |                  |
|---------------------------------------|------------------|------------------|
| Bronchopneumopathy                    |                  |                  |
| subjects affected / exposed           | 0 / 299 (0.00%)  | 1 / 298 (0.34%)  |
| occurrences (all)                     | 0                | 1                |
| Chronic obstructive pulmonary disease |                  |                  |
| subjects affected / exposed           | 1 / 299 (0.33%)  | 0 / 298 (0.00%)  |
| occurrences (all)                     | 1                | 0                |
| Cough                                 |                  |                  |
| subjects affected / exposed           | 23 / 299 (7.69%) | 10 / 298 (3.36%) |
| occurrences (all)                     | 25               | 10               |
| Dysphonia                             |                  |                  |
| subjects affected / exposed           | 4 / 299 (1.34%)  | 0 / 298 (0.00%)  |
| occurrences (all)                     | 7                | 0                |
| Dyspnoea                              |                  |                  |
| subjects affected / exposed           | 20 / 299 (6.69%) | 23 / 298 (7.72%) |
| occurrences (all)                     | 25               | 30               |
| Dyspnoea exertional                   |                  |                  |
| subjects affected / exposed           | 1 / 299 (0.33%)  | 6 / 298 (2.01%)  |
| occurrences (all)                     | 1                | 6                |
| Epistaxis                             |                  |                  |
| subjects affected / exposed           | 3 / 299 (1.00%)  | 5 / 298 (1.68%)  |
| occurrences (all)                     | 3                | 5                |
| Haemoptysis                           |                  |                  |
| subjects affected / exposed           | 1 / 299 (0.33%)  | 0 / 298 (0.00%)  |
| occurrences (all)                     | 1                | 0                |
| Hiccups                               |                  |                  |
| subjects affected / exposed           | 13 / 299 (4.35%) | 8 / 298 (2.68%)  |
| occurrences (all)                     | 18               | 10               |
| Hypoxia                               |                  |                  |
| subjects affected / exposed           | 0 / 299 (0.00%)  | 1 / 298 (0.34%)  |
| occurrences (all)                     | 0                | 1                |
| Increased upper airway secretion      |                  |                  |
| subjects affected / exposed           | 1 / 299 (0.33%)  | 0 / 298 (0.00%)  |
| occurrences (all)                     | 1                | 0                |
| Lung consolidation                    |                  |                  |

|                              |                 |                 |
|------------------------------|-----------------|-----------------|
| subjects affected / exposed  | 0 / 299 (0.00%) | 1 / 298 (0.34%) |
| occurrences (all)            | 0               | 1               |
| Nasal congestion             |                 |                 |
| subjects affected / exposed  | 1 / 299 (0.33%) | 0 / 298 (0.00%) |
| occurrences (all)            | 1               | 0               |
| Nasal discomfort             |                 |                 |
| subjects affected / exposed  | 1 / 299 (0.33%) | 0 / 298 (0.00%) |
| occurrences (all)            | 1               | 0               |
| Obstructive airways disorder |                 |                 |
| subjects affected / exposed  | 1 / 299 (0.33%) | 0 / 298 (0.00%) |
| occurrences (all)            | 1               | 0               |
| Oropharyngeal pain           |                 |                 |
| subjects affected / exposed  | 6 / 299 (2.01%) | 3 / 298 (1.01%) |
| occurrences (all)            | 6               | 3               |
| Pharyngeal erythema          |                 |                 |
| subjects affected / exposed  | 0 / 299 (0.00%) | 1 / 298 (0.34%) |
| occurrences (all)            | 0               | 1               |
| Pleural effusion             |                 |                 |
| subjects affected / exposed  | 3 / 299 (1.00%) | 3 / 298 (1.01%) |
| occurrences (all)            | 3               | 4               |
| Pleurisy                     |                 |                 |
| subjects affected / exposed  | 0 / 299 (0.00%) | 1 / 298 (0.34%) |
| occurrences (all)            | 0               | 1               |
| Pleuritic pain               |                 |                 |
| subjects affected / exposed  | 1 / 299 (0.33%) | 1 / 298 (0.34%) |
| occurrences (all)            | 1               | 1               |
| Pneumonia aspiration         |                 |                 |
| subjects affected / exposed  | 2 / 299 (0.67%) | 0 / 298 (0.00%) |
| occurrences (all)            | 2               | 0               |
| Pneumonitis                  |                 |                 |
| subjects affected / exposed  | 0 / 299 (0.00%) | 1 / 298 (0.34%) |
| occurrences (all)            | 0               | 1               |
| Productive cough             |                 |                 |
| subjects affected / exposed  | 2 / 299 (0.67%) | 0 / 298 (0.00%) |
| occurrences (all)            | 2               | 0               |
| Pulmonary artery thrombosis  |                 |                 |



|                             |                  |                  |  |
|-----------------------------|------------------|------------------|--|
| subjects affected / exposed | 0 / 299 (0.00%)  | 2 / 298 (0.67%)  |  |
| occurrences (all)           | 0                | 2                |  |
| Pulmonary embolism          |                  |                  |  |
| subjects affected / exposed | 13 / 299 (4.35%) | 15 / 298 (5.03%) |  |
| occurrences (all)           | 13               | 17               |  |
| Pulmonary thrombosis        |                  |                  |  |
| subjects affected / exposed | 0 / 299 (0.00%)  | 1 / 298 (0.34%)  |  |
| occurrences (all)           | 0                | 1                |  |
| Rhinitis allergic           |                  |                  |  |
| subjects affected / exposed | 0 / 299 (0.00%)  | 1 / 298 (0.34%)  |  |
| occurrences (all)           | 0                | 1                |  |
| Rhinorrhoea                 |                  |                  |  |
| subjects affected / exposed | 1 / 299 (0.33%)  | 3 / 298 (1.01%)  |  |
| occurrences (all)           | 1                | 3                |  |
| Throat tightness            |                  |                  |  |
| subjects affected / exposed | 1 / 299 (0.33%)  | 0 / 298 (0.00%)  |  |
| occurrences (all)           | 1                | 0                |  |
| Wheezing                    |                  |                  |  |
| subjects affected / exposed | 1 / 299 (0.33%)  | 0 / 298 (0.00%)  |  |
| occurrences (all)           | 1                | 0                |  |
| Psychiatric disorders       |                  |                  |  |
| Agitation                   |                  |                  |  |
| subjects affected / exposed | 1 / 299 (0.33%)  | 0 / 298 (0.00%)  |  |
| occurrences (all)           | 1                | 0                |  |
| Anxiety                     |                  |                  |  |
| subjects affected / exposed | 11 / 299 (3.68%) | 13 / 298 (4.36%) |  |
| occurrences (all)           | 11               | 14               |  |
| Bradyphrenia                |                  |                  |  |
| subjects affected / exposed | 0 / 299 (0.00%)  | 1 / 298 (0.34%)  |  |
| occurrences (all)           | 0                | 1                |  |
| Confusional state           |                  |                  |  |
| subjects affected / exposed | 0 / 299 (0.00%)  | 3 / 298 (1.01%)  |  |
| occurrences (all)           | 0                | 3                |  |
| Depressed mood              |                  |                  |  |
| subjects affected / exposed | 0 / 299 (0.00%)  | 3 / 298 (1.01%)  |  |
| occurrences (all)           | 0                | 4                |  |

|                                                   |                  |                  |
|---------------------------------------------------|------------------|------------------|
| Depression                                        |                  |                  |
| subjects affected / exposed                       | 9 / 299 (3.01%)  | 7 / 298 (2.35%)  |
| occurrences (all)                                 | 10               | 8                |
| Disorientation                                    |                  |                  |
| subjects affected / exposed                       | 1 / 299 (0.33%)  | 0 / 298 (0.00%)  |
| occurrences (all)                                 | 1                | 0                |
| Hallucination                                     |                  |                  |
| subjects affected / exposed                       | 1 / 299 (0.33%)  | 0 / 298 (0.00%)  |
| occurrences (all)                                 | 1                | 0                |
| Insomnia                                          |                  |                  |
| subjects affected / exposed                       | 19 / 299 (6.35%) | 19 / 298 (6.38%) |
| occurrences (all)                                 | 19               | 22               |
| Irritability                                      |                  |                  |
| subjects affected / exposed                       | 0 / 299 (0.00%)  | 1 / 298 (0.34%)  |
| occurrences (all)                                 | 0                | 1                |
| Libido decreased                                  |                  |                  |
| subjects affected / exposed                       | 1 / 299 (0.33%)  | 0 / 298 (0.00%)  |
| occurrences (all)                                 | 1                | 0                |
| Mood altered                                      |                  |                  |
| subjects affected / exposed                       | 1 / 299 (0.33%)  | 0 / 298 (0.00%)  |
| occurrences (all)                                 | 1                | 0                |
| Nervousness                                       |                  |                  |
| subjects affected / exposed                       | 0 / 299 (0.00%)  | 1 / 298 (0.34%)  |
| occurrences (all)                                 | 0                | 1                |
| Phobia                                            |                  |                  |
| subjects affected / exposed                       | 0 / 299 (0.00%)  | 1 / 298 (0.34%)  |
| occurrences (all)                                 | 0                | 1                |
| Sleep disorder                                    |                  |                  |
| subjects affected / exposed                       | 0 / 299 (0.00%)  | 1 / 298 (0.34%)  |
| occurrences (all)                                 | 0                | 1                |
| Sleep disorder due to a general medical condition |                  |                  |
| subjects affected / exposed                       | 0 / 299 (0.00%)  | 1 / 298 (0.34%)  |
| occurrences (all)                                 | 0                | 1                |
| Investigations                                    |                  |                  |

|                                                                                          |                        |                       |
|------------------------------------------------------------------------------------------|------------------------|-----------------------|
| Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)   | 6 / 299 (2.01%)<br>9   | 6 / 298 (2.01%)<br>8  |
| Amylase increased<br>subjects affected / exposed<br>occurrences (all)                    | 0 / 299 (0.00%)<br>0   | 1 / 298 (0.34%)<br>1  |
| Aspartate aminotransferase increased<br>subjects affected / exposed<br>occurrences (all) | 13 / 299 (4.35%)<br>15 | 7 / 298 (2.35%)<br>8  |
| Blood albumin decreased<br>subjects affected / exposed<br>occurrences (all)              | 2 / 299 (0.67%)<br>5   | 3 / 298 (1.01%)<br>4  |
| Blood alkaline phosphatase increased<br>subjects affected / exposed<br>occurrences (all) | 9 / 299 (3.01%)<br>12  | 7 / 298 (2.35%)<br>10 |
| Blood bicarbonate decreased<br>subjects affected / exposed<br>occurrences (all)          | 1 / 299 (0.33%)<br>1   | 0 / 298 (0.00%)<br>0  |
| Blood bilirubin<br>subjects affected / exposed<br>occurrences (all)                      | 1 / 299 (0.33%)<br>1   | 0 / 298 (0.00%)<br>0  |
| Blood bilirubin abnormal<br>subjects affected / exposed<br>occurrences (all)             | 1 / 299 (0.33%)<br>1   | 0 / 298 (0.00%)<br>0  |
| Blood bilirubin increased<br>subjects affected / exposed<br>occurrences (all)            | 6 / 299 (2.01%)<br>9   | 0 / 298 (0.00%)<br>0  |
| Blood calcium decreased<br>subjects affected / exposed<br>occurrences (all)              | 1 / 299 (0.33%)<br>1   | 0 / 298 (0.00%)<br>0  |
| Blood creatine abnormal<br>subjects affected / exposed<br>occurrences (all)              | 1 / 299 (0.33%)<br>1   | 0 / 298 (0.00%)<br>0  |
| Blood creatine increased                                                                 |                        |                       |

|                                       |                 |                 |
|---------------------------------------|-----------------|-----------------|
| subjects affected / exposed           | 4 / 299 (1.34%) | 4 / 298 (1.34%) |
| occurrences (all)                     | 4               | 5               |
| Blood creatinine increased            |                 |                 |
| subjects affected / exposed           | 7 / 299 (2.34%) | 9 / 298 (3.02%) |
| occurrences (all)                     | 8               | 12              |
| Blood glucose increased               |                 |                 |
| subjects affected / exposed           | 1 / 299 (0.33%) | 0 / 298 (0.00%) |
| occurrences (all)                     | 1               | 0               |
| Blood iron decreased                  |                 |                 |
| subjects affected / exposed           | 1 / 299 (0.33%) | 0 / 298 (0.00%) |
| occurrences (all)                     | 1               | 0               |
| Blood lactate dehydrogenase increased |                 |                 |
| subjects affected / exposed           | 1 / 299 (0.33%) | 1 / 298 (0.34%) |
| occurrences (all)                     | 1               | 1               |
| Blood magnesium decreased             |                 |                 |
| subjects affected / exposed           | 4 / 299 (1.34%) | 1 / 298 (0.34%) |
| occurrences (all)                     | 7               | 1               |
| Blood phosphorus decreased            |                 |                 |
| subjects affected / exposed           | 0 / 299 (0.00%) | 1 / 298 (0.34%) |
| occurrences (all)                     | 0               | 1               |
| Blood potassium decreased             |                 |                 |
| subjects affected / exposed           | 1 / 299 (0.33%) | 2 / 298 (0.67%) |
| occurrences (all)                     | 2               | 2               |
| Blood sodium decreased                |                 |                 |
| subjects affected / exposed           | 0 / 299 (0.00%) | 1 / 298 (0.34%) |
| occurrences (all)                     | 0               | 1               |
| Blood testosterone decreased          |                 |                 |
| subjects affected / exposed           | 1 / 299 (0.33%) | 0 / 298 (0.00%) |
| occurrences (all)                     | 1               | 0               |
| Blood urea increased                  |                 |                 |
| subjects affected / exposed           | 1 / 299 (0.33%) | 1 / 298 (0.34%) |
| occurrences (all)                     | 1               | 1               |
| Body temperature increased            |                 |                 |
| subjects affected / exposed           | 0 / 299 (0.00%) | 1 / 298 (0.34%) |
| occurrences (all)                     | 0               | 1               |

|                                                                                                                       |                        |                        |
|-----------------------------------------------------------------------------------------------------------------------|------------------------|------------------------|
| C-reactive protein increased<br>subjects affected / exposed<br>occurrences (all)                                      | 1 / 299 (0.33%)<br>1   | 2 / 298 (0.67%)<br>2   |
| Capillary fragility increased<br>subjects affected / exposed<br>occurrences (all)                                     | 1 / 299 (0.33%)<br>1   | 0 / 298 (0.00%)<br>0   |
| Clostridium test positive<br>subjects affected / exposed<br>occurrences (all)                                         | 0 / 299 (0.00%)<br>0   | 1 / 298 (0.34%)<br>1   |
| Creatinine renal clearance decreased<br>subjects affected / exposed<br>occurrences (all)                              | 21 / 299 (7.02%)<br>33 | 15 / 298 (5.03%)<br>20 |
| Creatinine renal clearance increased<br>subjects affected / exposed<br>occurrences (all)                              | 0 / 299 (0.00%)<br>0   | 1 / 298 (0.34%)<br>1   |
| Eastern Cooperative Oncology Group<br>performance status worsened<br>subjects affected / exposed<br>occurrences (all) | 0 / 299 (0.00%)<br>0   | 1 / 298 (0.34%)<br>1   |
| Ejection fraction decreased<br>subjects affected / exposed<br>occurrences (all)                                       | 2 / 299 (0.67%)<br>2   | 2 / 298 (0.67%)<br>2   |
| Fibrin D dimer increased<br>subjects affected / exposed<br>occurrences (all)                                          | 0 / 299 (0.00%)<br>0   | 1 / 298 (0.34%)<br>1   |
| Gamma-glutamyltransferase<br>increased<br>subjects affected / exposed<br>occurrences (all)                            | 2 / 299 (0.67%)<br>2   | 1 / 298 (0.34%)<br>1   |
| Glomerular filtration rate<br>subjects affected / exposed<br>occurrences (all)                                        | 0 / 299 (0.00%)<br>0   | 1 / 298 (0.34%)<br>1   |
| Glomerular filtration rate abnormal<br>subjects affected / exposed<br>occurrences (all)                               | 0 / 299 (0.00%)<br>0   | 1 / 298 (0.34%)<br>1   |
| Glomerular filtration rate decreased                                                                                  |                        |                        |

|                                          |                  |                  |
|------------------------------------------|------------------|------------------|
| subjects affected / exposed              | 2 / 299 (0.67%)  | 9 / 298 (3.02%)  |
| occurrences (all)                        | 2                | 16               |
| Granulocyte count decreased              |                  |                  |
| subjects affected / exposed              | 0 / 299 (0.00%)  | 1 / 298 (0.34%)  |
| occurrences (all)                        | 0                | 1                |
| Haemoglobin                              |                  |                  |
| subjects affected / exposed              | 0 / 299 (0.00%)  | 1 / 298 (0.34%)  |
| occurrences (all)                        | 0                | 1                |
| Haemoglobin abnormal                     |                  |                  |
| subjects affected / exposed              | 1 / 299 (0.33%)  | 0 / 298 (0.00%)  |
| occurrences (all)                        | 1                | 0                |
| Haemoglobin decreased                    |                  |                  |
| subjects affected / exposed              | 8 / 299 (2.68%)  | 3 / 298 (1.01%)  |
| occurrences (all)                        | 11               | 16               |
| Heart rate increased                     |                  |                  |
| subjects affected / exposed              | 1 / 299 (0.33%)  | 0 / 298 (0.00%)  |
| occurrences (all)                        | 1                | 0                |
| International normalised ratio increased |                  |                  |
| subjects affected / exposed              | 1 / 299 (0.33%)  | 1 / 298 (0.34%)  |
| occurrences (all)                        | 1                | 1                |
| Neutrophil count                         |                  |                  |
| subjects affected / exposed              | 1 / 299 (0.33%)  | 0 / 298 (0.00%)  |
| occurrences (all)                        | 5                | 0                |
| Neutrophil count decreased               |                  |                  |
| subjects affected / exposed              | 11 / 299 (3.68%) | 11 / 298 (3.69%) |
| occurrences (all)                        | 42               | 24               |
| Platelet count decreased                 |                  |                  |
| subjects affected / exposed              | 11 / 299 (3.68%) | 11 / 298 (3.69%) |
| occurrences (all)                        | 18               | 22               |
| Platelet count increased                 |                  |                  |
| subjects affected / exposed              | 1 / 299 (0.33%)  | 0 / 298 (0.00%)  |
| occurrences (all)                        | 1                | 0                |
| Prothrombin time shortened               |                  |                  |
| subjects affected / exposed              | 0 / 299 (0.00%)  | 1 / 298 (0.34%)  |
| occurrences (all)                        | 0                | 1                |

|                                                                                      |                         |                        |  |
|--------------------------------------------------------------------------------------|-------------------------|------------------------|--|
| Red blood cell count decreased<br>subjects affected / exposed<br>occurrences (all)   | 0 / 299 (0.00%)<br>0    | 1 / 298 (0.34%)<br>1   |  |
| Renal function test abnormal<br>subjects affected / exposed<br>occurrences (all)     | 1 / 299 (0.33%)<br>1    | 2 / 298 (0.67%)<br>2   |  |
| Transaminases increased<br>subjects affected / exposed<br>occurrences (all)          | 0 / 299 (0.00%)<br>0    | 1 / 298 (0.34%)<br>1   |  |
| Troponin I increased<br>subjects affected / exposed<br>occurrences (all)             | 1 / 299 (0.33%)<br>1    | 0 / 298 (0.00%)<br>0   |  |
| Urine output increased<br>subjects affected / exposed<br>occurrences (all)           | 1 / 299 (0.33%)<br>1    | 0 / 298 (0.00%)<br>0   |  |
| Weight decreased<br>subjects affected / exposed<br>occurrences (all)                 | 49 / 299 (16.39%)<br>63 | 23 / 298 (7.72%)<br>33 |  |
| Weight increased<br>subjects affected / exposed<br>occurrences (all)                 | 3 / 299 (1.00%)<br>3    | 1 / 298 (0.34%)<br>1   |  |
| White blood cell count decreased<br>subjects affected / exposed<br>occurrences (all) | 14 / 299 (4.68%)<br>28  | 13 / 298 (4.36%)<br>42 |  |
| Injury, poisoning and procedural complications                                       |                         |                        |  |
| Contusion<br>subjects affected / exposed<br>occurrences (all)                        | 2 / 299 (0.67%)<br>2    | 1 / 298 (0.34%)<br>1   |  |
| Dumping syndrome<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 299 (0.00%)<br>0    | 1 / 298 (0.34%)<br>1   |  |
| Eye injury<br>subjects affected / exposed<br>occurrences (all)                       | 1 / 299 (0.33%)<br>1    | 0 / 298 (0.00%)<br>0   |  |
| Face injury                                                                          |                         |                        |  |

|                                   |                 |                 |  |
|-----------------------------------|-----------------|-----------------|--|
| subjects affected / exposed       | 0 / 299 (0.00%) | 1 / 298 (0.34%) |  |
| occurrences (all)                 | 0               | 1               |  |
| Fall                              |                 |                 |  |
| subjects affected / exposed       | 5 / 299 (1.67%) | 2 / 298 (0.67%) |  |
| occurrences (all)                 | 5               | 2               |  |
| Gastrointestinal anastomotic leak |                 |                 |  |
| subjects affected / exposed       | 0 / 299 (0.00%) | 1 / 298 (0.34%) |  |
| occurrences (all)                 | 0               | 1               |  |
| Infusion related reaction         |                 |                 |  |
| subjects affected / exposed       | 1 / 299 (0.33%) | 2 / 298 (0.67%) |  |
| occurrences (all)                 | 1               | 2               |  |
| Joint injury                      |                 |                 |  |
| subjects affected / exposed       | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences (all)                 | 1               | 0               |  |
| Laceration                        |                 |                 |  |
| subjects affected / exposed       | 1 / 299 (0.33%) | 1 / 298 (0.34%) |  |
| occurrences (all)                 | 1               | 1               |  |
| Nail injury                       |                 |                 |  |
| subjects affected / exposed       | 0 / 299 (0.00%) | 1 / 298 (0.34%) |  |
| occurrences (all)                 | 0               | 1               |  |
| Procedural pain                   |                 |                 |  |
| subjects affected / exposed       | 0 / 299 (0.00%) | 3 / 298 (1.01%) |  |
| occurrences (all)                 | 0               | 4               |  |
| Rib fracture                      |                 |                 |  |
| subjects affected / exposed       | 1 / 299 (0.33%) | 1 / 298 (0.34%) |  |
| occurrences (all)                 | 1               | 1               |  |
| Urethral injury                   |                 |                 |  |
| subjects affected / exposed       | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences (all)                 | 1               | 0               |  |
| Vascular injury                   |                 |                 |  |
| subjects affected / exposed       | 0 / 299 (0.00%) | 1 / 298 (0.34%) |  |
| occurrences (all)                 | 0               | 1               |  |
| Wound                             |                 |                 |  |
| subjects affected / exposed       | 0 / 299 (0.00%) | 2 / 298 (0.67%) |  |
| occurrences (all)                 | 0               | 2               |  |
| Congenital, familial and genetic  |                 |                 |  |



|                             |                 |                 |  |
|-----------------------------|-----------------|-----------------|--|
| disorders                   |                 |                 |  |
| Epidermolysis bullosa       |                 |                 |  |
| subjects affected / exposed | 0 / 299 (0.00%) | 1 / 298 (0.34%) |  |
| occurrences (all)           | 0               | 2               |  |
| Phimosi                     |                 |                 |  |
| subjects affected / exposed | 0 / 299 (0.00%) | 1 / 298 (0.34%) |  |
| occurrences (all)           | 0               | 1               |  |
| Cardiac disorders           |                 |                 |  |
| Angina pectoris             |                 |                 |  |
| subjects affected / exposed | 0 / 299 (0.00%) | 1 / 298 (0.34%) |  |
| occurrences (all)           | 0               | 1               |  |
| Atrial fibrillation         |                 |                 |  |
| subjects affected / exposed | 4 / 299 (1.34%) | 0 / 298 (0.00%) |  |
| occurrences (all)           | 4               | 0               |  |
| Bradycardia                 |                 |                 |  |
| subjects affected / exposed | 3 / 299 (1.00%) | 1 / 298 (0.34%) |  |
| occurrences (all)           | 3               | 1               |  |
| Bundle branch block left    |                 |                 |  |
| subjects affected / exposed | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences (all)           | 1               | 0               |  |
| Cardiac failure             |                 |                 |  |
| subjects affected / exposed | 0 / 299 (0.00%) | 1 / 298 (0.34%) |  |
| occurrences (all)           | 0               | 1               |  |
| Cardiomyopathy              |                 |                 |  |
| subjects affected / exposed | 2 / 299 (0.67%) | 0 / 298 (0.00%) |  |
| occurrences (all)           | 2               | 0               |  |
| Cardiovascular disorder     |                 |                 |  |
| subjects affected / exposed | 1 / 299 (0.33%) | 2 / 298 (0.67%) |  |
| occurrences (all)           | 1               | 2               |  |
| Cyanosis                    |                 |                 |  |
| subjects affected / exposed | 0 / 299 (0.00%) | 1 / 298 (0.34%) |  |
| occurrences (all)           | 0               | 1               |  |
| Extrasystoles               |                 |                 |  |
| subjects affected / exposed | 0 / 299 (0.00%) | 1 / 298 (0.34%) |  |
| occurrences (all)           | 0               | 2               |  |
| Myocardial fibrosis         |                 |                 |  |

|                                |                 |                 |  |
|--------------------------------|-----------------|-----------------|--|
| subjects affected / exposed    | 0 / 299 (0.00%) | 1 / 298 (0.34%) |  |
| occurrences (all)              | 0               | 1               |  |
| Palpitations                   |                 |                 |  |
| subjects affected / exposed    | 0 / 299 (0.00%) | 4 / 298 (1.34%) |  |
| occurrences (all)              | 0               | 4               |  |
| Pericardial effusion           |                 |                 |  |
| subjects affected / exposed    | 0 / 299 (0.00%) | 1 / 298 (0.34%) |  |
| occurrences (all)              | 0               | 2               |  |
| Right ventricular dysfunction  |                 |                 |  |
| subjects affected / exposed    | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences (all)              | 1               | 0               |  |
| Sinus tachycardia              |                 |                 |  |
| subjects affected / exposed    | 3 / 299 (1.00%) | 1 / 298 (0.34%) |  |
| occurrences (all)              | 3               | 1               |  |
| Tachycardia                    |                 |                 |  |
| subjects affected / exposed    | 3 / 299 (1.00%) | 5 / 298 (1.68%) |  |
| occurrences (all)              | 4               | 5               |  |
| Ventricular extrasystoles      |                 |                 |  |
| subjects affected / exposed    | 0 / 299 (0.00%) | 1 / 298 (0.34%) |  |
| occurrences (all)              | 0               | 1               |  |
| Ventricular tachycardia        |                 |                 |  |
| subjects affected / exposed    | 0 / 299 (0.00%) | 1 / 298 (0.34%) |  |
| occurrences (all)              | 0               | 1               |  |
| Nervous system disorders       |                 |                 |  |
| Ageusia                        |                 |                 |  |
| subjects affected / exposed    | 1 / 299 (0.33%) | 1 / 298 (0.34%) |  |
| occurrences (all)              | 1               | 1               |  |
| Altered state of consciousness |                 |                 |  |
| subjects affected / exposed    | 0 / 299 (0.00%) | 1 / 298 (0.34%) |  |
| occurrences (all)              | 0               | 1               |  |
| Amnesia                        |                 |                 |  |
| subjects affected / exposed    | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences (all)              | 1               | 0               |  |
| Anaesthesia                    |                 |                 |  |
| subjects affected / exposed    | 1 / 299 (0.33%) | 0 / 298 (0.00%) |  |
| occurrences (all)              | 1               | 0               |  |

|                             |                  |                   |
|-----------------------------|------------------|-------------------|
| Aphasia                     |                  |                   |
| subjects affected / exposed | 1 / 299 (0.33%)  | 1 / 298 (0.34%)   |
| occurrences (all)           | 1                | 1                 |
| Ataxia                      |                  |                   |
| subjects affected / exposed | 1 / 299 (0.33%)  | 1 / 298 (0.34%)   |
| occurrences (all)           | 1                | 1                 |
| Balance disorder            |                  |                   |
| subjects affected / exposed | 1 / 299 (0.33%)  | 0 / 298 (0.00%)   |
| occurrences (all)           | 1                | 0                 |
| Cerebrovascular accident    |                  |                   |
| subjects affected / exposed | 0 / 299 (0.00%)  | 1 / 298 (0.34%)   |
| occurrences (all)           | 0                | 1                 |
| Cognitive disorder          |                  |                   |
| subjects affected / exposed | 2 / 299 (0.67%)  | 1 / 298 (0.34%)   |
| occurrences (all)           | 2                | 1                 |
| Disturbance in attention    |                  |                   |
| subjects affected / exposed | 0 / 299 (0.00%)  | 1 / 298 (0.34%)   |
| occurrences (all)           | 0                | 1                 |
| Dizziness                   |                  |                   |
| subjects affected / exposed | 26 / 299 (8.70%) | 32 / 298 (10.74%) |
| occurrences (all)           | 32               | 39                |
| Dizziness postural          |                  |                   |
| subjects affected / exposed | 0 / 299 (0.00%)  | 2 / 298 (0.67%)   |
| occurrences (all)           | 0                | 2                 |
| Dysgeusia                   |                  |                   |
| subjects affected / exposed | 19 / 299 (6.35%) | 16 / 298 (5.37%)  |
| occurrences (all)           | 24               | 23                |
| Headache                    |                  |                   |
| subjects affected / exposed | 23 / 299 (7.69%) | 18 / 298 (6.04%)  |
| occurrences (all)           | 28               | 21                |
| Hypoaesthesia               |                  |                   |
| subjects affected / exposed | 5 / 299 (1.67%)  | 4 / 298 (1.34%)   |
| occurrences (all)           | 5                | 4                 |
| Hypotonia                   |                  |                   |
| subjects affected / exposed | 0 / 299 (0.00%)  | 1 / 298 (0.34%)   |
| occurrences (all)           | 0                | 1                 |

|                               |                   |                  |
|-------------------------------|-------------------|------------------|
| Lethargy                      |                   |                  |
| subjects affected / exposed   | 6 / 299 (2.01%)   | 2 / 298 (0.67%)  |
| occurrences (all)             | 8                 | 2                |
| Memory impairment             |                   |                  |
| subjects affected / exposed   | 0 / 299 (0.00%)   | 1 / 298 (0.34%)  |
| occurrences (all)             | 0                 | 1                |
| Mental retardation            |                   |                  |
| subjects affected / exposed   | 1 / 299 (0.33%)   | 0 / 298 (0.00%)  |
| occurrences (all)             | 1                 | 0                |
| Neuropathy peripheral         |                   |                  |
| subjects affected / exposed   | 33 / 299 (11.04%) | 24 / 298 (8.05%) |
| occurrences (all)             | 52                | 34               |
| Neurotoxicity                 |                   |                  |
| subjects affected / exposed   | 2 / 299 (0.67%)   | 1 / 298 (0.34%)  |
| occurrences (all)             | 2                 | 2                |
| Paraesthesia                  |                   |                  |
| subjects affected / exposed   | 11 / 299 (3.68%)  | 5 / 298 (1.68%)  |
| occurrences (all)             | 13                | 5                |
| Parkinson's disease           |                   |                  |
| subjects affected / exposed   | 0 / 299 (0.00%)   | 1 / 298 (0.34%)  |
| occurrences (all)             | 0                 | 1                |
| Parosmia                      |                   |                  |
| subjects affected / exposed   | 0 / 299 (0.00%)   | 1 / 298 (0.34%)  |
| occurrences (all)             | 0                 | 1                |
| Peripheral motor neuropathy   |                   |                  |
| subjects affected / exposed   | 2 / 299 (0.67%)   | 1 / 298 (0.34%)  |
| occurrences (all)             | 4                 | 2                |
| Peripheral sensory neuropathy |                   |                  |
| subjects affected / exposed   | 11 / 299 (3.68%)  | 8 / 298 (2.68%)  |
| occurrences (all)             | 13                | 10               |
| Polyneuropathy                |                   |                  |
| subjects affected / exposed   | 4 / 299 (1.34%)   | 7 / 298 (2.35%)  |
| occurrences (all)             | 5                 | 11               |
| Post herpetic neuralgia       |                   |                  |
| subjects affected / exposed   | 1 / 299 (0.33%)   | 0 / 298 (0.00%)  |
| occurrences (all)             | 1                 | 0                |

|                                      |                    |                   |  |
|--------------------------------------|--------------------|-------------------|--|
| Presyncope                           |                    |                   |  |
| subjects affected / exposed          | 3 / 299 (1.00%)    | 0 / 298 (0.00%)   |  |
| occurrences (all)                    | 3                  | 0                 |  |
| Sciatica                             |                    |                   |  |
| subjects affected / exposed          | 3 / 299 (1.00%)    | 1 / 298 (0.34%)   |  |
| occurrences (all)                    | 3                  | 1                 |  |
| Seizure                              |                    |                   |  |
| subjects affected / exposed          | 1 / 299 (0.33%)    | 1 / 298 (0.34%)   |  |
| occurrences (all)                    | 1                  | 1                 |  |
| Sensory disturbance                  |                    |                   |  |
| subjects affected / exposed          | 0 / 299 (0.00%)    | 1 / 298 (0.34%)   |  |
| occurrences (all)                    | 0                  | 1                 |  |
| Somnolence                           |                    |                   |  |
| subjects affected / exposed          | 3 / 299 (1.00%)    | 3 / 298 (1.01%)   |  |
| occurrences (all)                    | 3                  | 3                 |  |
| Speech disorder                      |                    |                   |  |
| subjects affected / exposed          | 1 / 299 (0.33%)    | 0 / 298 (0.00%)   |  |
| occurrences (all)                    | 1                  | 0                 |  |
| Syncope                              |                    |                   |  |
| subjects affected / exposed          | 5 / 299 (1.67%)    | 8 / 298 (2.68%)   |  |
| occurrences (all)                    | 6                  | 8                 |  |
| Tension headache                     |                    |                   |  |
| subjects affected / exposed          | 1 / 299 (0.33%)    | 0 / 298 (0.00%)   |  |
| occurrences (all)                    | 1                  | 0                 |  |
| Tremor                               |                    |                   |  |
| subjects affected / exposed          | 4 / 299 (1.34%)    | 0 / 298 (0.00%)   |  |
| occurrences (all)                    | 4                  | 0                 |  |
| Blood and lymphatic system disorders |                    |                   |  |
| Anaemia                              |                    |                   |  |
| subjects affected / exposed          | 117 / 299 (39.13%) | 92 / 298 (30.87%) |  |
| occurrences (all)                    | 256                | 203               |  |
| Anaemia macrocytic                   |                    |                   |  |
| subjects affected / exposed          | 1 / 299 (0.33%)    | 1 / 298 (0.34%)   |  |
| occurrences (all)                    | 1                  | 1                 |  |
| Bone marrow failure                  |                    |                   |  |

|                             |                    |                    |  |
|-----------------------------|--------------------|--------------------|--|
| subjects affected / exposed | 1 / 299 (0.33%)    | 0 / 298 (0.00%)    |  |
| occurrences (all)           | 1                  | 0                  |  |
| Coagulopathy                |                    |                    |  |
| subjects affected / exposed | 0 / 299 (0.00%)    | 2 / 298 (0.67%)    |  |
| occurrences (all)           | 0                  | 2                  |  |
| Febrile neutropenia         |                    |                    |  |
| subjects affected / exposed | 4 / 299 (1.34%)    | 3 / 298 (1.01%)    |  |
| occurrences (all)           | 4                  | 3                  |  |
| Haemorrhagic disorder       |                    |                    |  |
| subjects affected / exposed | 1 / 299 (0.33%)    | 0 / 298 (0.00%)    |  |
| occurrences (all)           | 1                  | 0                  |  |
| Hypofibrinogenaemia         |                    |                    |  |
| subjects affected / exposed | 0 / 299 (0.00%)    | 2 / 298 (0.67%)    |  |
| occurrences (all)           | 0                  | 7                  |  |
| Leukocytosis                |                    |                    |  |
| subjects affected / exposed | 1 / 299 (0.33%)    | 0 / 298 (0.00%)    |  |
| occurrences (all)           | 1                  | 0                  |  |
| Leukopenia                  |                    |                    |  |
| subjects affected / exposed | 31 / 299 (10.37%)  | 22 / 298 (7.38%)   |  |
| occurrences (all)           | 68                 | 40                 |  |
| Lymphadenopathy             |                    |                    |  |
| subjects affected / exposed | 1 / 299 (0.33%)    | 1 / 298 (0.34%)    |  |
| occurrences (all)           | 1                  | 1                  |  |
| Lymphopenia                 |                    |                    |  |
| subjects affected / exposed | 5 / 299 (1.67%)    | 2 / 298 (0.67%)    |  |
| occurrences (all)           | 13                 | 2                  |  |
| Neutropenia                 |                    |                    |  |
| subjects affected / exposed | 122 / 299 (40.80%) | 105 / 298 (35.23%) |  |
| occurrences (all)           | 314                | 245                |  |
| Pancytopenia                |                    |                    |  |
| subjects affected / exposed | 1 / 299 (0.33%)    | 1 / 298 (0.34%)    |  |
| occurrences (all)           | 3                  | 3                  |  |
| Thrombocytopenia            |                    |                    |  |
| subjects affected / exposed | 16 / 299 (5.35%)   | 19 / 298 (6.38%)   |  |
| occurrences (all)           | 37                 | 40                 |  |
| Ear and labyrinth disorders |                    |                    |  |

|                             |                  |                 |  |
|-----------------------------|------------------|-----------------|--|
| Deafness                    |                  |                 |  |
| subjects affected / exposed | 2 / 299 (0.67%)  | 1 / 298 (0.34%) |  |
| occurrences (all)           | 2                | 1               |  |
| Deafness neurosensory       |                  |                 |  |
| subjects affected / exposed | 1 / 299 (0.33%)  | 0 / 298 (0.00%) |  |
| occurrences (all)           | 1                | 0               |  |
| Ear congestion              |                  |                 |  |
| subjects affected / exposed | 1 / 299 (0.33%)  | 0 / 298 (0.00%) |  |
| occurrences (all)           | 1                | 0               |  |
| Ear pain                    |                  |                 |  |
| subjects affected / exposed | 1 / 299 (0.33%)  | 4 / 298 (1.34%) |  |
| occurrences (all)           | 1                | 4               |  |
| Hearing impaired            |                  |                 |  |
| subjects affected / exposed | 1 / 299 (0.33%)  | 2 / 298 (0.67%) |  |
| occurrences (all)           | 1                | 2               |  |
| Hypoacusis                  |                  |                 |  |
| subjects affected / exposed | 0 / 299 (0.00%)  | 1 / 298 (0.34%) |  |
| occurrences (all)           | 0                | 1               |  |
| Ototoxicity                 |                  |                 |  |
| subjects affected / exposed | 1 / 299 (0.33%)  | 0 / 298 (0.00%) |  |
| occurrences (all)           | 1                | 0               |  |
| Tinnitus                    |                  |                 |  |
| subjects affected / exposed | 12 / 299 (4.01%) | 6 / 298 (2.01%) |  |
| occurrences (all)           | 14               | 6               |  |
| Vertigo                     |                  |                 |  |
| subjects affected / exposed | 2 / 299 (0.67%)  | 6 / 298 (2.01%) |  |
| occurrences (all)           | 2                | 6               |  |
| Eye disorders               |                  |                 |  |
| Abnormal sensation in eye   |                  |                 |  |
| subjects affected / exposed | 1 / 299 (0.33%)  | 0 / 298 (0.00%) |  |
| occurrences (all)           | 1                | 0               |  |
| Cataract                    |                  |                 |  |
| subjects affected / exposed | 0 / 299 (0.00%)  | 1 / 298 (0.34%) |  |
| occurrences (all)           | 0                | 1               |  |
| Diplopia                    |                  |                 |  |

|                                |                 |                 |
|--------------------------------|-----------------|-----------------|
| subjects affected / exposed    | 1 / 299 (0.33%) | 1 / 298 (0.34%) |
| occurrences (all)              | 1               | 1               |
| Dry eye                        |                 |                 |
| subjects affected / exposed    | 1 / 299 (0.33%) | 3 / 298 (1.01%) |
| occurrences (all)              | 1               | 3               |
| Eye irritation                 |                 |                 |
| subjects affected / exposed    | 2 / 299 (0.67%) | 0 / 298 (0.00%) |
| occurrences (all)              | 2               | 0               |
| Eye oedema                     |                 |                 |
| subjects affected / exposed    | 1 / 299 (0.33%) | 0 / 298 (0.00%) |
| occurrences (all)              | 1               | 0               |
| Eye pruritus                   |                 |                 |
| subjects affected / exposed    | 1 / 299 (0.33%) | 0 / 298 (0.00%) |
| occurrences (all)              | 1               | 0               |
| Eyelid oedema                  |                 |                 |
| subjects affected / exposed    | 0 / 299 (0.00%) | 2 / 298 (0.67%) |
| occurrences (all)              | 0               | 2               |
| Foreign body sensation in eyes |                 |                 |
| subjects affected / exposed    | 1 / 299 (0.33%) | 0 / 298 (0.00%) |
| occurrences (all)              | 1               | 0               |
| Lacrimation increased          |                 |                 |
| subjects affected / exposed    | 6 / 299 (2.01%) | 5 / 298 (1.68%) |
| occurrences (all)              | 6               | 7               |
| Periorbital oedema             |                 |                 |
| subjects affected / exposed    | 0 / 299 (0.00%) | 2 / 298 (0.67%) |
| occurrences (all)              | 0               | 2               |
| Photophobia                    |                 |                 |
| subjects affected / exposed    | 1 / 299 (0.33%) | 0 / 298 (0.00%) |
| occurrences (all)              | 1               | 0               |
| Photopsia                      |                 |                 |
| subjects affected / exposed    | 1 / 299 (0.33%) | 0 / 298 (0.00%) |
| occurrences (all)              | 1               | 0               |
| Uveitis                        |                 |                 |
| subjects affected / exposed    | 0 / 299 (0.00%) | 1 / 298 (0.34%) |
| occurrences (all)              | 0               | 1               |
| Vision blurred                 |                 |                 |



|                                                                           |                         |                         |  |
|---------------------------------------------------------------------------|-------------------------|-------------------------|--|
| subjects affected / exposed<br>occurrences (all)                          | 3 / 299 (1.00%)<br>3    | 1 / 298 (0.34%)<br>1    |  |
| Visual acuity reduced<br>subjects affected / exposed<br>occurrences (all) | 0 / 299 (0.00%)<br>0    | 1 / 298 (0.34%)<br>1    |  |
| Visual impairment<br>subjects affected / exposed<br>occurrences (all)     | 2 / 299 (0.67%)<br>2    | 1 / 298 (0.34%)<br>1    |  |
| Gastrointestinal disorders                                                |                         |                         |  |
| Abdominal discomfort<br>subjects affected / exposed<br>occurrences (all)  | 1 / 299 (0.33%)<br>1    | 1 / 298 (0.34%)<br>1    |  |
| Abdominal distension<br>subjects affected / exposed<br>occurrences (all)  | 9 / 299 (3.01%)<br>10   | 10 / 298 (3.36%)<br>10  |  |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)        | 49 / 299 (16.39%)<br>56 | 43 / 298 (14.43%)<br>64 |  |
| Abdominal pain lower<br>subjects affected / exposed<br>occurrences (all)  | 3 / 299 (1.00%)<br>3    | 1 / 298 (0.34%)<br>1    |  |
| Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all)  | 22 / 299 (7.36%)<br>27  | 16 / 298 (5.37%)<br>17  |  |
| Anal fissure<br>subjects affected / exposed<br>occurrences (all)          | 1 / 299 (0.33%)<br>1    | 0 / 298 (0.00%)<br>0    |  |
| Anorectal discomfort<br>subjects affected / exposed<br>occurrences (all)  | 0 / 299 (0.00%)<br>0    | 2 / 298 (0.67%)<br>2    |  |
| Aphagia<br>subjects affected / exposed<br>occurrences (all)               | 0 / 299 (0.00%)<br>0    | 1 / 298 (0.34%)<br>1    |  |
| Aphthous stomatitis<br>subjects affected / exposed<br>occurrences (all)   | 3 / 299 (1.00%)<br>3    | 4 / 298 (1.34%)<br>4    |  |

|                             |                   |                   |
|-----------------------------|-------------------|-------------------|
| Ascites                     |                   |                   |
| subjects affected / exposed | 11 / 299 (3.68%)  | 10 / 298 (3.36%)  |
| occurrences (all)           | 13                | 10                |
| Chapped lips                |                   |                   |
| subjects affected / exposed | 1 / 299 (0.33%)   | 0 / 298 (0.00%)   |
| occurrences (all)           | 1                 | 0                 |
| Cheilitis                   |                   |                   |
| subjects affected / exposed | 2 / 299 (0.67%)   | 0 / 298 (0.00%)   |
| occurrences (all)           | 2                 | 0                 |
| Colitis                     |                   |                   |
| subjects affected / exposed | 0 / 299 (0.00%)   | 3 / 298 (1.01%)   |
| occurrences (all)           | 0                 | 3                 |
| Constipation                |                   |                   |
| subjects affected / exposed | 61 / 299 (20.40%) | 67 / 298 (22.48%) |
| occurrences (all)           | 86                | 81                |
| Diarrhoea                   |                   |                   |
| subjects affected / exposed | 78 / 299 (26.09%) | 59 / 298 (19.80%) |
| occurrences (all)           | 115               | 80                |
| Dry mouth                   |                   |                   |
| subjects affected / exposed | 6 / 299 (2.01%)   | 5 / 298 (1.68%)   |
| occurrences (all)           | 8                 | 5                 |
| Duodenal obstruction        |                   |                   |
| subjects affected / exposed | 1 / 299 (0.33%)   | 0 / 298 (0.00%)   |
| occurrences (all)           | 1                 | 0                 |
| Dyspepsia                   |                   |                   |
| subjects affected / exposed | 18 / 299 (6.02%)  | 9 / 298 (3.02%)   |
| occurrences (all)           | 19                | 12                |
| Dysphagia                   |                   |                   |
| subjects affected / exposed | 16 / 299 (5.35%)  | 18 / 298 (6.04%)  |
| occurrences (all)           | 19                | 23                |
| Eructation                  |                   |                   |
| subjects affected / exposed | 3 / 299 (1.00%)   | 0 / 298 (0.00%)   |
| occurrences (all)           | 3                 | 0                 |
| Faecaloma                   |                   |                   |
| subjects affected / exposed | 0 / 299 (0.00%)   | 1 / 298 (0.34%)   |
| occurrences (all)           | 0                 | 1                 |

|                                  |                 |                 |
|----------------------------------|-----------------|-----------------|
| Faeces discoloured               |                 |                 |
| subjects affected / exposed      | 1 / 299 (0.33%) | 0 / 298 (0.00%) |
| occurrences (all)                | 1               | 0               |
| Faeces hard                      |                 |                 |
| subjects affected / exposed      | 0 / 299 (0.00%) | 1 / 298 (0.34%) |
| occurrences (all)                | 0               | 1               |
| Faeces soft                      |                 |                 |
| subjects affected / exposed      | 0 / 299 (0.00%) | 1 / 298 (0.34%) |
| occurrences (all)                | 0               | 2               |
| Flatulence                       |                 |                 |
| subjects affected / exposed      | 6 / 299 (2.01%) | 3 / 298 (1.01%) |
| occurrences (all)                | 6               | 4               |
| Gastritis                        |                 |                 |
| subjects affected / exposed      | 1 / 299 (0.33%) | 1 / 298 (0.34%) |
| occurrences (all)                | 1               | 1               |
| Gastrointestinal fistula         |                 |                 |
| subjects affected / exposed      | 1 / 299 (0.33%) | 0 / 298 (0.00%) |
| occurrences (all)                | 1               | 0               |
| Gastrointestinal haemorrhage     |                 |                 |
| subjects affected / exposed      | 1 / 299 (0.33%) | 0 / 298 (0.00%) |
| occurrences (all)                | 1               | 0               |
| Gastrointestinal perforation     |                 |                 |
| subjects affected / exposed      | 1 / 299 (0.33%) | 0 / 298 (0.00%) |
| occurrences (all)                | 1               | 0               |
| Gastrooesophageal reflux disease |                 |                 |
| subjects affected / exposed      | 4 / 299 (1.34%) | 7 / 298 (2.35%) |
| occurrences (all)                | 6               | 7               |
| Gingival pain                    |                 |                 |
| subjects affected / exposed      | 0 / 299 (0.00%) | 2 / 298 (0.67%) |
| occurrences (all)                | 0               | 2               |
| Haematochezia                    |                 |                 |
| subjects affected / exposed      | 0 / 299 (0.00%) | 1 / 298 (0.34%) |
| occurrences (all)                | 0               | 1               |
| Haemorrhoids                     |                 |                 |
| subjects affected / exposed      | 6 / 299 (2.01%) | 3 / 298 (1.01%) |
| occurrences (all)                | 6               | 4               |

|                             |                    |                    |
|-----------------------------|--------------------|--------------------|
| Lip swelling                |                    |                    |
| subjects affected / exposed | 0 / 299 (0.00%)    | 1 / 298 (0.34%)    |
| occurrences (all)           | 0                  | 1                  |
| Lip ulceration              |                    |                    |
| subjects affected / exposed | 0 / 299 (0.00%)    | 1 / 298 (0.34%)    |
| occurrences (all)           | 0                  | 1                  |
| Malignant dysphagia         |                    |                    |
| subjects affected / exposed | 1 / 299 (0.33%)    | 1 / 298 (0.34%)    |
| occurrences (all)           | 1                  | 2                  |
| Melaena                     |                    |                    |
| subjects affected / exposed | 1 / 299 (0.33%)    | 1 / 298 (0.34%)    |
| occurrences (all)           | 1                  | 1                  |
| Mouth ulceration            |                    |                    |
| subjects affected / exposed | 5 / 299 (1.67%)    | 3 / 298 (1.01%)    |
| occurrences (all)           | 5                  | 3                  |
| Nausea                      |                    |                    |
| subjects affected / exposed | 152 / 299 (50.84%) | 128 / 298 (42.95%) |
| occurrences (all)           | 315                | 241                |
| Obstruction gastric         |                    |                    |
| subjects affected / exposed | 0 / 299 (0.00%)    | 1 / 298 (0.34%)    |
| occurrences (all)           | 0                  | 1                  |
| Odynophagia                 |                    |                    |
| subjects affected / exposed | 4 / 299 (1.34%)    | 0 / 298 (0.00%)    |
| occurrences (all)           | 4                  | 0                  |
| Oesophageal disorder        |                    |                    |
| subjects affected / exposed | 1 / 299 (0.33%)    | 0 / 298 (0.00%)    |
| occurrences (all)           | 1                  | 0                  |
| Oesophageal haemorrhage     |                    |                    |
| subjects affected / exposed | 1 / 299 (0.33%)    | 0 / 298 (0.00%)    |
| occurrences (all)           | 1                  | 0                  |
| Oesophageal stenosis        |                    |                    |
| subjects affected / exposed | 0 / 299 (0.00%)    | 1 / 298 (0.34%)    |
| occurrences (all)           | 0                  | 1                  |
| Oesophagitis                |                    |                    |
| subjects affected / exposed | 2 / 299 (0.67%)    | 1 / 298 (0.34%)    |
| occurrences (all)           | 2                  | 1                  |

|                              |                  |                  |
|------------------------------|------------------|------------------|
| Oral pain                    |                  |                  |
| subjects affected / exposed  | 1 / 299 (0.33%)  | 2 / 298 (0.67%)  |
| occurrences (all)            | 1                | 3                |
| Pancreatitis chronic         |                  |                  |
| subjects affected / exposed  | 1 / 299 (0.33%)  | 0 / 298 (0.00%)  |
| occurrences (all)            | 1                | 0                |
| Proctalgia                   |                  |                  |
| subjects affected / exposed  | 0 / 299 (0.00%)  | 1 / 298 (0.34%)  |
| occurrences (all)            | 0                | 1                |
| Rectal haemorrhage           |                  |                  |
| subjects affected / exposed  | 0 / 299 (0.00%)  | 2 / 298 (0.67%)  |
| occurrences (all)            | 0                | 2                |
| Reflux gastritis             |                  |                  |
| subjects affected / exposed  | 3 / 299 (1.00%)  | 0 / 298 (0.00%)  |
| occurrences (all)            | 3                | 0                |
| Retching                     |                  |                  |
| subjects affected / exposed  | 1 / 299 (0.33%)  | 0 / 298 (0.00%)  |
| occurrences (all)            | 1                | 0                |
| Salivary hypersecretion      |                  |                  |
| subjects affected / exposed  | 3 / 299 (1.00%)  | 1 / 298 (0.34%)  |
| occurrences (all)            | 3                | 6                |
| Small intestinal obstruction |                  |                  |
| subjects affected / exposed  | 0 / 299 (0.00%)  | 1 / 298 (0.34%)  |
| occurrences (all)            | 0                | 1                |
| Stomatitis                   |                  |                  |
| subjects affected / exposed  | 25 / 299 (8.36%) | 27 / 298 (9.06%) |
| occurrences (all)            | 38               | 34               |
| Subileus                     |                  |                  |
| subjects affected / exposed  | 0 / 299 (0.00%)  | 2 / 298 (0.67%)  |
| occurrences (all)            | 0                | 2                |
| Teething                     |                  |                  |
| subjects affected / exposed  | 0 / 299 (0.00%)  | 1 / 298 (0.34%)  |
| occurrences (all)            | 0                | 1                |
| Tongue discolouration        |                  |                  |
| subjects affected / exposed  | 0 / 299 (0.00%)  | 1 / 298 (0.34%)  |
| occurrences (all)            | 0                | 1                |

|                                                                         |                          |                          |  |
|-------------------------------------------------------------------------|--------------------------|--------------------------|--|
| Tooth loss<br>subjects affected / exposed<br>occurrences (all)          | 1 / 299 (0.33%)<br>1     | 0 / 298 (0.00%)<br>0     |  |
| Toothache<br>subjects affected / exposed<br>occurrences (all)           | 2 / 299 (0.67%)<br>2     | 1 / 298 (0.34%)<br>1     |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)            | 94 / 299 (31.44%)<br>153 | 94 / 298 (31.54%)<br>149 |  |
| Hepatobiliary disorders                                                 |                          |                          |  |
| Biliary colic<br>subjects affected / exposed<br>occurrences (all)       | 1 / 299 (0.33%)<br>1     | 0 / 298 (0.00%)<br>0     |  |
| Cholelithiasis<br>subjects affected / exposed<br>occurrences (all)      | 1 / 299 (0.33%)<br>1     | 0 / 298 (0.00%)<br>0     |  |
| Cholestasis<br>subjects affected / exposed<br>occurrences (all)         | 1 / 299 (0.33%)<br>1     | 0 / 298 (0.00%)<br>0     |  |
| Hepatic pain<br>subjects affected / exposed<br>occurrences (all)        | 0 / 299 (0.00%)<br>0     | 1 / 298 (0.34%)<br>1     |  |
| Hepatomegaly<br>subjects affected / exposed<br>occurrences (all)        | 0 / 299 (0.00%)<br>0     | 1 / 298 (0.34%)<br>1     |  |
| Hepatotoxicity<br>subjects affected / exposed<br>occurrences (all)      | 1 / 299 (0.33%)<br>1     | 0 / 298 (0.00%)<br>0     |  |
| Hyperbilirubinaemia<br>subjects affected / exposed<br>occurrences (all) | 11 / 299 (3.68%)<br>16   | 9 / 298 (3.02%)<br>9     |  |
| Jaundice<br>subjects affected / exposed<br>occurrences (all)            | 2 / 299 (0.67%)<br>3     | 1 / 298 (0.34%)<br>1     |  |
| Jaundice cholestatic                                                    |                          |                          |  |

|                                                  |                      |                      |  |
|--------------------------------------------------|----------------------|----------------------|--|
| subjects affected / exposed<br>occurrences (all) | 1 / 299 (0.33%)<br>1 | 0 / 298 (0.00%)<br>0 |  |
| Skin and subcutaneous tissue disorders           |                      |                      |  |
| Alopecia                                         |                      |                      |  |
| subjects affected / exposed                      | 94 / 299 (31.44%)    | 74 / 298 (24.83%)    |  |
| occurrences (all)                                | 120                  | 88                   |  |
| Alopecia totalis                                 |                      |                      |  |
| subjects affected / exposed                      | 1 / 299 (0.33%)      | 0 / 298 (0.00%)      |  |
| occurrences (all)                                | 1                    | 0                    |  |
| Alopecia universalis                             |                      |                      |  |
| subjects affected / exposed                      | 1 / 299 (0.33%)      | 0 / 298 (0.00%)      |  |
| occurrences (all)                                | 1                    | 0                    |  |
| Blister                                          |                      |                      |  |
| subjects affected / exposed                      | 2 / 299 (0.67%)      | 1 / 298 (0.34%)      |  |
| occurrences (all)                                | 2                    | 1                    |  |
| Dermatitis                                       |                      |                      |  |
| subjects affected / exposed                      | 3 / 299 (1.00%)      | 1 / 298 (0.34%)      |  |
| occurrences (all)                                | 4                    | 1                    |  |
| Dermatitis acneiform                             |                      |                      |  |
| subjects affected / exposed                      | 0 / 299 (0.00%)      | 1 / 298 (0.34%)      |  |
| occurrences (all)                                | 0                    | 1                    |  |
| Dermatitis allergic                              |                      |                      |  |
| subjects affected / exposed                      | 1 / 299 (0.33%)      | 0 / 298 (0.00%)      |  |
| occurrences (all)                                | 1                    | 0                    |  |
| Dermatosis                                       |                      |                      |  |
| subjects affected / exposed                      | 0 / 299 (0.00%)      | 1 / 298 (0.34%)      |  |
| occurrences (all)                                | 0                    | 1                    |  |
| Dry skin                                         |                      |                      |  |
| subjects affected / exposed                      | 12 / 299 (4.01%)     | 14 / 298 (4.70%)     |  |
| occurrences (all)                                | 14                   | 16                   |  |
| Ecchymosis                                       |                      |                      |  |
| subjects affected / exposed                      | 1 / 299 (0.33%)      | 0 / 298 (0.00%)      |  |
| occurrences (all)                                | 1                    | 0                    |  |
| Erythema                                         |                      |                      |  |
| subjects affected / exposed                      | 5 / 299 (1.67%)      | 4 / 298 (1.34%)      |  |
| occurrences (all)                                | 7                    | 5                    |  |

|                             |                 |                 |
|-----------------------------|-----------------|-----------------|
| Exfoliative rash            |                 |                 |
| subjects affected / exposed | 0 / 299 (0.00%) | 1 / 298 (0.34%) |
| occurrences (all)           | 0               | 1               |
| Hyperhidrosis               |                 |                 |
| subjects affected / exposed | 1 / 299 (0.33%) | 1 / 298 (0.34%) |
| occurrences (all)           | 1               | 1               |
| Hyperkeratosis              |                 |                 |
| subjects affected / exposed | 0 / 299 (0.00%) | 1 / 298 (0.34%) |
| occurrences (all)           | 0               | 1               |
| Ingrowing nail              |                 |                 |
| subjects affected / exposed | 1 / 299 (0.33%) | 1 / 298 (0.34%) |
| occurrences (all)           | 1               | 1               |
| Miliaria                    |                 |                 |
| subjects affected / exposed | 0 / 299 (0.00%) | 1 / 298 (0.34%) |
| occurrences (all)           | 0               | 1               |
| Nail discolouration         |                 |                 |
| subjects affected / exposed | 2 / 299 (0.67%) | 3 / 298 (1.01%) |
| occurrences (all)           | 2               | 3               |
| Nail disorder               |                 |                 |
| subjects affected / exposed | 8 / 299 (2.68%) | 6 / 298 (2.01%) |
| occurrences (all)           | 8               | 8               |
| Nail dystrophy              |                 |                 |
| subjects affected / exposed | 0 / 299 (0.00%) | 1 / 298 (0.34%) |
| occurrences (all)           | 0               | 1               |
| Nail ridging                |                 |                 |
| subjects affected / exposed | 1 / 299 (0.33%) | 1 / 298 (0.34%) |
| occurrences (all)           | 1               | 1               |
| Nail toxicity               |                 |                 |
| subjects affected / exposed | 0 / 299 (0.00%) | 1 / 298 (0.34%) |
| occurrences (all)           | 0               | 4               |
| Night sweats                |                 |                 |
| subjects affected / exposed | 1 / 299 (0.33%) | 1 / 298 (0.34%) |
| occurrences (all)           | 1               | 1               |
| Onychalgia                  |                 |                 |
| subjects affected / exposed | 0 / 299 (0.00%) | 1 / 298 (0.34%) |
| occurrences (all)           | 0               | 1               |



|                                            |                   |                   |
|--------------------------------------------|-------------------|-------------------|
| Onychoclasia                               |                   |                   |
| subjects affected / exposed                | 0 / 299 (0.00%)   | 1 / 298 (0.34%)   |
| occurrences (all)                          | 0                 | 1                 |
| Onycholysis                                |                   |                   |
| subjects affected / exposed                | 4 / 299 (1.34%)   | 1 / 298 (0.34%)   |
| occurrences (all)                          | 6                 | 2                 |
| Onychomadesis                              |                   |                   |
| subjects affected / exposed                | 3 / 299 (1.00%)   | 2 / 298 (0.67%)   |
| occurrences (all)                          | 3                 | 2                 |
| Pain of skin                               |                   |                   |
| subjects affected / exposed                | 1 / 299 (0.33%)   | 0 / 298 (0.00%)   |
| occurrences (all)                          | 1                 | 0                 |
| Palmar erythema                            |                   |                   |
| subjects affected / exposed                | 1 / 299 (0.33%)   | 0 / 298 (0.00%)   |
| occurrences (all)                          | 1                 | 0                 |
| Palmar-plantar erythrodysesthesia syndrome |                   |                   |
| subjects affected / exposed                | 81 / 299 (27.09%) | 59 / 298 (19.80%) |
| occurrences (all)                          | 161               | 144               |
| Petechiae                                  |                   |                   |
| subjects affected / exposed                | 0 / 299 (0.00%)   | 1 / 298 (0.34%)   |
| occurrences (all)                          | 0                 | 1                 |
| Photosensitivity reaction                  |                   |                   |
| subjects affected / exposed                | 1 / 299 (0.33%)   | 1 / 298 (0.34%)   |
| occurrences (all)                          | 1                 | 1                 |
| Pigmentation disorder                      |                   |                   |
| subjects affected / exposed                | 1 / 299 (0.33%)   | 0 / 298 (0.00%)   |
| occurrences (all)                          | 1                 | 0                 |
| Plantar erythema                           |                   |                   |
| subjects affected / exposed                | 1 / 299 (0.33%)   | 0 / 298 (0.00%)   |
| occurrences (all)                          | 1                 | 0                 |
| Pruritus                                   |                   |                   |
| subjects affected / exposed                | 2 / 299 (0.67%)   | 4 / 298 (1.34%)   |
| occurrences (all)                          | 2                 | 4                 |
| Pruritus generalised                       |                   |                   |

|                             |                  |                 |
|-----------------------------|------------------|-----------------|
| subjects affected / exposed | 1 / 299 (0.33%)  | 0 / 298 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Psoriasis                   |                  |                 |
| subjects affected / exposed | 0 / 299 (0.00%)  | 1 / 298 (0.34%) |
| occurrences (all)           | 0                | 3               |
| Rash                        |                  |                 |
| subjects affected / exposed | 11 / 299 (3.68%) | 9 / 298 (3.02%) |
| occurrences (all)           | 11               | 14              |
| Rash erythematous           |                  |                 |
| subjects affected / exposed | 1 / 299 (0.33%)  | 1 / 298 (0.34%) |
| occurrences (all)           | 1                | 1               |
| Rash generalised            |                  |                 |
| subjects affected / exposed | 1 / 299 (0.33%)  | 0 / 298 (0.00%) |
| occurrences (all)           | 2                | 0               |
| Rash macular                |                  |                 |
| subjects affected / exposed | 1 / 299 (0.33%)  | 1 / 298 (0.34%) |
| occurrences (all)           | 1                | 2               |
| Rash maculo-papular         |                  |                 |
| subjects affected / exposed | 2 / 299 (0.67%)  | 0 / 298 (0.00%) |
| occurrences (all)           | 2                | 0               |
| Rash papular                |                  |                 |
| subjects affected / exposed | 0 / 299 (0.00%)  | 1 / 298 (0.34%) |
| occurrences (all)           | 0                | 1               |
| Skin depigmentation         |                  |                 |
| subjects affected / exposed | 1 / 299 (0.33%)  | 0 / 298 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Skin discolouration         |                  |                 |
| subjects affected / exposed | 0 / 299 (0.00%)  | 2 / 298 (0.67%) |
| occurrences (all)           | 0                | 3               |
| Skin disorder               |                  |                 |
| subjects affected / exposed | 3 / 299 (1.00%)  | 1 / 298 (0.34%) |
| occurrences (all)           | 3                | 1               |
| Skin exfoliation            |                  |                 |
| subjects affected / exposed | 2 / 299 (0.67%)  | 1 / 298 (0.34%) |
| occurrences (all)           | 2                | 2               |
| Skin fissures               |                  |                 |

|                                                                                                        |                      |                      |  |
|--------------------------------------------------------------------------------------------------------|----------------------|----------------------|--|
| subjects affected / exposed<br>occurrences (all)                                                       | 3 / 299 (1.00%)<br>3 | 3 / 298 (1.01%)<br>3 |  |
| Skin hyperpigmentation<br>subjects affected / exposed<br>occurrences (all)                             | 7 / 299 (2.34%)<br>7 | 2 / 298 (0.67%)<br>2 |  |
| Skin irritation<br>subjects affected / exposed<br>occurrences (all)                                    | 1 / 299 (0.33%)<br>2 | 0 / 298 (0.00%)<br>0 |  |
| Skin lesion<br>subjects affected / exposed<br>occurrences (all)                                        | 1 / 299 (0.33%)<br>1 | 0 / 298 (0.00%)<br>0 |  |
| Skin reaction<br>subjects affected / exposed<br>occurrences (all)                                      | 1 / 299 (0.33%)<br>1 | 1 / 298 (0.34%)<br>1 |  |
| Skin ulcer<br>subjects affected / exposed<br>occurrences (all)                                         | 3 / 299 (1.00%)<br>3 | 0 / 298 (0.00%)<br>0 |  |
| Urticaria<br>subjects affected / exposed<br>occurrences (all)                                          | 1 / 299 (0.33%)<br>1 | 1 / 298 (0.34%)<br>1 |  |
| Renal and urinary disorders<br>Acute kidney injury<br>subjects affected / exposed<br>occurrences (all) | 1 / 299 (0.33%)<br>1 | 2 / 298 (0.67%)<br>2 |  |
| Bladder pain<br>subjects affected / exposed<br>occurrences (all)                                       | 1 / 299 (0.33%)<br>1 | 0 / 298 (0.00%)<br>0 |  |
| Bladder stenosis<br>subjects affected / exposed<br>occurrences (all)                                   | 0 / 299 (0.00%)<br>0 | 1 / 298 (0.34%)<br>1 |  |
| Chromaturia<br>subjects affected / exposed<br>occurrences (all)                                        | 0 / 299 (0.00%)<br>0 | 1 / 298 (0.34%)<br>1 |  |
| Chronic kidney disease<br>subjects affected / exposed<br>occurrences (all)                             | 0 / 299 (0.00%)<br>0 | 1 / 298 (0.34%)<br>2 |  |

|                             |                 |                 |
|-----------------------------|-----------------|-----------------|
| Dysuria                     |                 |                 |
| subjects affected / exposed | 3 / 299 (1.00%) | 2 / 298 (0.67%) |
| occurrences (all)           | 3               | 2               |
| Haematuria                  |                 |                 |
| subjects affected / exposed | 3 / 299 (1.00%) | 4 / 298 (1.34%) |
| occurrences (all)           | 3               | 5               |
| Hydronephrosis              |                 |                 |
| subjects affected / exposed | 0 / 299 (0.00%) | 1 / 298 (0.34%) |
| occurrences (all)           | 0               | 1               |
| Nephrolithiasis             |                 |                 |
| subjects affected / exposed | 1 / 299 (0.33%) | 0 / 298 (0.00%) |
| occurrences (all)           | 1               | 0               |
| Nephropathy toxic           |                 |                 |
| subjects affected / exposed | 1 / 299 (0.33%) | 1 / 298 (0.34%) |
| occurrences (all)           | 1               | 1               |
| Nocturia                    |                 |                 |
| subjects affected / exposed | 2 / 299 (0.67%) | 0 / 298 (0.00%) |
| occurrences (all)           | 2               | 0               |
| Pollakiuria                 |                 |                 |
| subjects affected / exposed | 3 / 299 (1.00%) | 1 / 298 (0.34%) |
| occurrences (all)           | 4               | 1               |
| Polyuria                    |                 |                 |
| subjects affected / exposed | 0 / 299 (0.00%) | 1 / 298 (0.34%) |
| occurrences (all)           | 0               | 1               |
| Proteinuria                 |                 |                 |
| subjects affected / exposed | 2 / 299 (0.67%) | 0 / 298 (0.00%) |
| occurrences (all)           | 2               | 0               |
| Renal colic                 |                 |                 |
| subjects affected / exposed | 1 / 299 (0.33%) | 0 / 298 (0.00%) |
| occurrences (all)           | 1               | 0               |
| Renal failure               |                 |                 |
| subjects affected / exposed | 2 / 299 (0.67%) | 3 / 298 (1.01%) |
| occurrences (all)           | 2               | 6               |
| Renal impairment            |                 |                 |
| subjects affected / exposed | 1 / 299 (0.33%) | 2 / 298 (0.67%) |
| occurrences (all)           | 1               | 2               |

|                                                                             |                        |                        |  |
|-----------------------------------------------------------------------------|------------------------|------------------------|--|
| Ureteric obstruction<br>subjects affected / exposed<br>occurrences (all)    | 1 / 299 (0.33%)<br>1   | 1 / 298 (0.34%)<br>1   |  |
| Urethritis noninfective<br>subjects affected / exposed<br>occurrences (all) | 1 / 299 (0.33%)<br>1   | 0 / 298 (0.00%)<br>0   |  |
| Urinary retention<br>subjects affected / exposed<br>occurrences (all)       | 3 / 299 (1.00%)<br>3   | 4 / 298 (1.34%)<br>4   |  |
| Urine odour abnormal<br>subjects affected / exposed<br>occurrences (all)    | 1 / 299 (0.33%)<br>1   | 0 / 298 (0.00%)<br>0   |  |
| Musculoskeletal and connective tissue disorders                             |                        |                        |  |
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)              | 7 / 299 (2.34%)<br>8   | 2 / 298 (0.67%)<br>2   |  |
| Back pain<br>subjects affected / exposed<br>occurrences (all)               | 25 / 299 (8.36%)<br>30 | 14 / 298 (4.70%)<br>16 |  |
| Bone pain<br>subjects affected / exposed<br>occurrences (all)               | 4 / 299 (1.34%)<br>4   | 0 / 298 (0.00%)<br>0   |  |
| Flank pain<br>subjects affected / exposed<br>occurrences (all)              | 1 / 299 (0.33%)<br>3   | 3 / 298 (1.01%)<br>3   |  |
| Gouty arthritis<br>subjects affected / exposed<br>occurrences (all)         | 1 / 299 (0.33%)<br>1   | 0 / 298 (0.00%)<br>0   |  |
| Groin pain<br>subjects affected / exposed<br>occurrences (all)              | 0 / 299 (0.00%)<br>0   | 1 / 298 (0.34%)<br>1   |  |
| Joint effusion<br>subjects affected / exposed<br>occurrences (all)          | 1 / 299 (0.33%)<br>1   | 0 / 298 (0.00%)<br>0   |  |
| Joint range of motion decreased                                             |                        |                        |  |

|                             |                  |                  |
|-----------------------------|------------------|------------------|
| subjects affected / exposed | 0 / 299 (0.00%)  | 1 / 298 (0.34%)  |
| occurrences (all)           | 0                | 1                |
| Joint swelling              |                  |                  |
| subjects affected / exposed | 1 / 299 (0.33%)  | 0 / 298 (0.00%)  |
| occurrences (all)           | 1                | 0                |
| Muscle spasms               |                  |                  |
| subjects affected / exposed | 7 / 299 (2.34%)  | 5 / 298 (1.68%)  |
| occurrences (all)           | 7                | 7                |
| Muscular weakness           |                  |                  |
| subjects affected / exposed | 1 / 299 (0.33%)  | 3 / 298 (1.01%)  |
| occurrences (all)           | 1                | 4                |
| Musculoskeletal chest pain  |                  |                  |
| subjects affected / exposed | 8 / 299 (2.68%)  | 4 / 298 (1.34%)  |
| occurrences (all)           | 8                | 4                |
| Musculoskeletal discomfort  |                  |                  |
| subjects affected / exposed | 1 / 299 (0.33%)  | 3 / 298 (1.01%)  |
| occurrences (all)           | 1                | 4                |
| Musculoskeletal pain        |                  |                  |
| subjects affected / exposed | 6 / 299 (2.01%)  | 1 / 298 (0.34%)  |
| occurrences (all)           | 6                | 1                |
| Musculoskeletal stiffness   |                  |                  |
| subjects affected / exposed | 1 / 299 (0.33%)  | 0 / 298 (0.00%)  |
| occurrences (all)           | 1                | 0                |
| Myalgia                     |                  |                  |
| subjects affected / exposed | 5 / 299 (1.67%)  | 3 / 298 (1.01%)  |
| occurrences (all)           | 5                | 3                |
| Neck pain                   |                  |                  |
| subjects affected / exposed | 0 / 299 (0.00%)  | 3 / 298 (1.01%)  |
| occurrences (all)           | 0                | 3                |
| Pain in extremity           |                  |                  |
| subjects affected / exposed | 10 / 299 (3.34%) | 11 / 298 (3.69%) |
| occurrences (all)           | 13               | 15               |
| Pain in jaw                 |                  |                  |
| subjects affected / exposed | 0 / 299 (0.00%)  | 1 / 298 (0.34%)  |
| occurrences (all)           | 0                | 1                |
| Sjogren's syndrome          |                  |                  |

|                                                                              |                      |                      |  |
|------------------------------------------------------------------------------|----------------------|----------------------|--|
| subjects affected / exposed<br>occurrences (all)                             | 0 / 299 (0.00%)<br>0 | 1 / 298 (0.34%)<br>1 |  |
| Spinal pain<br>subjects affected / exposed<br>occurrences (all)              | 3 / 299 (1.00%)<br>4 | 2 / 298 (0.67%)<br>2 |  |
| Tendonitis<br>subjects affected / exposed<br>occurrences (all)               | 1 / 299 (0.33%)<br>1 | 0 / 298 (0.00%)<br>0 |  |
| Infections and infestations                                                  |                      |                      |  |
| Anorectal infection<br>subjects affected / exposed<br>occurrences (all)      | 0 / 299 (0.00%)<br>0 | 1 / 298 (0.34%)<br>1 |  |
| Arthritis infective<br>subjects affected / exposed<br>occurrences (all)      | 0 / 299 (0.00%)<br>0 | 1 / 298 (0.34%)<br>1 |  |
| Asymptomatic bacteriuria<br>subjects affected / exposed<br>occurrences (all) | 1 / 299 (0.33%)<br>2 | 0 / 298 (0.00%)<br>0 |  |
| Bacteraemia<br>subjects affected / exposed<br>occurrences (all)              | 1 / 299 (0.33%)<br>1 | 0 / 298 (0.00%)<br>0 |  |
| Bacterial infection<br>subjects affected / exposed<br>occurrences (all)      | 1 / 299 (0.33%)<br>1 | 2 / 298 (0.67%)<br>2 |  |
| Bacteriuria<br>subjects affected / exposed<br>occurrences (all)              | 1 / 299 (0.33%)<br>1 | 1 / 298 (0.34%)<br>2 |  |
| Biliary sepsis<br>subjects affected / exposed<br>occurrences (all)           | 1 / 299 (0.33%)<br>1 | 0 / 298 (0.00%)<br>0 |  |
| Bronchitis<br>subjects affected / exposed<br>occurrences (all)               | 2 / 299 (0.67%)<br>2 | 4 / 298 (1.34%)<br>4 |  |
| Candida infection<br>subjects affected / exposed<br>occurrences (all)        | 1 / 299 (0.33%)<br>1 | 1 / 298 (0.34%)<br>1 |  |

|                             |                 |                 |
|-----------------------------|-----------------|-----------------|
| Cellulitis                  |                 |                 |
| subjects affected / exposed | 0 / 299 (0.00%) | 1 / 298 (0.34%) |
| occurrences (all)           | 0               | 1               |
| Conjunctivitis              |                 |                 |
| subjects affected / exposed | 2 / 299 (0.67%) | 2 / 298 (0.67%) |
| occurrences (all)           | 2               | 3               |
| Conjunctivitis bacterial    |                 |                 |
| subjects affected / exposed | 0 / 299 (0.00%) | 1 / 298 (0.34%) |
| occurrences (all)           | 0               | 1               |
| Cystitis                    |                 |                 |
| subjects affected / exposed | 1 / 299 (0.33%) | 2 / 298 (0.67%) |
| occurrences (all)           | 1               | 2               |
| Device related infection    |                 |                 |
| subjects affected / exposed | 2 / 299 (0.67%) | 2 / 298 (0.67%) |
| occurrences (all)           | 2               | 2               |
| Ear infection               |                 |                 |
| subjects affected / exposed | 1 / 299 (0.33%) | 0 / 298 (0.00%) |
| occurrences (all)           | 1               | 0               |
| Embolic pneumonia           |                 |                 |
| subjects affected / exposed | 1 / 299 (0.33%) | 1 / 298 (0.34%) |
| occurrences (all)           | 1               | 1               |
| Erysipelas                  |                 |                 |
| subjects affected / exposed | 1 / 299 (0.33%) | 0 / 298 (0.00%) |
| occurrences (all)           | 1               | 0               |
| Eye infection               |                 |                 |
| subjects affected / exposed | 0 / 299 (0.00%) | 1 / 298 (0.34%) |
| occurrences (all)           | 0               | 1               |
| Folliculitis                |                 |                 |
| subjects affected / exposed | 1 / 299 (0.33%) | 0 / 298 (0.00%) |
| occurrences (all)           | 1               | 0               |
| Fungal infection            |                 |                 |
| subjects affected / exposed | 2 / 299 (0.67%) | 1 / 298 (0.34%) |
| occurrences (all)           | 2               | 1               |
| Fungal skin infection       |                 |                 |
| subjects affected / exposed | 0 / 299 (0.00%) | 1 / 298 (0.34%) |
| occurrences (all)           | 0               | 1               |



|                                   |                 |                 |
|-----------------------------------|-----------------|-----------------|
| Gastroenteritis                   |                 |                 |
| subjects affected / exposed       | 1 / 299 (0.33%) | 0 / 298 (0.00%) |
| occurrences (all)                 | 1               | 0               |
| Gastrointestinal fungal infection |                 |                 |
| subjects affected / exposed       | 0 / 299 (0.00%) | 1 / 298 (0.34%) |
| occurrences (all)                 | 0               | 1               |
| Gastrointestinal infection        |                 |                 |
| subjects affected / exposed       | 1 / 299 (0.33%) | 1 / 298 (0.34%) |
| occurrences (all)                 | 1               | 1               |
| Genital herpes                    |                 |                 |
| subjects affected / exposed       | 1 / 299 (0.33%) | 0 / 298 (0.00%) |
| occurrences (all)                 | 1               | 0               |
| Giardiasis                        |                 |                 |
| subjects affected / exposed       | 0 / 299 (0.00%) | 1 / 298 (0.34%) |
| occurrences (all)                 | 0               | 1               |
| Herpes dermatitis                 |                 |                 |
| subjects affected / exposed       | 0 / 299 (0.00%) | 1 / 298 (0.34%) |
| occurrences (all)                 | 0               | 1               |
| Herpes simplex                    |                 |                 |
| subjects affected / exposed       | 1 / 299 (0.33%) | 0 / 298 (0.00%) |
| occurrences (all)                 | 1               | 0               |
| Herpes zoster                     |                 |                 |
| subjects affected / exposed       | 1 / 299 (0.33%) | 0 / 298 (0.00%) |
| occurrences (all)                 | 1               | 0               |
| Infection                         |                 |                 |
| subjects affected / exposed       | 3 / 299 (1.00%) | 0 / 298 (0.00%) |
| occurrences (all)                 | 4               | 0               |
| Infectious colitis                |                 |                 |
| subjects affected / exposed       | 1 / 299 (0.33%) | 0 / 298 (0.00%) |
| occurrences (all)                 | 1               | 0               |
| Influenza                         |                 |                 |
| subjects affected / exposed       | 3 / 299 (1.00%) | 4 / 298 (1.34%) |
| occurrences (all)                 | 3               | 5               |
| Localised infection               |                 |                 |
| subjects affected / exposed       | 3 / 299 (1.00%) | 1 / 298 (0.34%) |
| occurrences (all)                 | 3               | 1               |

|                                                                                       |                       |                        |
|---------------------------------------------------------------------------------------|-----------------------|------------------------|
| Lower respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 4 / 299 (1.34%)<br>4  | 3 / 298 (1.01%)<br>3   |
| Mucosal infection<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 299 (0.00%)<br>0  | 1 / 298 (0.34%)<br>1   |
| Nail bed infection<br>subjects affected / exposed<br>occurrences (all)                | 1 / 299 (0.33%)<br>1  | 0 / 298 (0.00%)<br>0   |
| Nail infection<br>subjects affected / exposed<br>occurrences (all)                    | 1 / 299 (0.33%)<br>1  | 1 / 298 (0.34%)<br>1   |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)                   | 4 / 299 (1.34%)<br>6  | 11 / 298 (3.69%)<br>12 |
| Oesophageal candidiasis<br>subjects affected / exposed<br>occurrences (all)           | 1 / 299 (0.33%)<br>1  | 0 / 298 (0.00%)<br>0   |
| Onychomycosis<br>subjects affected / exposed<br>occurrences (all)                     | 2 / 299 (0.67%)<br>2  | 2 / 298 (0.67%)<br>2   |
| Oral candidiasis<br>subjects affected / exposed<br>occurrences (all)                  | 8 / 299 (2.68%)<br>10 | 4 / 298 (1.34%)<br>5   |
| Oral fungal infection<br>subjects affected / exposed<br>occurrences (all)             | 1 / 299 (0.33%)<br>1  | 2 / 298 (0.67%)<br>4   |
| Oral herpes<br>subjects affected / exposed<br>occurrences (all)                       | 4 / 299 (1.34%)<br>4  | 1 / 298 (0.34%)<br>2   |
| Otitis media<br>subjects affected / exposed<br>occurrences (all)                      | 0 / 299 (0.00%)<br>0  | 1 / 298 (0.34%)<br>1   |
| Paronychia<br>subjects affected / exposed<br>occurrences (all)                        | 4 / 299 (1.34%)<br>5  | 7 / 298 (2.35%)<br>9   |

|                                   |                 |                 |
|-----------------------------------|-----------------|-----------------|
| Pharyngitis                       |                 |                 |
| subjects affected / exposed       | 0 / 299 (0.00%) | 1 / 298 (0.34%) |
| occurrences (all)                 | 0               | 1               |
| Pneumonia                         |                 |                 |
| subjects affected / exposed       | 0 / 299 (0.00%) | 4 / 298 (1.34%) |
| occurrences (all)                 | 0               | 4               |
| Respiratory tract infection       |                 |                 |
| subjects affected / exposed       | 6 / 299 (2.01%) | 2 / 298 (0.67%) |
| occurrences (all)                 | 6               | 2               |
| Respiratory tract infection viral |                 |                 |
| subjects affected / exposed       | 1 / 299 (0.33%) | 0 / 298 (0.00%) |
| occurrences (all)                 | 1               | 0               |
| Rhinitis                          |                 |                 |
| subjects affected / exposed       | 2 / 299 (0.67%) | 3 / 298 (1.01%) |
| occurrences (all)                 | 2               | 3               |
| Sepsis                            |                 |                 |
| subjects affected / exposed       | 0 / 299 (0.00%) | 1 / 298 (0.34%) |
| occurrences (all)                 | 0               | 1               |
| Sinusitis                         |                 |                 |
| subjects affected / exposed       | 0 / 299 (0.00%) | 1 / 298 (0.34%) |
| occurrences (all)                 | 0               | 1               |
| Skin bacterial infection          |                 |                 |
| subjects affected / exposed       | 0 / 299 (0.00%) | 1 / 298 (0.34%) |
| occurrences (all)                 | 0               | 2               |
| Skin candida                      |                 |                 |
| subjects affected / exposed       | 1 / 299 (0.33%) | 0 / 298 (0.00%) |
| occurrences (all)                 | 1               | 0               |
| Skin infection                    |                 |                 |
| subjects affected / exposed       | 0 / 299 (0.00%) | 1 / 298 (0.34%) |
| occurrences (all)                 | 0               | 1               |
| Soft tissue infection             |                 |                 |
| subjects affected / exposed       | 0 / 299 (0.00%) | 1 / 298 (0.34%) |
| occurrences (all)                 | 0               | 1               |
| Sputum purulent                   |                 |                 |
| subjects affected / exposed       | 1 / 299 (0.33%) | 0 / 298 (0.00%) |
| occurrences (all)                 | 1               | 0               |

|                                             |                  |                 |
|---------------------------------------------|------------------|-----------------|
| Tinea cruris                                |                  |                 |
| subjects affected / exposed                 | 0 / 299 (0.00%)  | 1 / 298 (0.34%) |
| occurrences (all)                           | 0                | 1               |
| Tinea pedis                                 |                  |                 |
| subjects affected / exposed                 | 0 / 299 (0.00%)  | 1 / 298 (0.34%) |
| occurrences (all)                           | 0                | 1               |
| Tooth infection                             |                  |                 |
| subjects affected / exposed                 | 0 / 299 (0.00%)  | 1 / 298 (0.34%) |
| occurrences (all)                           | 0                | 1               |
| Tracheobronchitis                           |                  |                 |
| subjects affected / exposed                 | 0 / 299 (0.00%)  | 1 / 298 (0.34%) |
| occurrences (all)                           | 0                | 2               |
| Upper respiratory tract infection           |                  |                 |
| subjects affected / exposed                 | 9 / 299 (3.01%)  | 6 / 298 (2.01%) |
| occurrences (all)                           | 9                | 7               |
| Upper respiratory tract infection bacterial |                  |                 |
| subjects affected / exposed                 | 1 / 299 (0.33%)  | 0 / 298 (0.00%) |
| occurrences (all)                           | 1                | 0               |
| Urinary tract infection                     |                  |                 |
| subjects affected / exposed                 | 16 / 299 (5.35%) | 9 / 298 (3.02%) |
| occurrences (all)                           | 20               | 10              |
| Urinary tract infection enterococcal        |                  |                 |
| subjects affected / exposed                 | 1 / 299 (0.33%)  | 0 / 298 (0.00%) |
| occurrences (all)                           | 1                | 0               |
| Urinary tract infection fungal              |                  |                 |
| subjects affected / exposed                 | 1 / 299 (0.33%)  | 0 / 298 (0.00%) |
| occurrences (all)                           | 1                | 0               |
| Viral infection                             |                  |                 |
| subjects affected / exposed                 | 2 / 299 (0.67%)  | 0 / 298 (0.00%) |
| occurrences (all)                           | 2                | 0               |
| Viral upper respiratory tract infection     |                  |                 |
| subjects affected / exposed                 | 1 / 299 (0.33%)  | 0 / 298 (0.00%) |
| occurrences (all)                           | 1                | 0               |
| Vulvovaginal candidiasis                    |                  |                 |

|                                                                                    |                         |                          |  |
|------------------------------------------------------------------------------------|-------------------------|--------------------------|--|
| subjects affected / exposed<br>occurrences (all)                                   | 1 / 299 (0.33%)<br>1    | 0 / 298 (0.00%)<br>0     |  |
| Wound infection<br>subjects affected / exposed<br>occurrences (all)                | 0 / 299 (0.00%)<br>0    | 1 / 298 (0.34%)<br>2     |  |
| Wound infection staphylococcal<br>subjects affected / exposed<br>occurrences (all) | 0 / 299 (0.00%)<br>0    | 1 / 298 (0.34%)<br>1     |  |
| Metabolism and nutrition disorders                                                 |                         |                          |  |
| Abnormal loss of weight<br>subjects affected / exposed<br>occurrences (all)        | 0 / 299 (0.00%)<br>0    | 1 / 298 (0.34%)<br>1     |  |
| Cachexia<br>subjects affected / exposed<br>occurrences (all)                       | 1 / 299 (0.33%)<br>1    | 3 / 298 (1.01%)<br>3     |  |
| Decreased appetite<br>subjects affected / exposed<br>occurrences (all)             | 72 / 299 (24.08%)<br>99 | 72 / 298 (24.16%)<br>106 |  |
| Dehydration<br>subjects affected / exposed<br>occurrences (all)                    | 10 / 299 (3.34%)<br>14  | 14 / 298 (4.70%)<br>23   |  |
| Diabetes mellitus<br>subjects affected / exposed<br>occurrences (all)              | 0 / 299 (0.00%)<br>0    | 1 / 298 (0.34%)<br>1     |  |
| Electrolyte imbalance<br>subjects affected / exposed<br>occurrences (all)          | 0 / 299 (0.00%)<br>0    | 1 / 298 (0.34%)<br>1     |  |
| Feeding disorder<br>subjects affected / exposed<br>occurrences (all)               | 1 / 299 (0.33%)<br>1    | 0 / 298 (0.00%)<br>0     |  |
| Fluid retention<br>subjects affected / exposed<br>occurrences (all)                | 1 / 299 (0.33%)<br>1    | 1 / 298 (0.34%)<br>7     |  |
| Folate deficiency<br>subjects affected / exposed<br>occurrences (all)              | 0 / 299 (0.00%)<br>0    | 1 / 298 (0.34%)<br>1     |  |

|                             |                  |                   |
|-----------------------------|------------------|-------------------|
| Gout                        |                  |                   |
| subjects affected / exposed | 2 / 299 (0.67%)  | 0 / 298 (0.00%)   |
| occurrences (all)           | 2                | 0                 |
| Hypercalcaemia              |                  |                   |
| subjects affected / exposed | 1 / 299 (0.33%)  | 1 / 298 (0.34%)   |
| occurrences (all)           | 1                | 1                 |
| Hypercreatininaemia         |                  |                   |
| subjects affected / exposed | 0 / 299 (0.00%)  | 1 / 298 (0.34%)   |
| occurrences (all)           | 0                | 1                 |
| Hyperglycaemia              |                  |                   |
| subjects affected / exposed | 7 / 299 (2.34%)  | 7 / 298 (2.35%)   |
| occurrences (all)           | 11               | 10                |
| Hyperkalaemia               |                  |                   |
| subjects affected / exposed | 6 / 299 (2.01%)  | 3 / 298 (1.01%)   |
| occurrences (all)           | 7                | 5                 |
| Hypermagnesaemia            |                  |                   |
| subjects affected / exposed | 0 / 299 (0.00%)  | 1 / 298 (0.34%)   |
| occurrences (all)           | 0                | 1                 |
| Hyperphosphataemia          |                  |                   |
| subjects affected / exposed | 1 / 299 (0.33%)  | 0 / 298 (0.00%)   |
| occurrences (all)           | 1                | 0                 |
| Hypertriglyceridaemia       |                  |                   |
| subjects affected / exposed | 1 / 299 (0.33%)  | 0 / 298 (0.00%)   |
| occurrences (all)           | 3                | 0                 |
| Hyperuricaemia              |                  |                   |
| subjects affected / exposed | 2 / 299 (0.67%)  | 1 / 298 (0.34%)   |
| occurrences (all)           | 2                | 1                 |
| Hypoalbuminaemia            |                  |                   |
| subjects affected / exposed | 10 / 299 (3.34%) | 34 / 298 (11.41%) |
| occurrences (all)           | 11               | 49                |
| Hypocalcaemia               |                  |                   |
| subjects affected / exposed | 8 / 299 (2.68%)  | 29 / 298 (9.73%)  |
| occurrences (all)           | 12               | 56                |
| Hypochloraemia              |                  |                   |
| subjects affected / exposed | 1 / 299 (0.33%)  | 1 / 298 (0.34%)   |
| occurrences (all)           | 1                | 1                 |

|                             |                   |                   |
|-----------------------------|-------------------|-------------------|
| Hypokalaemia                |                   |                   |
| subjects affected / exposed | 31 / 299 (10.37%) | 32 / 298 (10.74%) |
| occurrences (all)           | 50                | 63                |
| Hypokalaemic syndrome       |                   |                   |
| subjects affected / exposed | 1 / 299 (0.33%)   | 0 / 298 (0.00%)   |
| occurrences (all)           | 1                 | 0                 |
| Hypomagnesaemia             |                   |                   |
| subjects affected / exposed | 33 / 299 (11.04%) | 46 / 298 (15.44%) |
| occurrences (all)           | 57                | 78                |
| Hyponatraemia               |                   |                   |
| subjects affected / exposed | 6 / 299 (2.01%)   | 17 / 298 (5.70%)  |
| occurrences (all)           | 15                | 29                |
| Hypophosphataemia           |                   |                   |
| subjects affected / exposed | 11 / 299 (3.68%)  | 9 / 298 (3.02%)   |
| occurrences (all)           | 27                | 14                |
| Hypoproteinaemia            |                   |                   |
| subjects affected / exposed | 1 / 299 (0.33%)   | 5 / 298 (1.68%)   |
| occurrences (all)           | 1                 | 7                 |
| Magnesium deficiency        |                   |                   |
| subjects affected / exposed | 1 / 299 (0.33%)   | 0 / 298 (0.00%)   |
| occurrences (all)           | 1                 | 0                 |
| Malnutrition                |                   |                   |
| subjects affected / exposed | 1 / 299 (0.33%)   | 2 / 298 (0.67%)   |
| occurrences (all)           | 1                 | 3                 |
| Type 2 diabetes mellitus    |                   |                   |
| subjects affected / exposed | 0 / 299 (0.00%)   | 1 / 298 (0.34%)   |
| occurrences (all)           | 0                 | 1                 |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 14 December 2012 | 1. To clarify that when a subject's HER2 status is unknown at the time of screening, testing will be conducted at the central laboratory 2. To add that pregnancy testing can occur more frequently if required as part of standard of care or as required by local laws and regulations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| 10 February 2014 | The 20070622 protocol enrolls subjects who are tumor MET-positive by centralized immunohistochemistry testing. MET-positive has been defined as $\geq 25\%$ tumor membrane staining for MET. Amgen is amending the protocol to allow testing at a second pre-defined higher tumor MET-positive level if survival analysis based on the 25% level is not positive. The reasons for the proposed changes are: • Phase 2 data suggested a MET-positive rate of approximately 60% • Observed a higher than expected MET-positive rate in study 20070622 is higher than expected (approximately 80%) • Increased rate could result in including a MET insensitive population into the study In addition, the amendment includes updates, clarifications, and corrections of minor errors.                                                                                                                                                                                                                                                                                 |
| 12 December 2014 | As a result of the important information shared with investigators in a letter dated 21 November 2014, namely that an increase in the number of deaths in the rilotumumab and chemotherapy arm was observed when compared with the chemotherapy only arm, and that protocol-defined futility criteria would likely have been met at the planned interim analysis in March 2015, this protocol is being amended. The amendment reflects that subjects receiving rilotumumab in combination with chemotherapy were to discontinue all study treatments and to complete safety follow-up visits approximately 30 days after receipt of the last dose of the protocol-specified therapy. Subjects receiving chemotherapy and rilotumumab-placebo are permitted to continue treatment with chemotherapy according to physician discretion until other protocol specified stopping criteria occur at which time the subjects will complete safety follow-up visits. All subjects are to be followed in long-term safety follow-up for 6 months after the primary analysis. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported